A Feasibility Study of Implantable Loop Recorder Monitoring Capacity in Older Fallers

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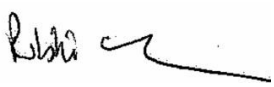
Declaration

I declare that the work in this thesis is entirely my own, except where credit is given in the acknowledgements.
The study was approved by the Faculty of Health Sciences Research Ethics Committee at Trinity College Dublin, and all participants provided written informed consent. All experimental procedures adhered to the Declaration of Helsinki.
I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work. I agree to deposit this thesis in the University's open access institutional repository or allow the Library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement. I consent to the examiner retaining a copy of the thesis beyond the examining period, should they so wish (EU GDPR May 2018).

Signed  Robert Bourke 27/6/24

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List of Figures and Tables

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Thesis list of Abbreviations

BTB	Beat-to-Beat
BBS	Berg Balance Scale
BSL	Baseline
ED	Emergency Departments
ESC	European Society of Cardiology
EUGMS	European Geriatric Medicine Society
HPRA	Health Products Regulatory Authority
IGS	Irish Gerontological Society
ILR	Implantable Loop recorder
FASU	Falls and Syncope Unit
FINV	Falls Investigation (Participant number)
FRIDS	Falls risk increasing drugs.
HRV	Heart Rate Variability
MD	Medical Doctorate
TUG	Timed Up and Go
VVS	Vasovagal Syncope
WHO	World Health Organisation
WFG	World Falls Guidelines

Abstract

INTRODUCTION: Falls are one of the most common causes of injury, prolonged hospitalisation, increased dependency and residential care admission amongst older people. There is a known association between cardiovascular disorders and falls. This thesis begins with a systematic review and meta-analysis to explore this relationship in detail. It then highlights gaps in current monitoring methods and introduces the potential of implantable loop recorders (ILRs) with an embedded triaxial accelerometers to provide detailed biophysiological data.

METHODS: The study comprises three validation studies aimed at interpreting data from ILRs with triaxial accelerometers. Subsequently, a clinical trial involving thirty 30 participants investigates the correlation between arrhythmias detected by ILRs and incidents of falls. Finally, a retrospective analysis of biophysiological parameters is performed to determine if certain changes or patterns may be predictive of falls.

RESULTS: The validation studies demonstrate robust interpretation of triaxial accelerometer data from ILRs, confirming their efficacy in capturing certain relevant physiological events. Analysis from the clinical trial demonstrates the ability of ILRs to detect significant arrhythmias in older fallers. Biophysiological parameters were not found to be related to falls.

CONCLUSIONS: This thesis highlights the potential of ILRs with triaxial accelerometers in monitoring physiological parameters in community dwelling older adults. While successful in detecting arrhythmias linked to falls, early physiological changes in gait, posture, and cardiac data were found insufficient predictors of future falls. Future research should focus on enhancing predictive models and exploring additional physiological parameters to improve fall risk assessment using ILRs.

Lay Abstract

INTRODUCTION: Falls are a serious problem for older adults, often linked to heart problems like irregular heartbeats. This thesis explores using implantable devices called loop recorders that detect irregular heart rhythms, equipped with additional special sensors called accelerometers to potentially predict falls. Accelerometers are found in smart phones to measure step counts and activity levels. Adding this to a loop recorder allows for the continuous measurement of heart and movement patterns in older people.

First, we reviewed existing studies to understand how heart conditions contribute to falls. Then, we tested the accuracy of the sensors in three different studies to see if they could detect movements related to falls. In a clinical trial involving thirty older adults, we found that irregular heart rhythms detected by these devices were strongly connected to falls. However, while the devices were effective at detecting heart problems linked to falls, they did not predict falls based on early changes in walking, posture or heart data.

This research shows promise for using implantable devices to monitor heart health in older adults and has highlighted certain areas that research cold target to potentially prevent falls in the future.

MD Hypothesis: The ability to predict falls is the holy grail for physicians caring for older adults. Technological advancements have led to the potential for implantable devices to measure biophysiological parameters in real time. I hypothesised that frail older adults may be more vulnerable to falling in certain circumstances that may represent “a perfect storm” where they would lack the physiological reserve to overcome certain stressors. Specifically, I sought to combine a number of cardiovascular parameters with activity, gait and posture change data generated from the embedded triaxial accelerometer to see if we could detect any patterns that may signal an increased likelihood of falling.

A secondary hypothesis was based on vasovagal syncope literature that appeared to demonstrate a decrease in the number of syncopal events suffered by people following the insertion of an Implantable Loop Recorder. Given the crossover between syncope and falls, I hypothesised that we would see a decrease in falls rates following implantation of the device.

Outputs

Publications:

Cardiovascular Disorders and Falls Among Older Adults: A Systematic Review and Meta-Analysis.
Bourke R, Doody P, Perez S, Moloney D, Lipsitz L, Kenny R.
The Journals of Gerontology: Series A, February 2024.
https://doi.org/10.1093/gerona/glad221

World guidelines for falls prevention and management for older adults: a global initiative.
Age and ageing.
Montero-Odasso M, van der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, Aguilar-Navarro S, Alexander NB, Becker C, Blain H, **Bourke R**. et al.
Age and ageing. September 2022
https://doi.org/10.1093/ageing/afac205

Abstract Publications:

Implantable Loop Recorders in unexplained falls
R Bourke, S Perez, M Leenders, A Maree, M Melis, T Foran, R A Kenny,
Age and Ageing, September 2023
https://doi.org/10.1093/ageing/afad156.038R Bourke, S

Monitoring Falls Risk in The Community Using an Implantable Cardiac Monitor with Embedded Accelerometer
R Bourke, S Perez, AZ Mogollo, C Finucane, M Leenders, F Roberts, G Morren, A Maree, M De Melis, RA Kenny, T Foran
Age and Ageing, November 2022
https://doi.org/10.1093/ageing/afac218.265

Platform Presentations:

Implantable Loop Recorders in unexplained falls
Bourke R.
Irish Gerontological Society (IGS) Annual Scientific Meeting, Galway, September 2023

Cardiovascular Abnormalities and Falls Among Older Adults: A Systematic Review for the Task Force on Global Guidelines for Falls in Older Adults.
Bourke R.
European Geriatric Medicine Society (EUGMS) Annual Congress, London, September 2022

Poster Presentations:

Monitoring Falls Risk in the Community Using an Implantable Cardiac Monitor with Embedded Accelerometer.
R Bourke
European Geriatric Medicine Society (EUGMS) Annual Congress, London, September 2022

SECTION ONE: FALLS

Chapter 1 : Introduction and Aims of Research

The genesis of this research lies in the recognition of the profound challenges posed by recurrent falls for older adults. As our population ages, the prevalence of falls rises. As I will outline below there are myriad risk factors for falls and a number of rudimentary falls prediction models. It is well known in the literature that there is rarely a single cause of for a fall. Rather people fall due to a failure to adapt to a variety of physiological and environmental challenges occurring at the same time. Hence there is a need to focus on more than one risk factor in any falls prediction modelling. Prolonged monitoring of several variables may be the answer. Given the technological advancements in recent years and the explosion in wearable and implantable health devices, it is conceivable that falls may ultimately be predicted and prevented from occurring utilising novel technology. Such technology could constantly monitor biophysiological parameters and detect potentially dangerous trends.

This research considers the integration of a triaxial accelerometer within an implantable cardiac monitoring device or Implantable loop recorder (ILR) leveraging the convergence of cardiovascular monitoring and motion-sensing technology. As a feasibility study, I wanted to take the first step in exploring the potential of this approach and hope to pave the way for future research projects.

Hypothesis: Changes in cardiovascular parameters and activity levels detected by an ILR with an embedded triaxial accelerometer, may signal an increased likelihood of falling.

Research Questions:

- Can a triaxial accelerometer embedded in an ILR generate useful, reproducible and reliable gait and activity data?
- Can early physiological changes in gait and activity combined with cardiovascular data predict falls?
- Do ILRs have a therapeutic as well as a diagnostic role in unexplained falls in older adults?

Section 1 will give a detailed background to the topic of falls, the relevant risk factors including a published systematic review and meta-analysis on associated cardiovascular disorders and finally, emerging technologies in the area. Section 2 provides an overview of

the validation tests I conducted with respect to postural changes, gait and activity levels as measured by the novel investigational device. These were conducted to help the study team understand how the device generated activity and posture change data. Section 3 details the clinical trial undertaken using an ILR to detect underlying cardiac data in unexplained fallers. Section 4 is an analysis of the physiological parameters associated with falls. Using temporal metrics, the retrospective analysis of physiological changes was performed in an attempt to predict falls. Section 5 summarises the studies and discusses directions for future research. Figure 1 below outlines the flow of the thesis in graphical form.

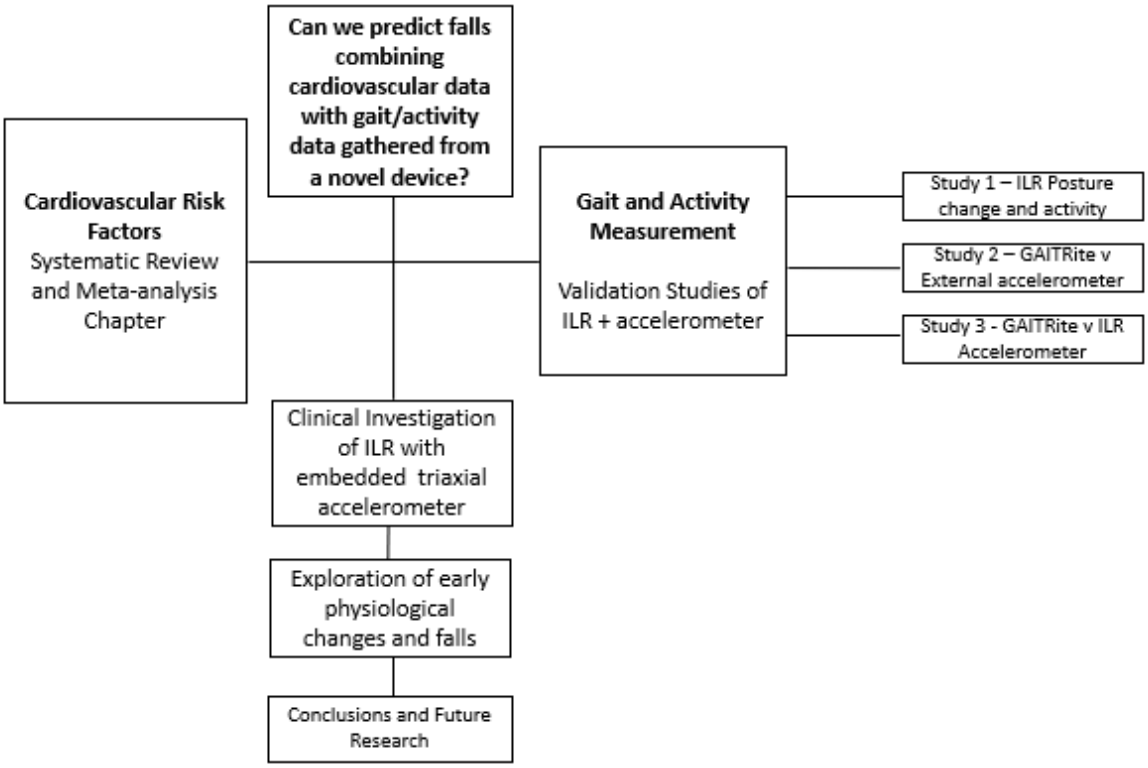


Figure 1: Thesis Flow Diagram

Chapter 2: Training and Personal Development

I was employed as a clinical research fellow in the Falls and Syncope Unit (FASU) in St James Hospital while completing my MD with Trinity College Dublin. I have benefited immensely from this time. FASU provides a world class service to patients and this is due to the culture of excellence that underpins every facet of the unit. This was the perfect place for me to develop both as a physician and a researcher. This also served as the setting for recruiting participants for the clinical investigation. In this chapter I will outline my specific learnings and highlight some of the skills I have acquired that will stand me in good stead as an academic geriatrician going forward.

2.1 Clinical Experience and Skills Acquisition

As a geriatrician in training, I decided to take time out from clinical training to broaden my horizons and gain in-depth specialist knowledge in the area of falls. Falls can occur for a variety of reasons from problems with the heart and blood pressure, to vestibular pathologies, to problems with gait and balance. Often there are dysfunctions in several of these systems in older adults, therefore it is essential to master a number of different disciplines to be an effective physician managing older fallers.

During the 3 years I have reviewed approximately 2000 patients presenting with a variety of complaints, from falls and blackouts to dizzy spells. This level of clinical exposure combined with the supervision of expert consultants has helped me to gain a significant level of expertise in managing these complex cases and to recruit patients to the study. In 2020 there were 6800 attendees to FASU between ages 16 and 100, 40% of whom were under 50. Managing a younger cohort of patient with this these presentations may be important in the future should I have a role as the general medical consultant on call in an acute hospital setting.

2.12 Cardiovascular Investigations

A key skillset I have gained relates to the interpretation of cardiovascular investigations that are performed in the unit. I have become adept at analysing 24-hour ambulatory blood pressure monitors (ABPM), cardiac rhythm event monitors and beat-to-beat blood pressure analysis. The beat-to-beat method of measuring blood pressure is a particularly useful piece of technology. In FASU this is performed using a Finometer (Finapres Medical Systems BV,

Arnhem, the Netherlands). This method utilises infrared photoplethysmography to detect changes in arterial diameter and volume of the patient's finger using a finger cuff. This information is combined with actual brachial artery sphygmomanometer readings to generate a validated estimated blood pressure for every heartbeat. This equipment allows us to assess real time beat-to-beat blood pressure responses to physiological and pharmacological challenges. The technology is used during active stand testing, carotid sinus massage and tilt table testing. These are essential tests used as part of a comprehensive cardiovascular falls risk assessment and are also transferrable to other areas of medicine. For example, the ability to interpret ABPMs and cardiac rhythm monitors and make therapeutic interventions plays a crucial role in the prevention of cardiovascular and cerebrovascular diseases.

2.13 ILR Insertion

During the clinical trial I was trained to implant ILRs in the cardiac catheterisation lab. ILRs are an important advancement in the area of falls to allow us to obtain symptom-rhythm correlation in unexplained fallers. This is a unique skill that I will be able to use in my future career as a consultant geriatrician. ILR implantation is also an essential part of a comprehensive stroke service where the ILR can be used to detect paroxysmal atrial fibrillation.

2.14 Vestibular Assessment and Treatment

The area of falls encompasses many interconnected topics. While cardiovascular health has been the primary focus of my clinical experience, disorders of the vestibular system and gait are equally important. For example, vertigo is a common presentation to any falls service, both as a distressing symptom and a direct cause of falls. I have learned how to adequately assess, diagnose and treat different causes of vertigo syndromes. In particular learning how to differentiate between peripheral and central vertigo and performing Hallpike and Epley manoeuvres has been very beneficial. I will use these skills going forward in my career in a variety of settings from the emergency department to rehabilitation wards to the ambulatory setting.

2.15 Gait analysis

I have gained experience in use and interpretation of different methodologies used to analyse gait including the Timed Up and Go Test and the GAITRite. GAITRite (CIR systems,

Havertown, PA, USA) is a sensored mat used to generate spatiotemporal gait variables. While this method is primarily used in the research setting, using the GAITRite has enabled me to gain a deeper understanding of disordered gait patterns, which has real world clinical utility.

2.2 Management and Organisational Skills

My role as the study doctor on the clinical trial led to development of my organisational and management skills.

I was responsible for the day-to-day management of the clinical component of the trial. I was responsible for contacting and scheduling all patient visits and the documentation of the results of all investigations in the case report forms. This meant I had to liaise carefully with FASU nursing and administration staff to ensure there was adequate space and staffing to safely perform the investigations. I was also responsible for bi-weekly phone calls to all participants and documenting the outcome of these calls. Any clinical problems or issues would be dealt with by myself in a timely manner.

An important part of this project was the collaboration with Medtronic™. Medtronic provided us with the investigational devices as well as technical and data support throughout the duration of the study. We had 2 weekly meetings with Medtronic's team of engineers and scientists to help us to process and analyse the data generated through the investigational device. This collaboration was a tremendous learning opportunity, not only providing exposure to other professionals working in health technology, but also in terms of my interpersonal skills. The group would meet via online teleconferencing technology and was comprised of professionals from various nationalities and disciplines. It was essential to develop a communication style that was clear and concise and could be easily understood by those who were not medically trained.

2.3 Research Skills

This research has led to the acquisition of a diverse array of research skills.
I have built on my knowledge of statistics and learned how to use the statistical software package STATA in order to generate, interpret and present relevant data.

Performing the systematic review and meta-analysis outlined in Chapter 4 below also meant becoming familiar with the systematic review software manager Covidence and the meta-analysis software package Review Manager (RevMan version 5.4, The Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen). These software packages allowed me to manage massive databases with thousands of references and ultimately to generate forest plots demonstrating the strength of various cardiac disorders with falls. The completion of the review was a great personal achievement and the findings were used to inform the World Falls Guidelines. Throughout the process I developed critical thinking skills and learned to evaluate the credibility and relevance of scientific publications.

The clinical trial presented in section 3 of this thesis represented a unique opportunity to work on a novel clinical investigation. This involved a hands-on role in recruitment and enrolment of participants and gaining informed consent. This trial involved implantation of a medical device and was regulated by the HPRA. We were supported by the clinical research facility in Trinity College Dublin and St James Hospital. Therefore, I learned about the day-to-day workings of clinical trial from a regulatory perspective and the responsibilities that this brings.

I have also learned how to effectively communicate the findings of my research for national and international conferences in the form of platform presentations and scientific posters. I presented an early version of the systematic review and meta-analysis at the EUGMNS international conference in London in September 2022. While my presentation of the clinical trial findings won the president's award for best presentation at the IGS annual scientific meeting In Galway in October 2023. Furthermore, I have learned how to write and publish academic papers to demonstrate the findings of the research. I have also prepared the manuscript detailing the outcomes of the clinical trial for publication.

Chapter 3: Falls: Epidemiology, Pathophysiology and Risk Factors

3.1 Epidemiology of Falls

Falls are one of the most common causes of injury, prolonged hospitalisation, increased dependency and residential care admission amongst older people[1-3]. Falls are very common with up to 35% of older adults living in the community falling each year, rising to up to 50% of those living in nursing homes[4,5]. Falls are also a significant cause of injury in older adults with 40-60% of falls leading to some form of injury, up to 10% of falls lead to significant injuries including fractures and head injuries with 1% leading to hip fracture[4]. Indeed, injurious falls are also the most common cause of accidental death in older adults[6]. Falls are a common reason for older people to seek urgent medical care. The risk of admission to hospital is higher for older adults who suffered a previous fall, those with dementia and those with frailty[7].

There is also a significant psychological burden associated with falls. "Fear of falling" is well described in the literature and has been shown to be associated with social isolation, worse quality of life and significant cognitive and functional decline[8-10].

Falls have a significant economic impact. U.K. data estimated an annual cost of falls of over £1.2 billion per year[11]. While in the US, falls involving older people was estimated to be $50 billion in 2015[12], a figure that had more than doubled since 2006[13]. In Ireland there are currently 768,900 people aged 65 or older[14]. This number is expected to rise to 1,007,000 by 2031 and to 1,597,000 by 2051[15]. This is a global issue; the World Health Organisation (WHO) estimates that between 2015 and 2050, the number of people aged over 60 will almost double. Those over 60 will go from representing 12% of the world's population to approximately 22%[16]. Increasing age and frailty are risk factors for falls, therefore the incidence of falls is predicted to rise significantly in the coming years posing serious challenges at the individual level, for health systems and for the economy[17-19].

3.2 Definition of Falls

The WHO defines a fall as "an event which results in a person coming to rest inadvertently on the ground or floor or other lower level. Falls, trips and slips can occur on one level or from a height"[20]. It is worth drawing a distinction between a "fall" and an "unexplained fall". The World Falls Guidelines (WFG) deem a fall to be unexplained when "no apparent cause

has been found for a fall on performing a multifactorial falls risk assessment and it cannot be explained by a failure to adapt to an environmental hazard or by any other gait or balance abnormality"[21]. This research is particularly interested in these unexplained events due to the association of these events with underlying cardiovascular causes[22]. Indeed, it is suggested by the European Society of Cardiology (ESC) syncope guidelines and the WFG that unexplained falls be investigated in a similar manner to unexplained syncope[21,23].

3.3 Pathogenesis and Risk Factors for Falls.

It is probably impossible to define a "pathogenesis" for falls. Falls are better conceptualised by the individual risk factors that may predispose someone to falling. The aetiology of falls should be considered as being multifactorial in nature. The risk of falls tends to increase with both age and the number of other risk factors present[24,25]. These risk factors are traditionally categorised as intrinsic and extrinsic.

3.4 Intrinsic Risk Factors

Intrinsic risk factors relate to issues involving the individual themselves. They reflect a person's biophysiological status as well as their individual health history. These include non-modifiable characteristics such as age and gender, but also include muscle strength, balance, vision and gait. There a number of disease states, both acute and chronic, that can impair an individual's biophysiological status and are considered to be intrinsic risk factors for falls[26]. These include; stroke, diabetes, congestive heart failure, Parkinson's disease, dementia and delirium[26,27].

Older age is directly associated with increased rates and severity of falls. This is due to both features of normal physiological aging and also pathological processes that impair almost all physiological systems including visual, cardiovascular, vestibular, proprioceptive and cognition[26,28]. Age is the strongest predictor of overall decline in functional capacity and is closely related to frailty[29]. With increasing age and frailty status comes increased rates of falls[30]. Compared to adults aged 65-74, those aged over 85 have a 4 times higher risk of falling[26]. Women are also more likely to fall than men, this has been consistently reported across the literature although it would appear that men may be more likely to die following fall events[26,31-33].

Sarcopenia is also an important condition increasingly prevalent in older adults, that is characterised by the loss skeletal muscle mass and function[34]. It Is commonly associated with falls as well as functional decline, frailty and mortality[7,35].

It has long been established that dementia is associated with falls[36,37]. One study comparing people with a dementia diagnosis with controls showed an 8 times higher fall rate in patients with dementia[38] More recently mild cognitive impairment has also been shown to increase falls risk[28] and depression also appears to increase falls[39].

Intrinsic risk factors also includes substances that a person may ingest that predispose them to falls such as medication and alcohol[40]. Medications are a major iatrogenic cause of falls. There a number of falls risk increasing drugs (FRIDS) that have been consistently implicated in the literature. These include loop diuretics, opioids and psychotropic medications such as antiepileptics and psychotropic medications (including antidepressants and benzodiazepines)[41-43].

3.5 Extrinsic Risk Factors

Extrinsic risk factors for falls relate to a person's external environment. Environmental hazards in the home include loose rugs and carpets, poor lighting, inappropriately placed cords and cables, pets and excess clutter[44,45]. These hazards are incredibly common with up to up to 80% of homes having at least 1 environmental hazard while up to 40% of homes have upwards of 5 potential hazards[46]. Environmental hazards become a more of a significant risk factor for falls in adults with intrinsic risk factors.

In addition to the causes of syncope outlined below, cardiometabolic diseases like hypertension, type 2 diabetes and ischaemic heart disease can lead to damage to the vasculature of neural pathways governing gait and balance, thereby predisposing to falls[47].The reality is that most falls are multifactorial and the risk factors associated with falls may have a synergistic effect on increasing falls risk. This highlights the importance of multifactorial falls risk assessments as a means to try to modify individual falls risks.

3.6 The Overlap Between Falls and Syncope

The ESC definition of syncope describes a "transient loss of consciousness (TLOC) due to cerebral hypoperfusion, characterised, by a rapid onset, short duration, and spontaneous

complete recovery". TLOC is characterised by "a real or apparent loss of consciousness with loss of awareness, characterised by amnesia for the period of unconsciousness, abnormal motor control, loss of responsiveness, and a short duration"[23].Syncope is triggered in individuals when there is a decrease in systemic blood pressure that is significant enough to lead to a reduction in global cerebral blood flow. There are 3 subtypes of syncope that are classified by the mechanism that ultimately leads to the final common pathway of a decrease in global cerebral perfusion.

1. Reflex (neutrally mediated) syncope includes vasovagal syncope (cardioinhibitory, vasodepressor, mixed), situational syncope and carotid sinus syndrome.
2. Syncope due to orthostatic hypotension. This may be drug induced, due to volume depletion or due to autonomic failure.
3. Cardiac syncope is usually due an arrhythmia that results in an acute drop in cardiac output. These can be a bradyarrhythmia caused by sinus node disease or atrioventricular conduction deficits or tachycardia such as ventricular tachycardia. Less common causes of cardiac syncope include pulmonary embolism, valvular heart disease and atrial myxoma.

All three subtypes have been associated with falls[22,48-50]. In the 1990's there was increased interest in understanding the overlap between falls and syncope[51,52]. However, it is now generally accepted that there is a significant overlap and that making a clear distinction between the conditions is exceedingly difficult[53]. Mechanisms such as orthostatic hypotension (OH), tachyarrhythmia and bradyarrhythmia may cause falls through frank syncope or alternatively, transient disruption of gait and balance through transient cerebral hypoperfusion without frank syncope. Indeed, World falls guidelines note that the work up for unexplained falls should be the same as that for unexplained syncope[21].

From a diagnostic perspective, it can be difficult to distinguish between the two based on history alone. This is partly due to the amnesia that is often associated with syncope and also due to the unwitnessed nature of many falls affecting older people[54]. Of note, syncopal events have a significant injury burden with 33% of patients with vasovagal syncope (VVS) reporting injuries, 4-13.8% of these being classified as severe (fractures, burns or joint damage)[48,55].

Chapter 4: Cardiovascular Risk Factors for Falls

The link between cardiovascular disorders and falls has long been established if not fully understood. We have performed and published a systematic review and meta-analysis examining this relationship. This is included in its entirety below[22]. The findings of this review were used to help synthesise the recently published World Falls Guidelines[21].

Please note: As this element of the thesis has already been published, please refer to the online published paper to access the supplementary materials and view the eFigures eTables referenced throughout this chapter. These can be accessed here: https://academic.oup.com/biomedgerontology/article/79/2/glad221/7279335

Cardiovascular Disorders and Falls Among Older Adults: A Systematic Review and Meta-Analysis

4.1 Introduction

Falls are a growing global concern, and the WHO estimate that falls lead to 37 million hospitalisations each year[56]. Falls incidence rises significantly with increased age and frailty [30]. Moreover, falls are the commonest cause of injury in older adults frequently resulting in hospitalisation, accelerated functional decline, admission to residential care [1] and increased mortality [57,58]. Thirty-five percent of community-dwelling older adults fall at least once a year; rising to 50% among those in long-term care [5].

Over 3 million older people in the United States (US) attend emergency departments (EDs) following a fall each year [59], and falls represent 10% of all ED presentations in those over the age of 65 [60,61]. Falls can cause serious injuries, with 10-20% of falls leading to fractures, dislocation, head injury, and death [5]. Falls can also have profound psychological consequences, such as fear of falling, which is associated with poorer quality of life, social isolation, cognitive and physical decline, and negative mental health outcomes [8]. As demographic ageing rises so too will the incidence and cost of falls with direct implications for healthcare provision [17-19,62,63].

In 2006, the estimated medical cost of falls for people aged ≥ 65 in the US was $20 billion [13]. By 2015 this rose to $50 billion [12]. The mean cost of an individual fall resulting in hospitalization has been estimated to be $14,000 [64], while the length of stay is on average 8

days longer if a patient has an in-hospital fall resulting in further costs [65]. The overall burden of falls in both healthcare and community settings can be reduced by targeting known risk factors, including cardiovascular risk factors [66,67].

Several cardiovascular disorders are reported to be associated with falls in older adults. These include orthostatic hypotension, hypertension, bradyarrhythmia's (e.g., sick sinus syndrome, and atrioventricular block), tachyarrhythmias (e.g., atrial tachycardia including atrial fibrillation, and ventricular tachycardia), carotid sinus hypersensitivity (CSH), and vasovagal syncope[68,69].

Given projected changing global demographics and rising frequency of cardiovascular disease, the purpose of this review was to systematically explore the association between falls and common cardiovascular disorders in adults aged ≥ 50 years.

4.2 Methods

This systematic review and meta-analysis were designed and conducted in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) standards [70,71]. A comprehensive review protocol was developed, registered, and adhered to (PROSPERO registration: CRD42021272245).

4.21 Data sources and searches

Systematic searches were conducted on MEDLINE (Ovid) and EMBASE encompassing all available literature published prior to 31/12/2022 and supplemented with manual reference searches of all included articles (See online Appendix 1 https://academic.oup.com/biomedgerontology/article/79/2/glad221/7279335).

4.22 Study selection

Eligible studies addressed persons aged 50 years and older, were published as primary research papers in peer reviewed journals, measured falls as an outcome, included diagnosis or assessment of cardiovascular disorders and the association between cardiovascular disorders and falls or provided comparison of the prevalence of falls among individuals with and without specific cardiovascular disorders. Studies were ineligible if the sample comprised a specific disease, or condition defined population (e.g., Parkinson's disease, dementia); a full text was not available in the English language; the design was a case

report, or conference abstract. Interventional studies additionally included efficacy of cardiovascular intervention on falls outcome but did not include studies examining falls in treated hypertension.

Title and abstract, and full text screening were performed by two independent reviewers (RB and PD) using Covidence systematic review management software. During full text screening the reason for exclusion was recorded (See Online Appendix 2 https://academic.oup.com/biomedgerontology/article/79/2/glad221/7279335). Any conflicts were resolved by a third reviewer (SP). Studies of the same cohort were included only once, using the study with most information about the cohort. If two or more studies utilised the same dataset only the first published study was included to prevent duplication.

The WHO definition for falls was used to operationally define falls within the review: "*a fall is an event which results in a person coming to rest inadvertently on the ground or floor or other lower level*"[20]. Included prefixes to the word "*fall*" that appeared in the literature were also utilised including recurrent, accidental, non-accidental, and injurious.

4.23 Data Extraction and quality assessment

Data extraction was performed by two reviewers independently (PD and SP). Conflicts were resolved with a third reviewer (RB). Extracted data is available in Supplementary Tables (eTables 1 to 15).

Quality assessment was performed by two reviewers (SP and RB) (see online Appendix 3 https://academic.oup.com/biomedgerontology/article/79/2/glad221/7279335). Conflicts were resolved with a third reviewer (PD). Observational studies were assessed using a modified version of the Newcastle-Ottawa scale (NOS) [72] and were classified according to the following scoring system: 0-3 = low quality, 4-6 = intermediate quality, 7-10 high quality. Interventional studies were assessed using the Revised Cochrane risk of bias tool for randomised trials (RoB2) [73], and were classified as *"low risk of bias", "some concerns" or "high risk of bias".*

4.24 Data synthesis and analysis

A systematic narrative analysis of all outcomes was performed with findings presented in both textual and tabular formats. Further, a random-effects meta-analyses of studies with

unadjusted ORs (reported or calculated) were performed using RevMan. A 12-month reporting interval was chosen for main and stratified analyses due to its ubiquity in reported studies and likelihood that any cardiovascular disorders causing falls would likely do so within a year's time period of follow-up (supplementary eFigures 1-8). Stratified analyses by age (50-64, 65-79, and ≥ 80 years), setting (community, hospital, and residential care), and assessment method were performed for each disorder (Supplementary eFigures 9-26). Secondary analyses were also performed for alternative reporting intervals where relevant e.g., one month, six months, 24 months (Supplementary eFigures 27-33). Meta-analyses of unadjusted ORs were favoured over adjusted ORs due to the heterogenous nature of the adjusted analyses [74,75]. Non-meta-analysis forest plots for adjusted ORs are available as Supplementary eFigures 34-39.

4.3 Results

Systematic searches yielded a combined total of 19,891 results of which 184 studies were included: 181 observational, and 3 interventional (Figure 2). 73 studies were included in meta-analyses based on availability of unadjusted ORs.

Descriptive details of the 184 included studies are displayed in Supplementary eTables 1A and 1B.

Overall, there were consistent associations between cardiovascular disorders and falls. Certain subgroups of cardiovascular disorders were more consistently associated with falls than others such as stroke, coronary artery disease, valvular heart disease, arterial stiffness, arrhythmia, OH, and CSH. There was a wide variation in sampling frames, study designs, reporting interventions, assessment methods, and quality assessment scores. CSH was the only disorder for which there were eligible interventional studies.

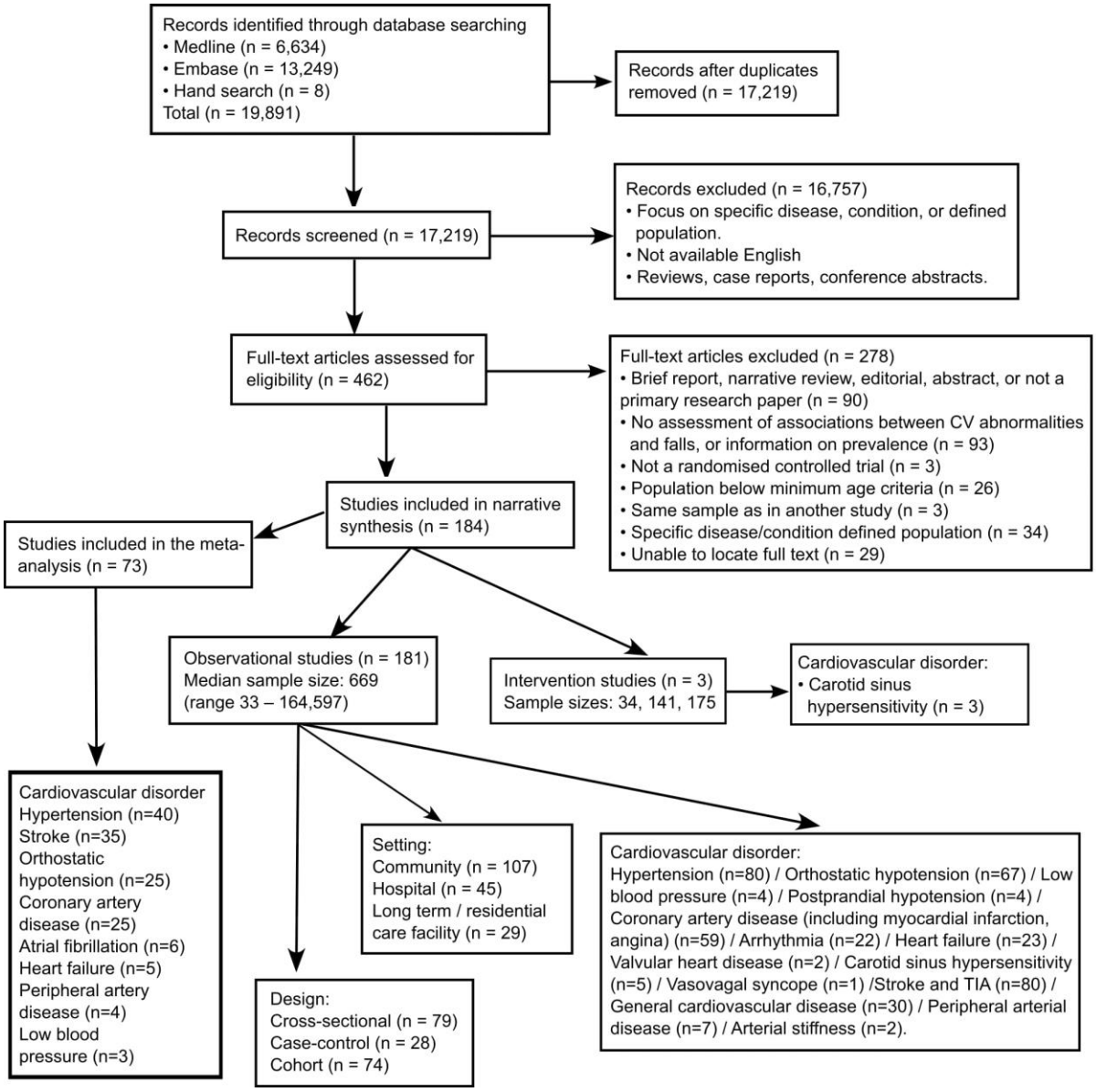


Figure 2. PRISMA flow diagram of systematic review and meta-analysis process and studies description

For the purposes of narrative presentation, cardiovascular disorders have been subdivided into 4 distinct categories (Supplementary eTable 1C):

1. Blood pressure related disorders
2. Cardiac (structural and arrhythmia)
3. Reflex syncope
4. Other

4.31 Blood pressure related disorders.

Overview: Conditions directly related to blood pressure, both hypertension and hypotension demonstrate a somewhat inconsistent association with falls. The association between falls and OH is more consistent when contemporary methods of measurement for OH are applied.

4.31.1 Hypertension

Eighty *observational studies* investigated the association between hypertension and falls. Sixty studies did not report an association [32,76-134] QA 7.0 (range 4-10). Twenty reported a significant association: 17 positive [135-151]; three negative [152-154]. Mean quality assessment score (QA) was 6.9 (range 5-8) for positive and 6.3 (range 5-9) for negative studies (eTable 2).

Of note the 3 largest studies (n>14, 000) demonstrated an inconsistent association, with intermediate to high QA scores. The largest of these studies (n=43,367) demonstrated a positive multivariate association with falls and had a high QA score. The next largest (n=17,712) demonstrated no association and had a high QA score. Finally, the third largest (n=14,881) demonstrated a univariate association with an intermediate QA score.

4.31.2 Orthostatic hypotension

Sixty-seven *observational studies* investigated OH and falls (eTable 3A). OH was assessed using beat-to-beat (BTB) measurement in 15 studies [91,100,112,155-166], oscillometric sphygmomanometer in 22 [87,90,103,106,115,116,119,128,167-180], and an auscultatory sphygmomanometer in 11 studies [123,147,153,181-188]. Thirteen studies utilised a sphygmomanometer but did not specify the type [31,81,88,105,166,189-196]. The measurement instrument was unspecified in 8 studies [77,84,111,129,145,196-198]. One study [166] measured OH with both BTB and a sphygmomanometer.

Results by measurement technique:

Of 15 studies utilising BTB, 12 reported a positive association , QA 7.4 (range 5-9) [112,155-161,163-166]; three reported no association QA 7.7 (range 7-8) [91,100,162].

Of 22 studies using an oscillometric sphygmomanometer, 3 studies reported a positive association, QA 10, 7, 7 [170,174,179]. Nineteen studies reported no association, QA 7.1 (range 4-9) [87,90,103,106,115,116,119,128,167-169,171-173,175-178,180].

Of 11 studies using an auscultatory sphygmomanometer, 3 studies reported a positive association, QA 9, 6, 7[182,184,186]. The remaining 9 studies reported no association, QA 7.2 (range 5-9) [123,147,153,181,183,185-188]. Aydin et al. [186] was counted in two of these analyses as the authors reported OH both in supine to tilted, and supine to standing positions.

Of 13 studies which utilised sphygmomanometers, but did not specify which type, 6 reported a positive association, QA 6.8 (range 5-9)[31,81,189,193,194,196]. Seven reported no association, QA 7.5 (range 4-9) [88,105,166,190-192,195].

Seven studies did not provide any details on the measurement instrument or assessment position. Five reported no association, QA 7.6 (range 7-10) [77,84,111,197,198]. Two reported a significant positive association, QA 7, 8 [129,145].

Results by OH measurement instrument and assessment position:

eTable 3B classifies studies by OH measurement instrument and assessment position. Overall, 80.0% (12/15) of studies using BTB showed a positive association between OH and falls, compared to 25.5% (12/47) of studies using any type of sphygmomanometer. In relation to the assessment position, 35.6% (16/45) of studies using supine to standing showed a positive association between OH and falls, compared to 75.0% (6/8) using supine to tilt (on a tilt bed) and 20% (1/5) using sitting to standing.

When OH was measured using the BTB method, the majority showed an association between OH and falls. However, no consistent association was noted when other OH measurement techniques were used. Of note postural change from supine to standing demonstrated a more consistent association than sitting to standing.

4.31.3 Low blood pressure

Four *observational studies* investigated low blood pressure and falls. Three studies reported no significant association each with a QA score of 8 [114,199,200]. One reported a positive association QA 5, [201] (eTable 4). There was an inconsistent association between low blood pressure and falls in the limited number of studies available.

1.4 Postprandial hypotension

Four *observational studies* examined postprandial hypotension and falls. Two identified a positive association QA 5, 8 [202,203]. Two studies did not report an association, QA 6, 8 [204,205] (eTable 5).

There were a limited number of studies, and each had a small sample size. The literature remains inconclusive.

4.32 Cardiac (structural and arrhythmia)

Cardiac disorders included coronary artery disease, arrhythmia, heart failure and valvular heart disease. Two studies that evaluated valvular heart disease found a positive association with falls.

4.32.1 Coronary artery disease (CAD)

Sixty *observational studies* investigated CAD and falls. Forty-two reported no association, QA 7.3 (range 4-10) [77-79,82,84,85,88,89,97,102,105,106,111,112,115-117,119-121,124,125,129,131-133,137,143,150-153,170,173,197,206-209]. Eighteen reported a significant association, 17 positive, QA 6.8 (range 4-8) [94,103,107,108,127,138,148,210-218], 1 negative, QA 6 [219] (eTable 6).

A positive association was found in the 3 largest studies (with n>100,000 participants and high QA scores), otherwise no consistent association was noted.

4.32.2 Heart failure

Twenty-three *observational studies* examined heart failure and falls. Fifteen studies showed no association, QA 6.9 (range 4-10) [78,82,105,106,111,112,120,125,127,129,132,173,211,214,219]. Eight identified a positive association, QA 6.8 (range 4-8) [85,92,94,96,104,144,212,220] (eTable 7).

The majority of studies showed no association with falls; of note, the four largest studies (n>10,000 participants) showed inconsistent associations (2 positive, with high QA, and 2 negative, with intermediate to high QA).

4.32.3 Arrhythmia

Twenty-two *observational studies* investigated cardiac arrhythmias and falls: 13 regarding atrial fibrillation [82,93,105,106,111,112,120,129,217,221-224], 1 ventricular arrhythmia [225], 1

atrioventricular block [120], 1 sinus bradycardia [120], and 6 unclassified arrhythmias [78,85,125,132,226,227].

Of the 13 studies which examined atrial fibrillation, 8 reported no association, QA 7.6 (range 6-10) [82,105,106,111,112,120,129,224], 5 reported a positive association, QA 6.4 (range 5-8) [93,217,221-223]. No association was evident for ventricular arrhythmia, QA 8 [225] atrioventricular block or sinus bradycardia, QA 10 [120].

Of 6 studies investigating arrhythmias in general, 3 reported positive associations, QA 8, 4, 6 [78,85,226]; and 3 reported no association, QA 7, 4, 6 [125,132,227] (eTable 8).

The majority of studies showed no association with falls; however, a positive association was found in the 2 largest studies (n>25,000 participants, and intermediate to high quality).

2.4 Valvular heart disease

Two *observational studies* examined valvular heart disease. One study reported a positive association between mitral, tricuspid, and pulmonary valve regurgitation and falls, QA 9 [228]. A second study reported a positive association between "heart murmurs" and falls, QA 8 [78] (eTable 9).

4.33 Reflex Syncope

Reflex (or neurally mediated) syncope includes CSH and VVS. The pathophysiology for these conditions is similar, with both conditions characterised by hypotension and/or bradyarrhythmia. There were limited observational studies for both conditions. CSH showed an inconsistent association with falls while VVS showed no association in a single study.

In the interventional studies for CSH, it was noted that implantation of a device, be it a pacemaker (PPM) switched on or off, or an implantable loop recorder (ILR), and a corresponding decrease in falls rates.

4.33.1 Carotid Sinus Hypersensitivity

Five *observational studies* investigated CSH and falls. Three reported no association, QA 6, 7, 8 [205,229,230]. Two reported a positive association, QA 6, 7 [155,231] (eTable 10).

Three *interventional studies* examined pacemaker intervention for falls reduction. In the first study, falls were reduced in paced patients compared to controls over a 12-month

follow up [232]. In the second, cross-over interventional design (PPM on, PPM off), there was no difference in fall rates [233]. A third study compared fall rates in patients with pacemakers against controls (ILR). The rate of falls was significantly reduced in both groups compared to the run-in period [234]. The RoB2 quality assessment for each of these studies concluded "some concerns" of bias (eTable 1B). However, the studies were underpowered and therefore deemed of low quality.

4.33.2 Vasovagal syncope

Only one study was included which reported no association with falls, QA 6 [229] (eTable 11).

4.34 Other

This grouping of other vascular conditions includes stroke/TIA, general cardiovascular disease, peripheral vascular disease, and arterial stiffness. Stroke was associated with falls in half the included studies while each of the two studies that evaluated arterial stiffness demonstrated a positive association. 'General cardiovascular disease' was a term used in 30 studies when specific conditions were not clarified, which demonstrated an inconsistent association with falls. Peripheral vascular disease was not associated with falls.

4.34.1 Stroke/Transient Ischemic Attack (TIA)

Eighty-two *observational studies* investigated stroke/transient ischaemic attack and falls. Forty-four reported a significant association: 42 positive, QA 7.0 (range 4-10) [31,32,77,82,88,99,102,104,107,109,116,117,120-122,126,131,133,137,145,148,197,198,201,206,210,213-215,219,226,235-245]; 2 negative, QA 7, 7 [246,247]. Thirty-seven studies reported no association, QA 7.2 (range 4-10) [76,78-80,83,84,86,96,97,101,105,106,110,111,113,115,124,125,127,129,132,134,139,150,151,156,170,173,207-209,216,248-252] (eTable 12).

Half of the studies demonstrated a positive association with falls. Of note, the 4 largest studies (n>100,000 participants and QA scores intermediate to high) showed a positive association.

4.34.2 General cardiovascular disease

Thirty *observational studies* investigated general cardiovascular disease (unspecified) and falls. Seventeen studies reported no association, QA 7.2 (range 5-

10)[80,83,98,99,109,126,130,133,153,156,169,170,199,252-255]. Thirteen reported a positive association, QA 6.9 (range 4-8) [32,92,110,113,118,138,146,206,215,220,249,256,257] (eTable 13). The majority of studies reported no association with falls. However due to limited and inconsistent operational definitions for the term 'general cardiovascular disorders' throughout the literature, it is difficult to provide further elucidation upon these specific results.

4.34.3 Peripheral arterial disease

Seven *observational studies* examined peripheral arterial disease and falls. Six studies reported no association, QA 7.3 (range 6-8) [106,116,129,139,216,252], whereas one reported a negative association, QA 10 [197] (eTable 14).

4.34.4 Arterial stiffness

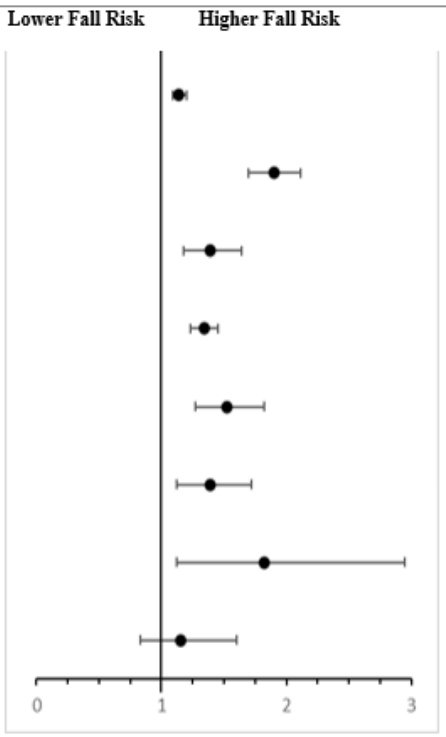
Two *observational studies* investigating arterial stiffness and falls reported a positive association, QA 9, 8 [116,119] (eTable 15).

Both are high quality studies. The measurement techniques utilised were carotid–femoral pulse wave velocity, and cardio-ankle vascular index respectively.

4.4 Meta-Analysis of unadjusted ORs

Eight cardiovascular disorders were eligible for inclusion in meta-analysis of unadjusted odds ratios for falls. Results are displayed in Table 1, and Supplementary eFigures 1-8).

CVD	N of studies	Studies included	Pooled unadjusted OR (95% CI)
HTN	40	32,76-78,86,89,94,96-99,102,103,106,108,110,112,113,116,119,120,122,123,128,131,133,134,137-139,141,143,146-150,169	1.14 (1.09-1.20)
Stroke	35	76,77,79,86,88,96,97,99,102,106,110,113,115,116,120,122,131,134,137,139,148,150,170,173,209,210,215,216,241,244,245,250,343	1.90 (1.70-2.11)
OH	25	77,100,103,106,112,116,119,147,159,161,163,166,167,169,170,173,179,183,184,186,188,192,196,343	1.39 (1.18- 1.64)
CAD	25	77,88,89,94,97,102,103,106,108,112,116,119,120,131,137,138,143,148,150,170,173,209,210,215	1.34 (1.23-1.45)
AF	6	106,112,120,221,222,227	1.52 (1.27-1.82)
HF	5	94,96,106,112,173	1.39 (1.12- 1.72)
PAD	4	106,116,139,216	1.82 (1.12-2.95)
Low BP	3	114,199,200	1.15 (0.83- 1.60)



Note. CVD: Cardiovascular Disorder. HTN: Hypertension. OH: Orthostatic Hypotension. CAD: Coronary Artery Disease. AF: Atrial Fibrillation. HF: Heart Failure. PHD: Peripheral Arterial Disease. BP: Blood Pressure

Table 1. Meta-analysis of unadjusted OR for falls among older adults with cardiovascular disorders within a 12-month period.

4.41 Stratified analyses

Stratified analysis by the age category, study setting, assessment method, and time intervals were conducted when sufficient data was available. These produced no significant differences in the association between any cardiovascular disorder and falls (Supplementary eFigures 9-39). There was a significant difference in stratified analysis by the assessment method for OH, contrasting assessment by sphygmomanometer (OR: 1.26 (95% CI: 1.03-1.53) versus beat-to-beat (OR: 1.96, 95% CI 1.40-2.73) (p=<0.02) (Figure 3).

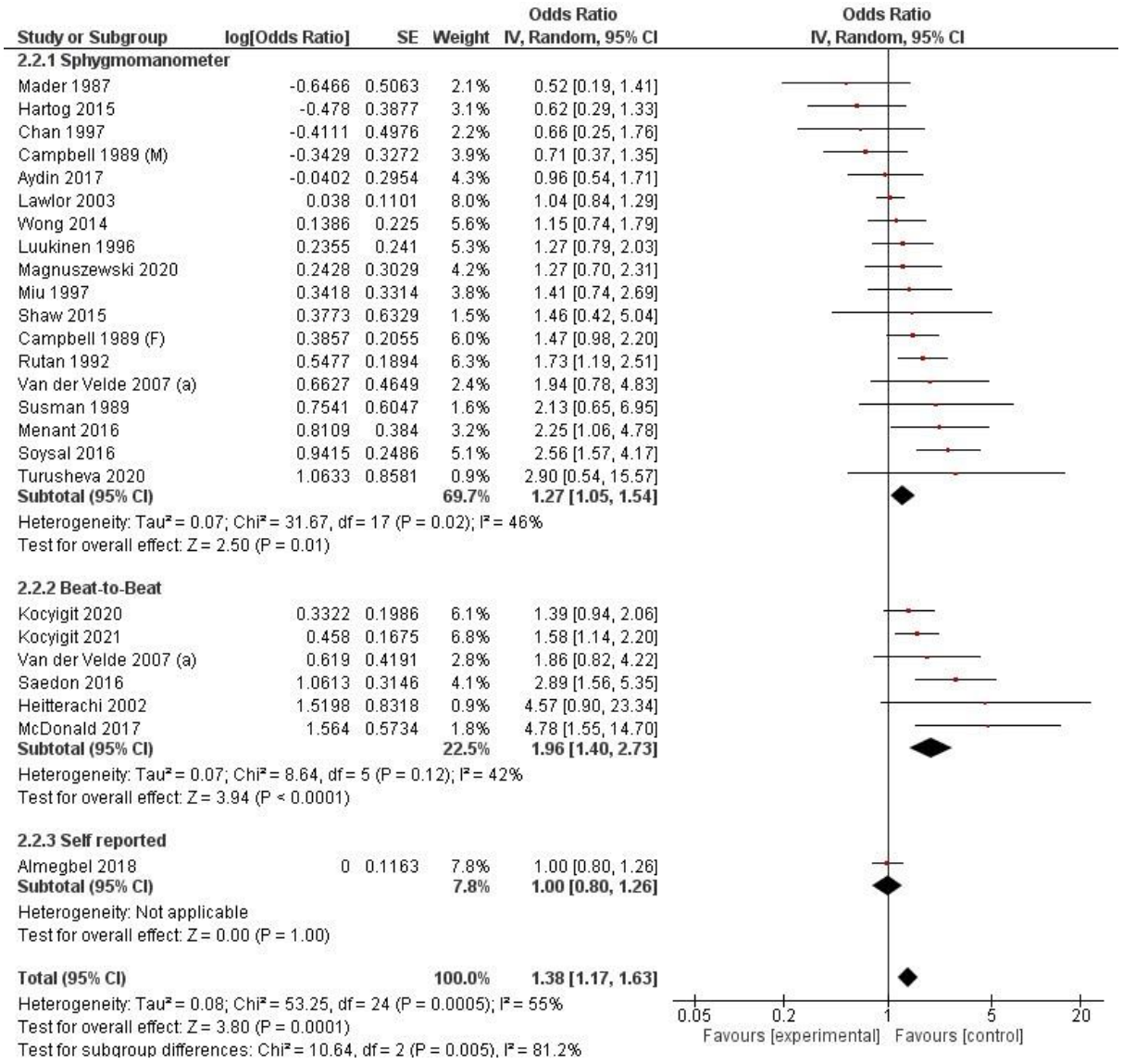


Figure 3. The association between orthostatic hypotension and falls among adults aged 50+ stratified by assessment method.

4.5 Discussion

There are several key findings from this systematic review and meta-analysis with potential clinical implications: This review clearly demonstrates an association between falls and several cardiovascular disorders, including stroke, peripheral arterial disease, AF, OH, heart failure, CAD and hypertension.

To the authors' knowledge there has been one previous systematic review examining the association between cardiovascular disorders and falls [68]. This present review updates the literature in this area and builds on the prior review by increasing the scope of

cardiovascular disorders examined, performing meta-analysis of unadjusted ORs, and including interventional trials, resulting in a more expansive review increasing from 86 studies to 184. This review was also used to inform the newly published World Guidelines for falls in older adults [21].

A recent consensus statement from the American Heart Association [258], emphasised that the association between cardiovascular risk factors and falls are poorly understood. The pathophysiological mechanisms that underpin the predisposition of older adults with cardiovascular disease to falls are complex. Mechanisms such as OH, tachyarrhythmia, and bradyarrhythmia may cause falls through frank syncope or alternatively, transient disruption of gait and balance through transient cerebral hypoperfusion without frank syncope. If syncope is unwitnessed, as is the case in many older people [259,260], and the person has amnesia for loss of consciousness [54], the clinical interpretation for syncope may be "a fall" [260,261]. Gait and balance disorders [262] are common in fallers – present in over 60% of adults aged > 80 years [263]. The overlap between gait and balance problems and conditions that may lead to transient cerebral hypoperfusion (OH in particular), have been implicated in falls in older adults [50,264].

Other cardiovascular disorders such as hypertension, ischaemic heart disease, and heart failure may share pathophysiological substrates, such as vascular damage to neural pathways governing gait and balance, thereby predisposing to falls [47]. These disorders are often accompanied by medications that may increase the likelihood of falls [265]. The possible associations between medications and falls, however, was beyond the scope of this review.

Hypertension is common with advanced age: 63% of adults aged > 60 years in the US are hypertensive [266]. The association between hypertension and falls is not consistent in the observational literature. In the meta-analysis there was an overall significant positive association between hypertension and falls, although only persisting within the stratified analysis for self-reported hypertension, community dwelling adults and adults under 80 years (eFigure 16). It is possible that the association between hypertension and falls was due to the hypotensive effects of hypertension itself or medications used to treat hypertension [267,268] or the results of hypertensive heart disease with left ventricular hypertrophy, reduced diastolic ventricular filling and an associated decrease in cardiac output during preload reduction.

Regarding OH, two important findings have emerged from this review. Firstly, the association between fallers and OH varied and was dependent on the method of measurement and the position of the patient during assessment. Studies using a BTB measurement demonstrated a stronger association than traditional sphygmomanometer-based methods. In meta-analysis of unadjusted ORs there was also a significant difference in stratified analysis by assessment method (BTB: OR=1.96 (95% CI: 1.4-2.73), Sphygmomanometer: OR=1.27 (95% CI: 1.05-1.54). p=0.02). BTB blood pressure measurement allows clinicians to accurately assess blood pressure changes within the first minute of standing therefore capturing early transient changes. Recent studies have identified "OH 40" (the failure of blood pressure to return to baseline within 40 seconds of standing) to be associated with greater falls risk, including a higher risk of injurious falls [157,158]. The definition of OH applied using rapid changes in systolic blood pressure (sBP) during the first minute compared with changes during the first 3 minutes may have influenced this outcome. This new technology is more complex to use and more time consuming than traditional technology (sphygmomanometer) and is not presently widely available. BTB measurement is adept at measuring rapid and transient changes in blood pressure behaviour and giving more granular information on different orthostatic haemodynamic patterns [269].

Meta-analysis demonstrates that studies using postural change from supine to standing show a significant association between OH and falls OR:1.3 (95% CI:1.06-1.6), but not sitting to standing OR:1.36 (95% CI:0.89-2.09), which suggest that initial supine measurements should be the preferred measurement choice [175,270].

The only accurate way to confirm a cardiovascular risk factor is to show that interventions that remove that risk, reduce the incidence of falls. In this context, one would think that pacemakers could eliminate the bradycardia associated with CSH and reflex syncope, but 3 intervention studies [232-234] showed that any implanted device reduced falls, even if they didn't eliminate bradycardic episodes. Therefore, there may be additional neuropsychological contributions to these types of falls, consistent with previous literature on reflex syncope [271,272].

Given the association between cardiovascular disorders and falls we concur with both the European Society of Cardiology Syncope Guidelines and the World Guidelines for falls in

older adults [21,23], that the initial falls assessment should include a review of cardiovascular history, cardiac auscultation, surface electrocardiogram, and lying and standing blood pressure measurement. Additionally, BTB measurement should be employed where possible.

This systematic review has several strengths and important findings. We have applied rigorous eligibility criteria, included interventional trials, and collated results to offer a comprehensive narrative synthesis generating novel findings (notably for OH, and CSH). We have also applied a random-effect meta-analysis of unadjusted ORs to conditions where appropriate comparable data were available. This has allowed for a quantitative component to be included in this review. These findings have potentially useful clinical implications for falls risk, suggest directions for future research, and provide a systematic evidence base for the recent World Guidelines for falls[21].

The majority of the studies included in the review are observational and as such it is not possible to draw definitive causal inferences from these associations. Most of the studies assessed falls retrospectively by self-report and clinical notes. We recommend well-designed prospective studies which account for complexity of vulnerable cohorts (i.e., co-occurrence of cardiovascular risk factors such as hypertension, OH and CSH) and heterogeneity of older fallers (co-occurrence of non-cardiovascular falls risk factors) in order to provide more definitive clinical guidance.

We did not include cardiovascular medications as this topic has already been dealt with comprehensively [41,267,273]. In brief, whereas loop diuretics, as treatment for heart failure, are associated with falls, other cardiovascular medications demonstrate an inconsistent association [274]. A recent meta-analysis of clinical trials showed that intensive lowering of blood pressure over the long-term with antihypertensive medications was not associated with an increased risk of orthostatic hypotension [268], although short-term effects or association to falls were not examined.

Other cardiovascular disorders such as hypertrophic cardiomyopathy, micturition syncope, and defecation syncope have been associated with falls in case reports and experimental literature but were not captured by the search strategy [127,275,276]. Likewise, the combination

of factors such as OH, medications, and post prandial hypotension can lead to falls in clinical practice in a given individual but this was not captured in our search.

A further challenge encountered in the review process was the inconsistency in operational definitions and nomenclature of key phrases used in studies, making it difficult for clear clinical inferences. For example, the term “cardiovascular disease” was used in 30 studies without defining, or providing distinctions to, exactly what cardiovascular disorders were being referred to and analysed [118,215,249]. Coronary artery disease is a similarly imprecise term used in 19 studies, the majority of which did not show an association with falls. It is difficult to make any clinical recommendations in these instances given the lack of specificity of these terms. Similarly, there was a lack of clinical time stamping in conditions such as atrial fibrillation or congestive heart failure [85,92,93]. Our interpretation of the methodologies is that these refer to chronic as opposed to acute conditions.

Also, the definition of “falls” was inconsistent, with few studies making a distinction between types of falls (i.e., accidental and non-accidental falls, or explained and un-explained falls). We included all of these subcategories in our analysis. These definitions also do not include loss of consciousness. Given the overlap between unwitnessed falls and syncope [52,53], clearer definitions around loss of consciousness and witnessed events will greatly enhance the literature.

4.6 Conclusion

There is a positive association between most common cardiovascular disorders and falls in adults aged over 50 years. These findings provide physicians potential targets for assessment and intervention for falls risk in clinical practice. They also highlight the need to further deepen our understanding of this complex association between cardiovascular disorders and falls in older adults with well-constructed interventional studies.

Chapter 5: Novel Approaches

This chapter represents a summary of commonly used technologies and considers how such technology can help to measure cardiovascular and human movement patterns in older fallers.

5.1 Introduction

Technological advancement is creating opportunities to improve patient outcomes and improve quality of life. This can be seen in devices like continuous glucose monitors which are revolutionising diabetes care, allowing for more accurate dosing of insulin and minimising the need for painful finger-prick blood glucose measurement[277]. The wellness and personalised-health industry has also leveraged new technology as evidenced by the explosion of the wearable device industry. Billions of dollars have been invested by large multinational corporations in the development of "smart" watches, straps and rings that allow users to track different health related metrics such as activity levels, heart rate, temperature, heart rate variability and sleep[278-281]. Further, from a public health point of view there are great opportunities to use technology to improve health at the individual level. For example the idea that people should "move more" and increase their "step count" has come into the public consciousness in recent years[282,283] with wearable step counters and accelerometers being widely utilised[284,285]. This research area has yielded positive results demonstrating the benefits of increasing activity levels even in later life[286]. Indeed recent research has used body worn sensors to demonstrate that this may be an effective intervention to help to reduce cardiovascular events, cancer and mortality.[287]

Moving beyond body-worn sensors, there is also growing interest in the use of implantable devices. Implantable devices are now widely used within cardiology. Their use goes as far back as the 1950s when the first cardiac pacemaker was inserted[288]. While pacemakers are used to treat cardiac arrhythmia, ILRs are used to diagnose arrhythmias. ILRs have proven to be a revolutionary tool in for arrhythmia detection in both stroke and syncope management. The ability to continuously monitor cardiac activity over extended periods has changed the nature of our understanding and management of syncope. However the utility of ILR in falls diagnosis has also become apparent in recent years[289,290]. This has led to both the ESC and the recently published World Falls Guidelines advocating for ILR use in cases of

unexplained fall[21,23]. Implantable devices offer intriguing possibilities in terms of measurement of biophysiological parameters and also potential treatment of medical conditions. For example, the Elon Musk owned company Neuralink has been examining the use of implantable technology to help people with neurodegenerative conditions and acquired brain injuries[291]. The use of technology in healthcare is a rapidly evolving field and with the advent of artificial intelligence it is difficult to tell what direction it will go next.

From a falls perspective, the holy grail for clinicians would be to predict increased likelihood of falls occurring and intervene before the event. Screening tools have thus far shown little promise in terms of falls prediction[292]. However, understanding underlying dynamic biophysiological changes may inform novel predictor models and potentially falls prevention. New technologies may help clinicians and patients alike. The potential for wearable technology has emerged in the last decade as a possible objective means of predicting falls and classifying frailty status.[293,294] But wearable technology has drawbacks in terms of adherence. This issue is resolved with the advent of implantable devices.

5.2 Cardiovascular Advancements

What is an ILR, and why and how are they used?

An ILR is device that is implanted under the skin to monitor and record the electrical activity of the heart. ILRs are commonly used for diagnosing and monitoring heart rhythm abnormalities or arrhythmias that may not occur frequently or may be difficult to capture with other monitoring methods. ILRs are typically small, about the size of a typical USB drive, and have been steadily decreasing in size since their inception (see Figure 4 below). ILRs are implanted just beneath the skin on the chest, near the heart. The insertion is usually performed under local anaesthesia as a day case. The purpose of ILRs from a falls and syncope point of view is to establish symptom-rhythm correlation. This is the gold standard and underlying principal for diagnosing cardiac arrhythmia as the cause of syncope and falls[23]. ILRs allow for continuous, long-term monitoring of cardiac activity. This allows for far higher diagnostic yield than more conventional short term monitoring methods[295]. In certain populations the use of holter monitor has a yield of 1-2%[296]. External loop recorders (or event recorders) have demonstrated more efficacy. In carefully selected early application of these monitors the yield can be as high as 24.5%[297]. Unlike external devices which are worn

for a limited time, ILRs provide continuous, long-term monitoring. They can record heart activity for several months to several years, depending on the device's battery life. The device works by transmitting electrical signals from the heart via electrodes on the surface of the device for recording and analysis .

Figure 4. Reveal LINQ™ implantable loop recorder.

The ILR can capture cardiovascular rhythms such as bradycardia, tachycardia, atrial fibrillation or other irregular heart rhythms depending on the pre-set parameters by the clinical team. The device detects abnormalities automatically and also records data when the patient activates the device. Most ILRs allow patients to manually activate the device when they experience certain symptoms, for example when a patient feels palpitations, dizziness or if they experience a fall or blackout. The patient will use a handheld activator to place a time stamp on the event for the clinical team to analyse cardiac activity at that time point retrospectively.

Most ILRs are equipped with wireless technology, allowing the recorded data to be transmitted remotely to a monitoring centre or their healthcare provider. This feature enables healthcare professionals to review the data remotely without the need for regular in-person visits. The ILR also stores the recorded heart rhythm data, which can be accessed by a healthcare professional for analysis and interpretation. The stored data can provide valuable insights into the patient's heart rhythm and help guide treatment decisions. They

are particularly useful for diagnosing and managing sporadic or infrequent events that would otherwise go undetected. Thus, they provide a more comprehensive and extended monitoring option, allowing for better detection, documentation and understanding of a patient's heart rhythm patterns. An important example of the value of an ILR from a falls perspective can be seen in the FUSE trial (Falls and Unexplained Syncope in the Elderly)[49]. This research demonstrated that arrhythmia was the cause of previously unexplained falls in 20% of participants, with 14% requiring pacemaker implantation.

5.3 Gait

An area of particular interest to this research is the feasibility of implantable device to capture gait parameters using a triaxial accelerometer embedded in the ILR.

Gait is a term commonly used to describe " the human locomotor movement of walking"[298]. Formal gait analysis is a valuable diagnostic tool for identifying gait abnormalities associated with certain diseases in older adults, such as musculoskeletal disorders, neurological diseases and balance impairments[299]. Gait analysis can also be used in assessing a person's overall mobility, functional capacity and falls risk[21]. Ambulation performance is commonly used as one of the key outcome measures in the rehabilitation setting helping therapists to assess progress with therapy, and it is a useful marker of functional independence. Traditionally this has been performed by visually inspecting a person as they ambulate. While this is certainly a useful endeavour and much important clinical information can be gleaned, it is limited by the expertise of the observer and the lack of quantitative data gathered that may help to detect earlier and more subtle changes in gait.[298] This led to the development of a series of more objective measures.

Some of the most commonly used methods to measure gait, balance and functional mobility include the Timed Up and Go (TUG)[300], The Berg Balance Scale (BBS)[301], Gait speed[302] and dual task assessments[303]. These are briefly summarised below.

- TUG: involves standing up from a chair, walking 3m, turning and returning to the seated position. This process is observed and timed in seconds. In general, slower times are related to an increased likelihood of falling.

- BBS: involves a series of 14 balance related tasks that assess a person's ability to safely balance in different positions and movements. These include sitting-to-standing, turning 360 degrees and single leg stands.
- Gait speed: the time taken to complete a walk over a given distance at the patients preferred or maximum walking speed.
- Dual task assessments: combine a physical task (usually walking) with either a cognitive task (counting/saying alternate letters of the alphabet) or a second physical task (holding an unsteady object)

In our study we analysed GAITRite, TUG and gait speed.

A recent review considered the diagnostic value of gait and balance tests in falls prediction with the authors concluding that no single test could accurately predict falls, but gait speed has the strongest predictive value and should be used in conjunction with other assessment methods[303]. Gait speed has been termed "the sixth vital sign", with slower speeds associated with increased levels of frailty, disability and morbidity and mortality[304]

Technological advances have led to an increased ability to quantify and measure several important spatiotemporal gait parameters. These objective measures can detect gait abnormalities and monitoring the effectiveness of interventions.

Commonly measured spatiotemporal gait variables include:

1. Gait Speed: velocity at which an individual walks, expressed in meters per second. It is calculated by dividing the distance travelled during a gait cycle by the time taken to cover that distance.
2. Step Length: the distance in centimetres between the heel strike of one foot and the subsequent heel strike of the opposite foot.
3. Step Time: the time in seconds between initial contact of one foot to initial contact of the opposite foot.
4. Stride length: the distance in centimetres between the heel strikes of two successive placements of the same foot.
5. Stride/cycle Time: the time in seconds between two consecutive heel strikes of the same foot. This includes the stance and swing phases of the gait cycle.

6. Stance Time: the time in seconds that a single foot remains in contact with the ground during a gait cycle, beginning with initial contact (heel strike) and ending with toe-off.
7. Swing Time: the time in seconds that a single foot is off the ground during a gait cycle. It starts at toe-off and ends at the subsequent heel strike of the same foot.
8. Single Support Time: the duration of time that only one foot is in contact with the ground during a gait cycle. It includes both the stance phase of one leg and the swing phase of the other leg.
9. Double Support Percentage: the proportion of the gait cycle during which both feet are in contact with the ground.
10. Cadence: the number of steps taken per unit of time, typically expressed as steps per minute.
11. Gait Variability: the stride-to-stride fluctuation that occurs during ambulation. Measures of variability can be applied to different elements of the gait cycle but typically include step time/length variability and stride time/length variability.

In Section 2 of this thesis, I demonstrate measurement of some of these variables using a triaxial accelerometer embedded in an ILR.

5.4 Age-Related Changes in Gait

As people age, they are more likely to develop problems with their gait. Gait abnormalities are estimated to effect 78% of adults aged 85 and older compared to just 15% of 60 year olds[305]. There are many reasons for this decline, some are neurological in nature, with age related atrophy to different regions of the brain leading to difficulties with motor, sensory, coordination and executive function [306]. Other problems are caused by declines in muscular strength and force production[307], while some people suffer from disabling events like stroke and others experience chronic musculoskeletal pain from osteoarthritis. Changes in gait in older adults are associated with worse outcomes including the need for nursing home placement, increased disability and higher mortality rates[308,309]. Some of the spatiotemporal parameters identified above have been shown to change with aging. There is a decrease in step and stride length, an increase in step time and step width and an increase in gait variability[306]. The increase in variability of step width and step length has an inverse association with gait speed[310]. Gait speed tends to decline with age particularly in

the presence of an increased number of comorbidities, cognitive deficits and depression[311]. Gait variability also tends to increase with age and is associated with increased falls rates. Early literature identified problems with "synchrony and guardedness of gait" as being higher in fallers[312]. This variability in aspects of human gait have since been shown to be associated with slower gait speeds, strength and balance deficits and increased levels frailty [313,314].

5.5 Measurement of Spatiotemporal Gait Variables

5.51 Laboratory Based Measurements

An effective method of measuring gait parameters is by using a specialised walkway, such as GAITRite (CIR systems, Havertown, PA, USA). This is considered the gold standard for the quantification of spatiotemporal gait parameters[315,316]. Participants are asked to walk along a 4.6 m long by 0.9 m wide instrumented walkway with embedded pressure sensors allowing for the generation of gait measurements (figure 5). Typically, participants are asked to walk at their normal speed, their maximum speed and sometimes perform a dual task assessment. This is usually completed in clinical or research setting, requires trained staff and the requisite equipment, making this form of testing relatively expensive.

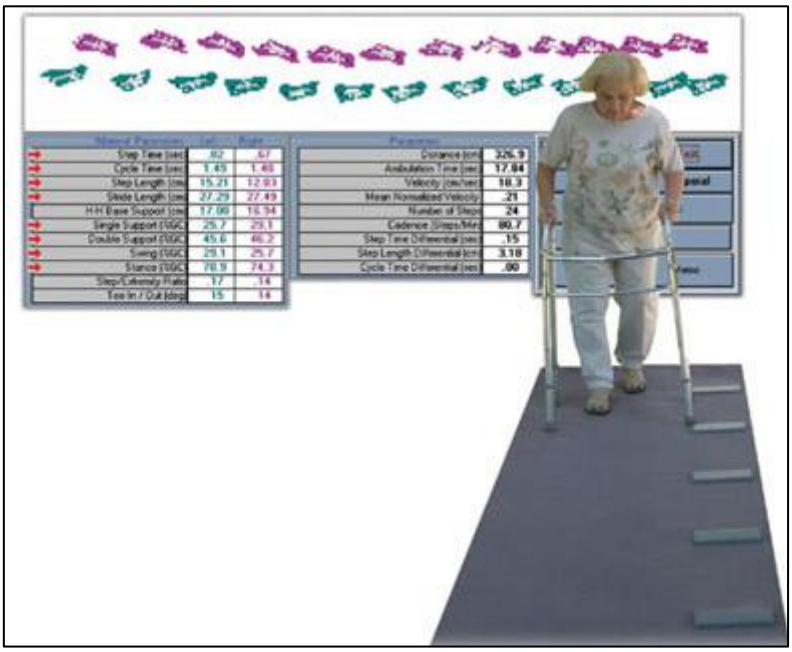


Figure 5. GAITRite sensored mat with sample data.

5.52 Body Worn Sensors

Traditionally the measurement of spatiotemporal gait variables has been limited the laboratory setting. Recently body worn sensors have been deployed in an attempt to make such measurements possible at scale, in any setting and at a fraction of the cost [317]. Body worn sensors are being used to measure overall activity levels as well as potential gait analysis. Gait analysis plays an important role in evaluating human locomotion and identifying abnormalities or changes in gait patterns. With the advancement of wearable sensor technology, external triaxial accelerometers and gyroscopes have gained popularity as promising tools for capturing spatiotemporal gait variables. Accelerometers are the most commonly used sensors in clinical motion studies[318]. Accelerometers measure acceleration: the rate of change of velocity of an object with respect to time. Gyroscopes on the other hand measure angular velocity although their use is limited in this context due to the their higher energy needs making them less useful as a long term method of measuring activity levels[319].

Clinical studies have demonstrated strong association between body worn accelerometers and gait speed in the laboratory setting[320]. There have been recent developments in trunk mounted accelerometers due to the potential for detailed gait analysis using this position. Trunk placement has been shown to accurately evaluate important spatio-temporal parameters including step/stride length[321]. Some of these systems have been validated using GAITRite gait analysis hardware and software to assess the quality of gait data generated[322]. While head-mounted systems have also been proposed and demonstrated comparable results[318], they are less practical than trunk based and are also less likely to be incorporated into an implantable device at this point[323].

In the validation studies described in Section 2 below, the study device (ILR with an embedded triaxial accelerometer) was compared to both GAITRite and an external trunk-based accelerometer, Axivity (https://axivity.com/product/ax3), to measure spatiotemporal gait parameters.

5.6 Activity

Physical activity is associated with reductions in all-cause mortality in adults with one study estimating that moderate physical activity compared to inactivity led to 20%–30% reduction

[324]. The majority of physical activity data has traditionally been self-reported[325]. The use of an objective measurement tool such as a body-worn sensor allows for more accurate and textured data to be generated, for example the quantity and intensity of the physical activity[286].

Accelerometers can measure overall activity levels and this measure correlates with improved cardiovascular outcomes[326]. In a recent publication, people who walked 10,000 steps a day tended to have better cardiovascular, cancer and mortality outcomes[287].

5.7 Falls and Technology

The use of technology may help to reduce falls in older adults. There is a body of research examining activity and falls prediction using different devices. For example, different sensor systems have been trialled in long term care facilities for decades, in an effort to identify at risk patients who begin to mobilise. Such systems may give feedback to both patients and care staff when an alarm is triggered, the results of these approaches have been mixed[327]. Body worn sensors also have a role to play in terms of falls prevention and prediction. Both external gyroscopes and triaxial accelerometers have been shown to predict falls[293]. In Parkinson's disease, sensors have been used to measure freezing of gait, an important feature of the condition that is associated with falls[328].

Triaxial accelerometers are the most commonly used body-worn sensor as evidenced by a recent systematic review where 26 out of 28 studies used them[329].

Physical activity has many benefits including potentially reduction of falls rates[330]. The intensity of activity has also been considered with a 2017 study demonstrating that older women who engaged in moderate to vigorous physical activity did not increase their fall risk, indeed older women with the lowest rates of physical activity had higher falls rates[331]. A short term (12 week) accelerometer based intervention has been shown to potentially reduce fractures in long term follow up [326]. A therapist's decision to mobilise a patient must be individualised to the patient's current physical and functional status as there is always a risk of falling.

Smartwatches may also play a future role in this area due to accelerometer and gyroscopy features but also by using their ability to measure and combine with other measurements such as heart rate variability [332].

When spatiotemporal gait parameters and falls are considered, the variables most associated with increased falls risk are the temporal measures of stride, swing and stance and their variability[314,333]. My research will examine the extent to which these variables can be measured using implantable technology.

5.8 The Role of Implantable Cardiac Devices

There is great potential for wearable technology in older adults to measure activity levels and gait variables, and possibly, in falls prevention. One of the main issues that has consistently hindered the utility of wearable accelerometery has been the consistency of sensor placement and the duration of time the sensor is worn[321]. This is a problem that could be solved by an implantable cardiac device with an embedded triaxial accelerometer.

Prior studies have demonstrated the potential for embedding an accelerometer in cardiac pacemakers [334,335]. Conraads et al. utilised a single axis accelerometer embedded in either an implantable cardioverter defibrillator (ICD) or a cardiac resynchronization therapy device (CRT) to measure activity levels in patients with heart failure and demonstrated the importance of physical activity in this cohort[334]. This method of activity measurement has also been validated against external accelerometery. Shoemaker et al. showed that embedded devices were able to accurately measure activity levels in heart failure patients when compared to an external accelerometer placed on the dominant hip of all participants[335].

Activity levels in these studies were considered as the number of minutes per day where a participant was active. A minute was deemed active once a threshold was reached that incorporated “both the number and magnitude of deflections in the accelerometer signal”[334]. This is useful in the context of considering overall levels of physical activity. Where our research differs is that the recording of activity and posture change takes place in 5-minute epochs allowing for a short time duration on which to focus on the time of falls. Having a more focused time frame may allow early detections in physiological changes around the time of falls and therefore allow for falls prediction models to be created.

SECTION TWO: VALIDATION STUDIES FOR ACTIVITY, POSTURE CHANGE AND GAIT ANALYSIS

Chapter 6: Introduction

As part of the overall study process, I sought to describe the utility of placing a triaxial accelerometer inside the Reveal LINQ™ (study device) in terms of measuring posture change, activity levels and gait parameters.

Unlike prior studies that analysed activity levels using an implantable device, this study measures activity in 5-minute epochs. The aim is to identify shorter time windows to examine brief periods for the purpose of detecting imminent falls.

I performed 3 studies:

- Study 1 was designed to characterise how the study device captured activity levels and posture changes[334,335].
- Study 2 was designed to validate an independently placed external accelerometer to a pressure sensitive floor mat system (GAITRite) in measuring spatiotemporal gait variables.
- Study 3 was designed to validate spatiotemporal gait variables captured by the study device compared to the GAITRite.

Chapter 7: Study 1 – Activity and Posture Change

Activity levels and posture changes are variables of interest in the context of potential falls and were measured using an embedded triaxial accelerometer within the study device. This study took place in the Falls and Syncope Unit (FASU) in St James Hospital. Three protocols were devised to assess how activity level and posture changes were registered by the study device. Movements were performed with the cooperation of a healthy volunteer (aged 40). See Appendix (A) for full protocols.

7.1 Aim

The aim of the experiment was to observe the prescribed precise movements of a healthy volunteer with the study device externally affixed to the chest wall in order to demonstrate recording of these variables in a controlled environment. This data would inform analysis of data generated during clinical investigation.

7.2 Methods

The study device was externally fixed to the volunteer's chest wall using an adhesive dressing in two orientations; horizontal and at 45 degrees to represent different implant positions of the ILR . Data output from the ILR was assessed according to the position of the device and was pre-calibrated to the correct orientations. This was performed prior to each protocol. An external accelerometer, Axivity tri-axial accelerometer, (https://axivity.com/product/ax3) was also fixed to the volunteer's chest wall to serve as a control during all protocols.

Protocols 1a and 1b

Protocols 1a and 1b involved a series of basic movements and posture changes to replicate a participant changing postures with the accelerometer placed in horizontal (1a) and 45-degree (1b) orientations.

The volunteer then carried out the following movements.

- Supine to seated . Changing posture every 15 seconds for 4 minutes
- Sit to stand with a neutral chest. Changing posture every 15 seconds for 4 minutes

- Sit to stand with toe touch (to exaggerate flexion at the hip). Changing posture every 15 seconds for 4 minutes.
- Lying supine and rotating in clockwise direction
- Lying supine and rotating in counterclockwise direction
- Lying to supine and sitting up swing legs to the side of bed
- A series of standardised walks at varying speeds (slow, normal pace and brisk)
- Lying supine and tilting angle of bed to 20 degrees and 45-degree angles.

The walks were performed at different speeds along a 55-metre walkway to determine if walking speed altered the variables recorded. Finally, a mechanical tilt bed was utilised to assess what angles would trigger a posture change.

The study team aimed to see precisely what activities would trigger posture changes and also how these activities were captured in terms of "activity levels".

Protocol 1c

Protocol 1c sought to replicate a nocturnal movement series. The goal was to replicate nocturnal activity and compare prescribed objective movements with the study device outputs, specifically posture changes and activity levels. This involved replicating several movements that a person may make while lying in bed such as turning over or sitting up. This was followed by the volunteer rising from the supine position and walking along a walkway and sitting down and returning to supine. And finally, the participant was asked to climb a flight of stairs and return to the supine position.

All movement/activity sequences as detailed in the protocols 1(a-c) were performed within 5-minute epochs, as the ILR study device internal algorithm collated posture and activity counts on a 5-minute basis. A 5-minute motionless epoch was interspersed between each 5-minute bout of posture change/activity. This allowed a precise comparison of known posture changes/ activity bouts with the values estimated by the study device.

Activity counts were also examined during these testing protocols. Activity recording was evaluated from both the magnitude and number of inflection peaks in the accelerometer signal. Between each movement series in the protocols the volunteer was completely still.

7.21 Data processing

Data was processed in collaboration with the Medtronic team. Following completion of each test protocol the data was transferred to the Medtronic team for processing and the raw 5-minute data was returned as a Matlab® compatible file for analysis. This was presented as a summary activity count and number of posture changes detected in each 5-minute epoch, including those baseline epochs of no posture change or motion.

The precise detail of how the algorithm on the study device calculates summary activity counts is not available as it is considered proprietary information. In general terms, a single axis from an embedded accelerometer is used to capture patient motion as an electric signal. The number of minutes a patient is active per day is counted, where a minute is considered active if a threshold is reached that incorporates both the number and magnitude of deflections in the accelerometer signal. With regards to posture counts, a single accelerometer axis (Z-axis) is sampled every 2 seconds and a significant change in the axis vector magnitude in consecutive 2 second windows are recorded as a posture change (of the torso). The Z-axis of the study device is expected to be sensitive to changes in torso orientation in both supine (rolling left or right), and vertical standing (e.g., stooping to upright position). A rapid posture change and recovery within a 2 second window would not record as a posture change due to the limited time resolution of the posture recording algorithm.

The tri-axial raw acceleration signals from the Axivity device, sampled at 100Hz, were recovered from the device using open-source software, OmGui, (Newcastle University, UK.) Acceleration signals in both the vertical and anterior-posterior axes were plotted in Matlab® to provide a graphical representation of the signals experienced by the study device (Figure B1 in appendix B) and to help corroborate any unusual or unexplained discrepancy potentially arising from the known posture change/activity levels and that estimated by the study device.

Time stamps from the physical recording of the protocol activities and the study device were subsequently aligned to ensure that identical 5-minute epochs were compared in the data analysis.

Figure 6. Validation Study - Healthy volunteer at 45-degree angle on tilt bed.

7.3 Results

Table 2 tabulates posture changes and activity counts measured by the study device during protocols 1a and 1b (horizontal compared to 45-degree axis orientation). The 'expected' posture count results were determined from a review of the physical number of body (torso) position changes as detailed in the respective protocols.

Table 3 shows posture changes and activity counts from protocol 1c. As the results from protocols 1a and 1b showed strong agreement, it was therefore accepted that just one orientation of the study device was sufficient for protocol 1c.

Realtime	Activity (4 min session)	Expected posture changes	Protocol 1a Actual posture changes	Protocol 1b Actual posture changes	Protocol 1a Activity	Protocol 1b Activity
10:31:30	Supine/Sit/Supine (8 reps)	16	21	21	82	82
10:36:30	Supine	0	2	1	47	43
10:41:30	Sit/Stand neutral torso (8 reps)	0	2	1	68	77
10:46:30	Sit	0	0	0	46	44
10:51:30	Sit/Stand forward bend (8 reps)	16	30	30	101	103
10:56:30	Supine	0	1	1	54	52
11:01:30	Supine rotations (8x90deg)	8	11	11	65	63
11:06:30	Supine	0	0	0	39	38
11:11:30	Supine/Sit/Stand	16	23	25	88	88
11:16:30	Move to walkway	2	3	2	90	99
11:21:30	Slow walk (4 mins)	0	0	0	137	151
11:26:30	Stand	0	0	0	83	76
11:31:30	Moderate walk (4 mins)	0	0	0	190	188
11:36:30	Stand	0	0	0	99	87
11:41:30	Fast walk (4 mins)	0	0	0	203	200
11:46:30	Move to clinic	0	0	0	143	142
11:51:30	Supine	1	1	1	47	51
11:56:30	Tilt (0^o – 20^o x 2)(0^o- 45^o x 2)	4-8	0	0	41	46

Table 2. Expected and obtained posture changes and activity (Protocols 1a and 1b.)

Realtime	Activity (4 min session)	Expected Posture Changes	Actual Posture changes	Activity
14:36:30	Supine/L Shoulder/R shoulder	9	17	102
14:41:30	Supine	0	0	54
14:46:30	Supine/Sit/Reach	9	13	73
14:51:30	Supine	0	0	41
14:56:30	Supine/Sit/Slow walk/Sit/Return	9	9	71
15:01:30	Supine	0	0	36
15:06:30	Supine/Sit/Walk/Sit/Return	8	9	77
15:11:30	Supine(move to stairs)	2	3	57
15:16:30	Stand/Slow stairs/Sit/Return	2	2	85
15:21:30	Stand	0	0	45
15:26:30	Stand/Stairs/Sit/Return	0	3	87
15:31:30	Supine	2	3	66
15:36:30	Supine/Sit/Slow Walk/Stairs/Ret	8	8	117
15:41:30	Supine	0	0	39
15:46:30	Supine/Sit/Walk/Stairs/Ret	0	4	118
15:51:30	Supine	0	0	33

Table 3. Expected and obtained posture changes and activity during Protocol 1c.

Figures 7 and 8 below graphically illustrate the acceleration signals experienced during the execution of the protocol manoeuvres. The number and changes in signal amplitude can be seen to correspond to the detailed instructions contained in the respective protocols. The blue and orange signals correspond to the direction of the axes as shown attached to the figure in the diagram.

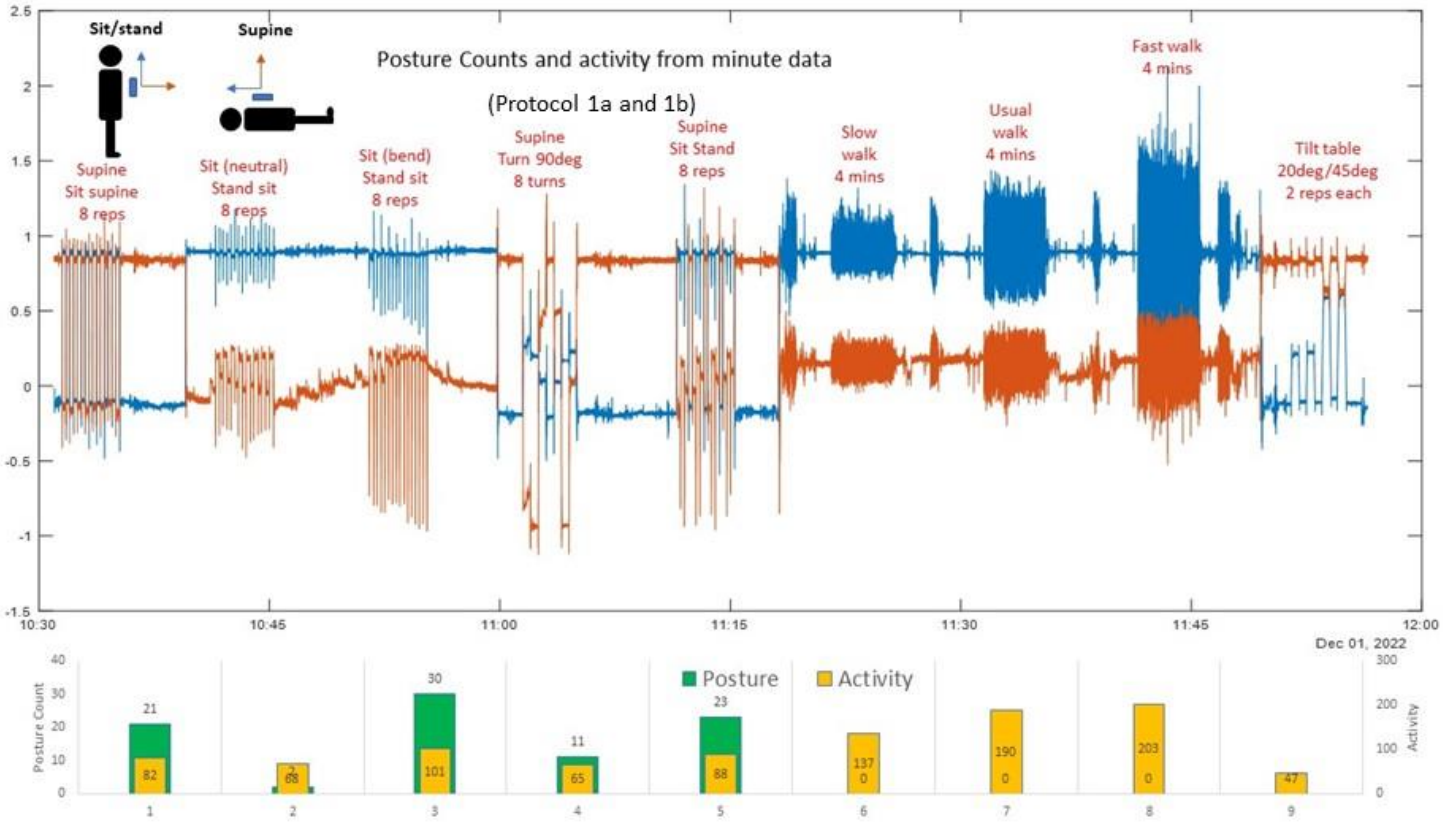


Figure 7. Posture and activity counts, and accelerometer signals during validation tests (Protocol 1a and 1b).

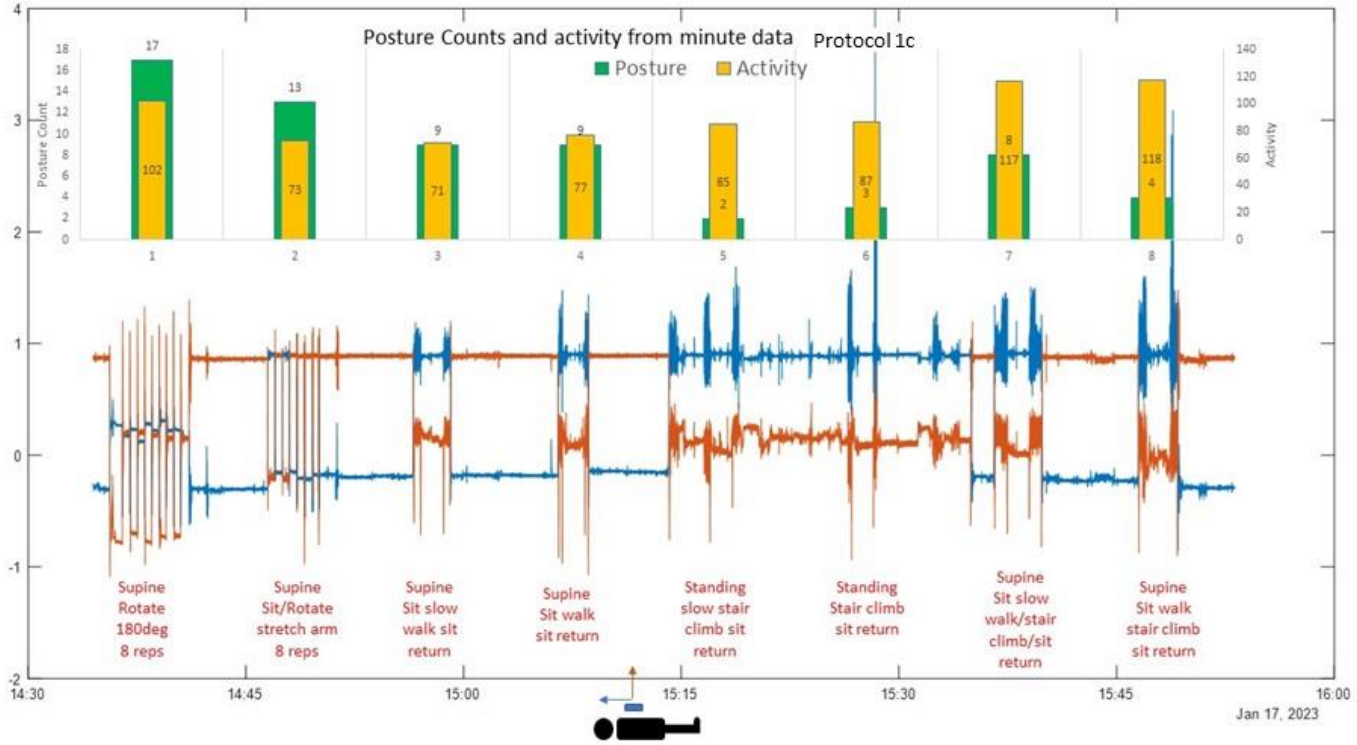


Figure 8. Posture and activity counts, and accelerometer signals during validation tests (Protocol 1c).

7.4 Discussion

The main findings from Study 1 are as follows.

- For both activity levels and posture changes, the orientation that the accelerometer has been inserted has little bearing on the results generated.
- Posture change counts tend to be overestimated by the study device.
- To infer ambulation both activity level and posture change should be assessed in tandem (the activity count should be >50.)

Study 1 was performed to quantify activity counts and to test the effect that the orientation of the device may have on activity and posture change count measurements. Table 2 shows minimal difference between the activity levels and posture changes generated from protocols 1a (device in horizontal position) and protocol 1b (device in 45-degree position). This has clinical relevance because in practice ILRs are inserted at slightly different orientations.

Regarding posture changes, tables 2 and 3 demonstrate that there is a tendency for the study device to overestimate posture change. For example, in table 2 during supine/sit/supine, 16 changes in posture were expected to be detected as the volunteer had moved from lying supine to sitting and back to the supine position 16 times. In reality the device detected 21 posture changes. Similarly, on moving from sitting to standing with an exaggerated bend forward (hip flexion) led to 30 posture changes being registered while 16 were expected. The movement from sitting to standing would be considered as one posture change, but the inclusion of a (slightly exaggerated) hip flexion and extension also counted as a posture change within the overall movement.

Table 2 also highlights that supine rotations trigger a posture change. Quiet rest epochs did not for the most part register any changes in posture.

Posture changes are not triggered by steady state walking, regardless of the speed of walking this is illustrated numerically in tables 2 and graphically in figures 7 and 8. They are however triggered by the volunteer rotating while lying down suggesting that posture changes registered at nighttime don’t necessarily suggest ambulation. Therefore, it is important to consider activity counts at the same time in order to infer nocturnal ambulation.

Finally, placing the participant on a tilt bed with the participant lying supine and then elevating the bed to 20 degrees and then 45 degrees (Figure 6) did not trigger a posture change. This may be due to the slow nature of the transition combined with the relatively small degree of change of angle, which did not trigger the device threshold for registering a posture change. It is not clear therefore if, for example, a very slow nocturnal movement of rising from a bed would in fact register as a posture change of significance.

An interesting and important observation with respect to activity levels is demonstrated in table 2. The volunteer lies supine for 5 minutes ILR time stamp (10:40:01 to 10:45:01) there are still a number of activity counts detected: 47 in protocol 1a and 43 in protocol 1b. This suggests that immobility still generates some level of activity counts, perhaps due to respiration. Similar results can be seen when the volunteer was static in either the sitting or standing positions. The significance of this finding is that in order to infer ambulation an activity level at least > 50 but perhaps >100 must be present. It would appear that the study device has a low threshold level for defining activity, but it is not clear whether this is due to a noise component in the signal. This may be due to the combination of heartbeat artifact combined with a respiratory cyclical signal. It is reassuring however that the activity count increased in a predictable manner across slow, moderate and fast walking, indicating that activity counts in general can reflect varying levels of physical activity.

It is probably useful to assess both posture changes and activity levels to infer ambulation, particularly in the context of nocturnal ambulation and falls risk. This is highlighted graphically in figures 7 and 8.

7.5 Conclusions

Study 1 demonstrated that for the collection of activity and posture change data, the orientation that the accelerometer is inserted has no bearing on the results. However, it must be noted that for these studies the device was placed externally over the sternum and therefore the Z-axis (A-P direction) of the device was aligned with the sagittal plane. In real world ILRs, as shown in figure B1 of Appendix B, implanted devices may show some deviation of the X-axis from the sagittal plane.

I have shown that “posture changes” need to be interpreted in context. Turning over while in the supine position can trigger a posture change. Similarly on transitioning from sitting to

standing, depending on the extent that a participant leans forward it can trigger additional posture change counts. In general posture changes tend to be overestimated by the experimental device. The results suggest that to infer ambulation, the activity count must be at least 50 but likely closer to 100.

This section of the thesis aimed to evaluate how the study device interpreted predefined movement patterns and how this was translated into numerical data. Ultimately this type of data may have clinical relevance if it can reveal unusual patterns of posture changes or activity around the time of a fall event.

For both activity levels and posture changes, the orientation that the accelerometer has been inserted has no bearing on the results generated. This differs from the ability of the accelerometer to generate spatiotemporal gait parameters which appears to be reliant on the orientation of the device as will become evident in Chapter 9.

Chapter 8 : Study 2- GAITRite v External Accelerometer

8.1 Aim

The purpose of study two was to compare gait variables generated from an independent, ideally positioned, external accelerometer (Axivity) placed on the sternum compared to GAITRite. The Axivity tri-axial accelerometer has been validated in studies for the derivation of the mean spatiotemporal parameters of gait[323] and the methodology proposed in this paper is followed in this section, as developed by Czech et al. in the GaitPy Python package[336] . While most gait studies evaluate accelerometer signals attached to the lower back (L1/L2), it has been suggested that signals acquired from the sternum are also valid for the derivation of spatiotemporal parameters of gait[337].

8.2 Methods

In total, 16 of the study participants had an external accelerometer vertically attached to the sternum following appropriate programming so that one axis of the accelerometer aligned vertically The Axivity sensor was programmed to 100Hz sampling rate and a range of +/-4g. The GAITRite system was also calibrated prior to use. The participant was instructed to begin walking 1 metre before stepping on the GAITRite mat and to walk at a normal speed across the mat stopping 1 metre past the mat. The participant had therefore reached steady state as they walked the length of the mat. They were advised to turn immediately and walk back along the GAITRite to the starting position. They were asked to walk for six lengths of the mat in total. Data was collected simultaneously from both instruments. The data was processed at the end of the participant visit. A segment of signal data was extracted during a steady state walking period and spatiotemporal variables were extracted using the algorithms validated in the GaitPy package[336]. The algorithm determines the heel strike and toe off events in the gait cycles using a continuous wavelet transform, from which the temporal parameters of gait e.g., step time, swing time, cycle time can be derived. Step length/stride length is estimated from calculation of the vertical displacement of the vertical signal during each gait cycle, where the height of the sensor relative to body height is accounted for.

A comparative analysis was performed between GAITRite and the external accelerometer across a number of spatiotemporal variables. Microsoft Excel was used to create correlation

coefficients and agreement was visualised using Bland Altman plots based on means and mean absolute difference between 2 methods of measurement. The 95% limits of agreement were calculated as the mean absolute difference ±2SD. Bland Altman plots were selected to provide a visual representation of the agreement between the two measurement methods. Statistical tests were not performed to compare groups as the actual sample numbers obtained were small.

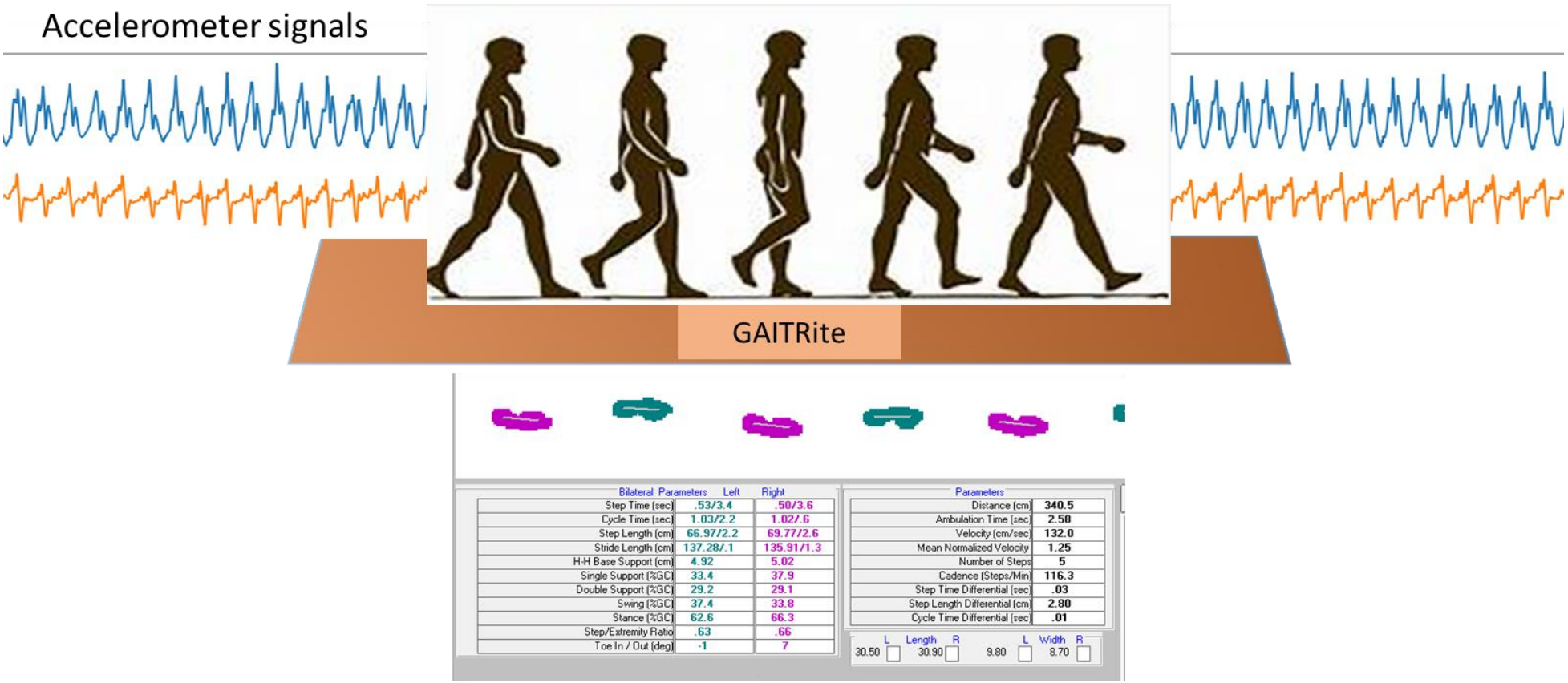


Figure 9. Graphical representation of Accelerometer and GAITRite data.

8.3 Results

The differences between the measurements are displayed on the y-axis and the average of the measurements on the x-axis, allowing for a clear visualization of any systematic bias, outliers, or patterns of disagreement. The solid red line represents the mean of the differences demonstrating bias, while the dotted red line represents the upper and lower levels of agreement (95% confidence intervals).

Spatial gait variables

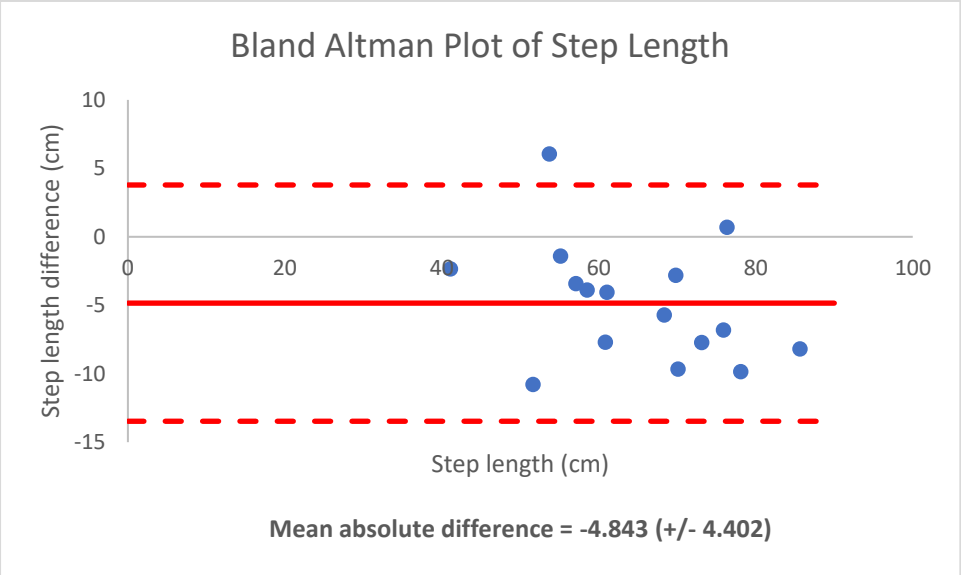


Figure 10. Bland Altman Plot: difference in step length measured on external accelerometer compared to GAITRite.

Figure 10 demonstrates the mean absolute difference in step length measured on external accelerometer compared to GAITRite is -4.843(+/-4.40).

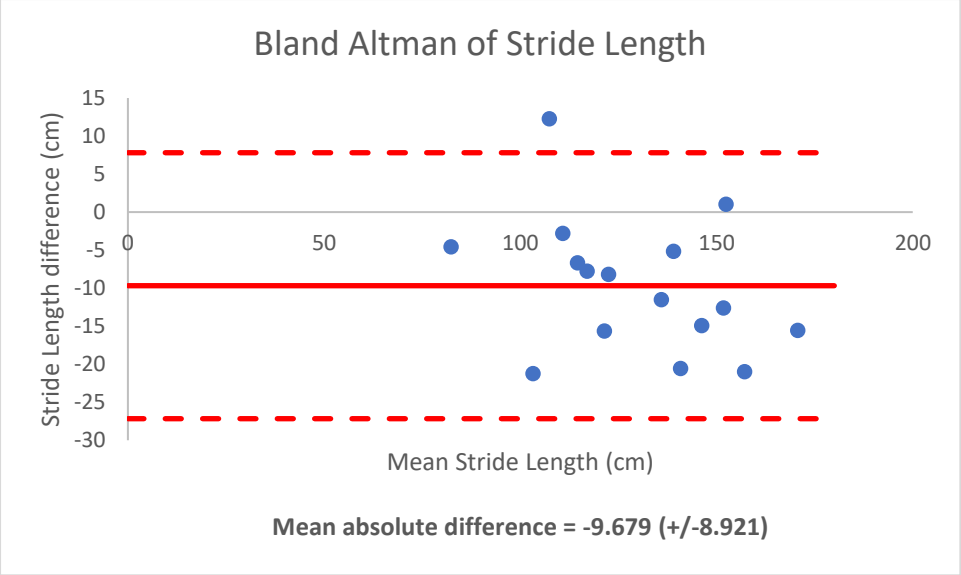


Figure 11. Bland Altman Plot: difference in stride length measured on external accelerometer compared to GAITRite.

Figure 11 demonstrates the mean absolute difference in stride length measured on external accelerometer compared to GAITRite is -9.679(+/-8.921).

Temporal Gait Variables

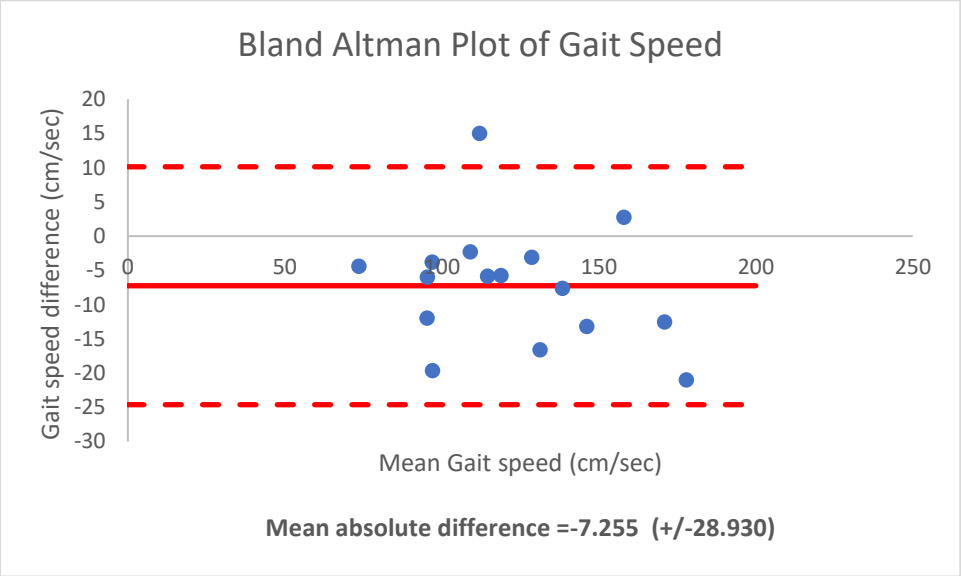


Figure 12. Bland Altman Plot: difference in gait speed measured on external accelerometer compared to GAITRite.

Figure 12 demonstrates the mean absolute difference in gait speed measured on external accelerometer compared to GAITRite is -7.255(+/-28.930).

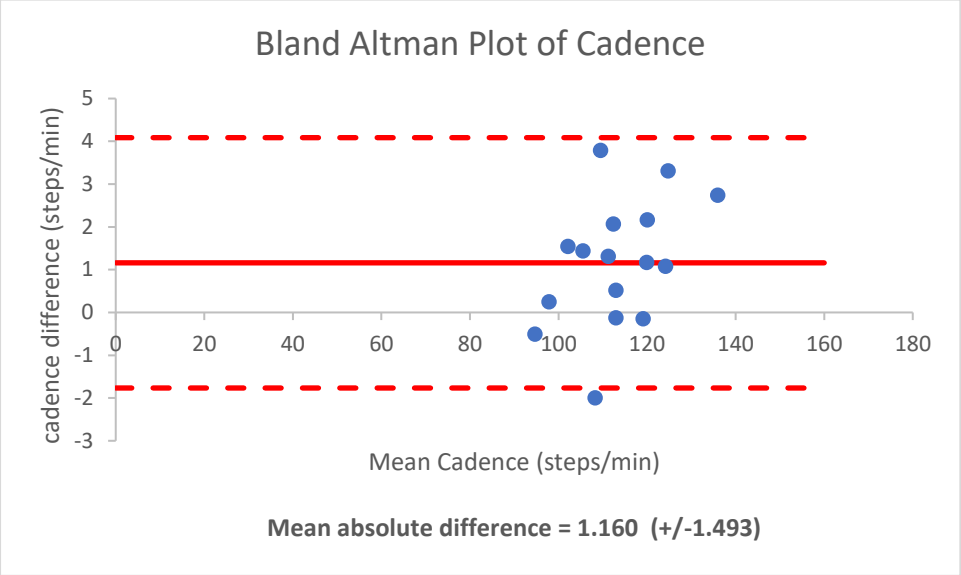


Figure 13. Bland Altman Plot: difference in cadence measured on external accelerometer compared to GAITRite.

Figure 13 demonstrates the mean absolute difference in cadence measured on external accelerometer compared to GAITRite is -1.16(+/-1.493).

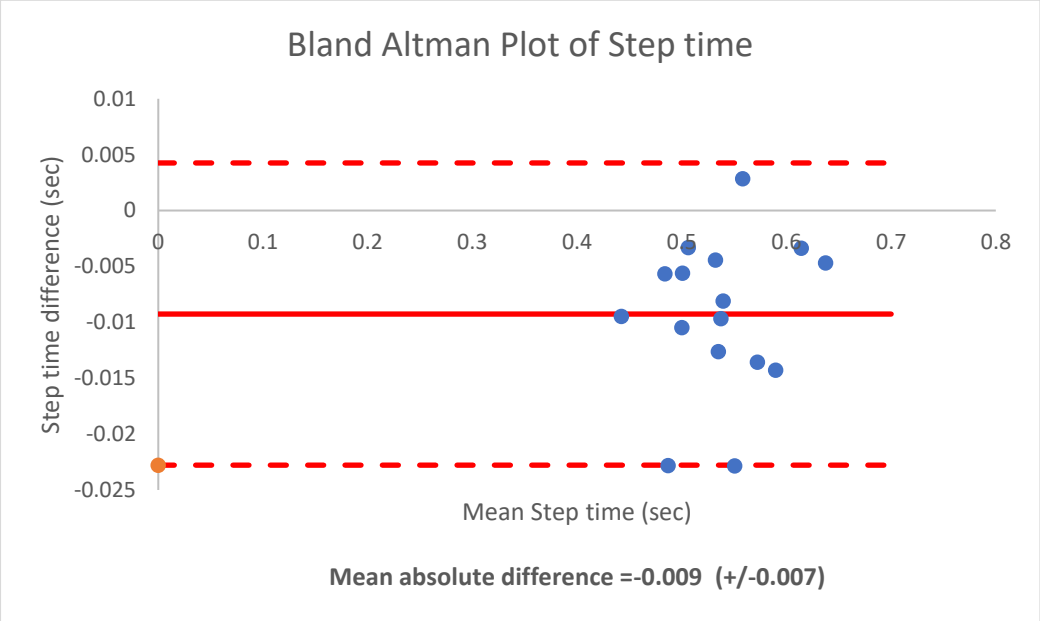


Figure 14. Bland Altman Plot: difference in step time measured on external accelerometer compared to GAITRite.

Figure 14 demonstrates the mean absolute difference in step time measured on external accelerometer compared to GAITRite is -0.009(+/-0.007).

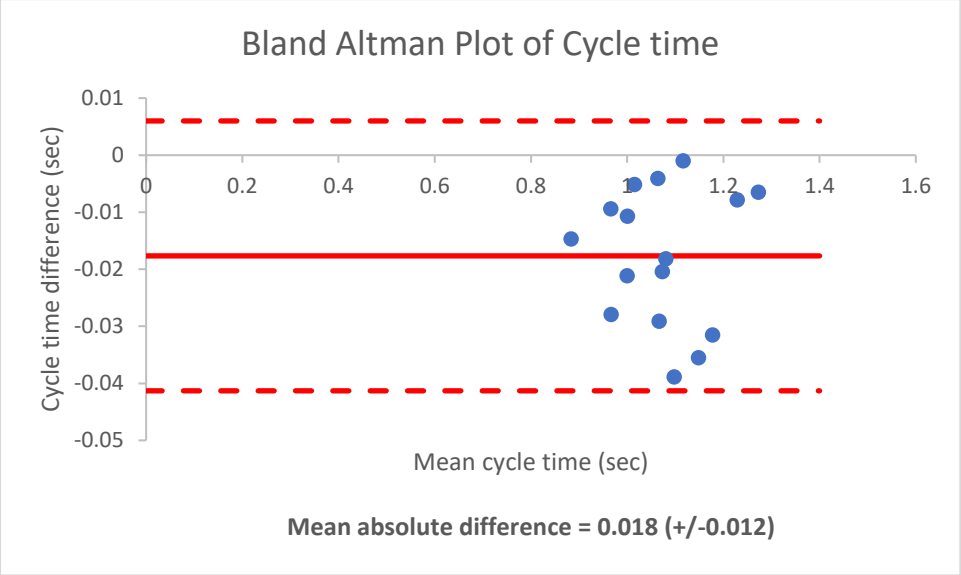


Figure 15. Bland Altman Plot: difference in cycle time measured on external accelerometer compared to GAITRite.

Figure 15 demonstrates the mean absolute difference in cycle time measured on external accelerometer compared to GAITRite is 0.0018(+/-0.012).

8.4 Discussion

Study 2 demonstrates that it was possible to generate both spatial and temporal gait variables using an appropriately positioned external accelerometer on the trunk (sternum) of participants.

Regarding the spatial variables, for example step length, the mean absolute difference of -4.84 cm (+/-4.40) suggests that, on average, the GAITRite measures step length approximately 4.84 centimetres longer than the accelerometer (Figure 10). Similarly for stride length the mean absolute difference = -9.7 cm (+/-8.9) suggesting that GAITRite measures stride length approximately 9.68 centimetres longer (Figure 11). This indicates a systematic bias where the GAITRite tends to provide longer length measurements compared to the accelerometer. The

standard deviations are also relatively large suggesting considerable variability in agreement between both measurement techniques.

There is variance in the temporal gait parameters when comparing methods of measurement. For example, with gait speed, the mean absolute difference of -7.26 suggests that, on average, the accelerometer measures gait speed approximately 7.26 centimetres per second less than the GAITRite (Figure 12). This indicates a systematic bias where the accelerometer tends to underestimate gait speed compared to the GAITRite method. The standard deviation of +/- 28.89 represents the variability or dispersion of the differences between the two measurement methods. The fact that this standard deviation is relatively large suggests that there is considerable variability in the differences between the accelerometer and GAITRite measurements. In other words, the agreement between the two methods is not consistent, and there may be many factors causing fluctuations in the differences. Gait speed is a combined spatial and temporal variable (m/sec) and so a poor stride length estimation will introduce variability into the gait speed comparison.

However, examining the Bland Altman plots for cadence, step time and cycle time reveal closer agreement between the methods. Regarding cadence, the mean absolute difference of 1.16 (SD=+/- 1.49) indicates a relatively small systematic bias between the two methods, where the accelerometer tends to provide slightly higher cadence values compared to the GAITRite (Figure 13). The standard deviation of +/- 1.49 is relatively small indicating that there is less variability in the difference between the methods. Similarly, both step time (Mean absolute difference =-0.009(SD=+/-0.007)) (Figure 14) and cycle time (mean absolute difference = 0.018(SD=+/-0.012)) (Figure 15) demonstrate good agreement with relatively small standard deviations indicating that the accelerometer and GAITRite methods demonstrate agreement when measuring temporal variables. The systematic bias is minimal and the differences between the two methods are consistent with low variability. The closer agreement of temporal variables when compared to spatial variables is likely a reflection of the algorithm that tries to identify heel strike and toe off events in the accelerometer data. Gait speed is a combined spatial and temporal variable (m/sec); therefore, a poor stride length estimation will introduce variability into the gait speed comparison. These findings suggest that certain temporal variables obtained from the accelerometer and GAITRite are largely interchangeable and reliable for research and clinical purposes.

8.5 Conclusions

Validation study 2 has demonstrated that an ideally placed external accelerometer is comparable to GAITRite for some temporal variables notably step time, but less agreement was noted for spatial variables.

Chapter 9 : Study 3 - GAITRite v ILR Accelerometer

9.1 Introduction

A key part of this research is to evaluate the utility of embedding a triaxial accelerometer in an implantable loop recorder (Study device). In particular I sought to determine if the study device could generate spatiotemporal gait variables as this may lead to opportunities for the remote assessment of gait performance in the home and community environment for older adults.

9.2 Aim

The purpose of validation study 3 was to compare gait variables generated by the study device to variables generated via GAITRite.

9.3 Methods

The study device was programmed for each of the following position vector measurements; supine, lying on right shoulder and lying on the left shoulder and upright using a specific programming computer with the new research software. The purpose of this procedure was to ascertain the likely orientation of the implanted study device, which could provide context for the suitable application of the gait algorithms.

The GAITRite system was also calibrated prior to use. Each participant was instructed to begin walking 1 metre before stepping on the GAITRite mat and to walk at a normal speed across the mat stopping 1 metre past the mat. The participant had therefore reached steady state as they walked the length of the mat. They were advised to turn immediately return along the mat to the starting position. This was repeated 6 times. Data was collected simultaneously from both instruments. The data was processed at the end of the participant visit. A segment of signal data was extracted during a steady state walking period and examined for the appropriate extraction of spatiotemporal variables.

A comparative analysis was performed between GAITRite and the experimental accelerometer. Microsoft excel was used to create correlation coefficients and agreement was visualised using Bland Altman plots based on means and mean absolute difference between 2 methods of measurement. The 95% limits of agreement were calculated as the mean absolute difference ±2SD. Bland Altman plots were selected to provide a visual

representation of the agreement between the two measurement methods. Statistical tests were not performed to compare groups as the actual sample numbers obtained were small.

9.4 Results

22 participants were included in the analysis with a total of 61 individual walks analysed. The differences between the measurements are displayed on the y-axis and the average of the measurements on the x-axis, allowing for a clear visualization of any systematic bias, outliers, or patterns of disagreement.

9.41 Spatial Variables

It was not possible to generate spatial variables using the study device. This is due to a technical issue that relates to basic principles of accelerometery. This is outlined in detail in the discussion section.

9.42 Temporal Variables

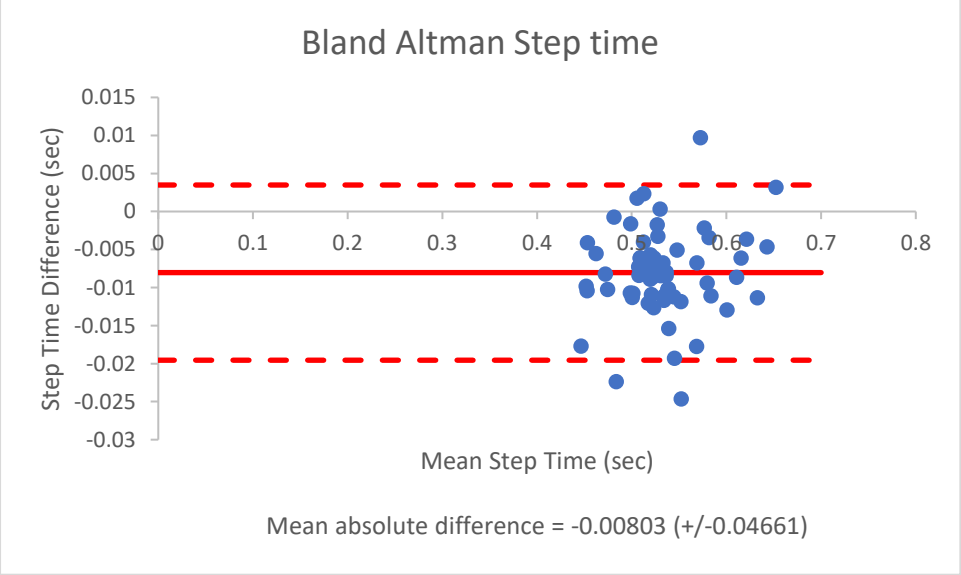


Figure 16. Bland Altman Plot: difference in step time measured using experimental ILR accelerometer compared to GAITRite.

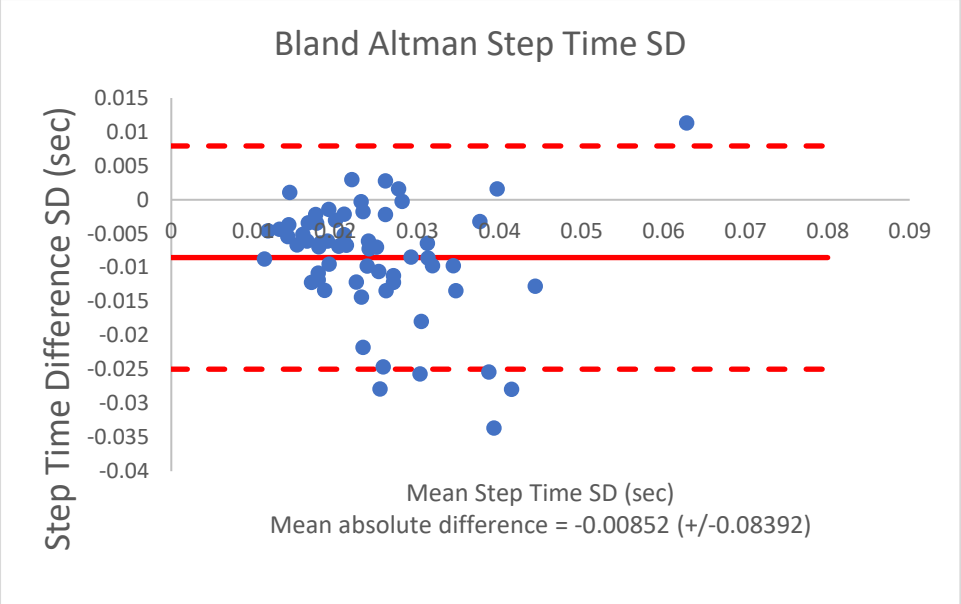


Figure 17. Bland Altman Plot: difference in step time standard deviations measured using experimental ILR accelerometer compared to GAITRite.

The Bland Altman plots above (Figures 16 and 17) demonstrate the agreement between the measurements generated from the ILR and the GAITRite. Again, the differences between the measurements are displayed on the y-axis and the average on the x-axis. The large standard deviations in both step time and step time variability suggest poor agreement between the two methods.

9.5 Discussion

Study 3 demonstrates that it was not possible to generate spatial variables using the study device. While temporal variables could be generated, the extent to which these can be relied upon is limited given the inconsistent level of agreement.

Given the ability of a well-positioned external accelerometer to generate temporal gait variables that are comparable to GAITRite, I sought to compare the variables generated from the study device accelerometer against GAITRite. Ultimately it was not possible to generate spatial variables using this method.

The alignment of a triaxial accelerometer with anatomical axes is crucial for accurate measurement of accelerations in vertical, medio-lateral, and anterior-posterior directions

(Figure 18). Ideally, the accelerometer should experience a full 1g gravity on the vertical (X) axis and zero gravity on the Y and Z axes during quiet standing. The algorithm used to estimate step length relies on calculating the vertical displacement of the sensor. If the vertical axis is tilted, the calculated displacement, and thus the step length estimation, becomes inaccurate. However, the Implantable Loop Recorder (ILR) is typically not implanted exactly along the vertical axis. As a result, static accelerometer data recorded in various postures show different orientations of the ILR for each subject. This is illustrated by the vector positional data (standing) from the Reveal LINQ™ in Figure B1 of Appendix B, demonstrating the diverse orientations influenced by gravity on all three axes. Consequently, this variability in orientation limits the ability to generate accurate spatial gait variables with the ILR. A more complete explanation of vector calculation can be found in Appendix B.

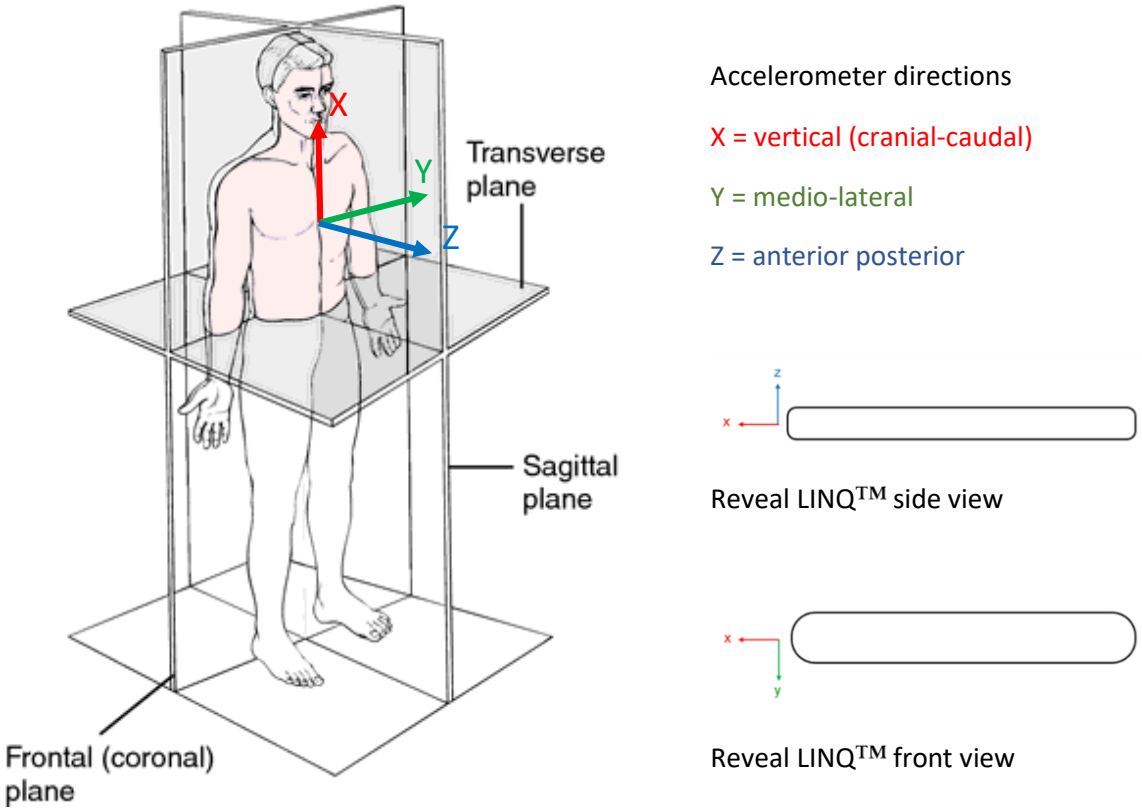


Figure 18. Anatomical axes and accelerometer directions.

Regarding the temporal variables, step time demonstrates some agreement between testing modalities although the accelerometer seems to provide slightly shorter step time

measurements than GAITRite demonstrated in figure 16 (Mean absolute difference = -0.008 (SD= +/-0.046). While the relatively large standard deviation suggesting poor agreement between methods. This is similar to step time standard deviation (mean absolute difference = -0.008 (SD=+/-0.084))shown in figure 17. These data demonstrate that there are issues with using the study device to generate temporal variables accurately and consistently.

9.6 Conclusions

The study device was unable to generate satisfactory spatiotemporal gait variables. The limitations and variability in accelerometer alignment prevented the generation of spatial variables. Although temporal variables such as step time could be measured, the large standard deviation rendered this method unreliable. Consequently, it is unlikely that the device can accurately detect gait variables, a finding demonstrated for the first time in this study.

Further research and extensive calibration of both devices may improve agreement levels. However, controlling the insertion angle of the investigational device is challenging, as this depends on clinical decisions made by physicians who consider the patient's anatomy, body habitus, cosmetic preferences, and the primary function of the ILR to obtain cardiac data.

SECTION THREE: CLINICAL INVESTIGATION

Chapter 10: Introduction

A number of cardiovascular disorders are associated with falls including arrhythmia and reflex syncope[22,68,94,258], as evidenced by my systematic review and meta-analysis above[22]. The pathophysiological mechanisms that predispose older adults with cardiovascular disease to falls are complex. Mechanisms such as OH, tachyarrhythmia and bradyarrhythmia may cause falls through frank syncope or alternatively, transient disruption of gait and balance through transient cerebral hypoperfusion without frank syncope. An ILR can be diagnostic in these circumstances if symptom-rhythm correlation is achieved. Therefore, an ILR can also out-rule arrhythmia as a cause of falls if falls are occurring in the absence of arrhythmia. Certain arrhythmias, if detected, can be treated with either medications or more definitively with pacemaker insertion.

The aim of the study was to add to the growing evidence base assessing the extent to which arrhythmia contributes to unexplained falls and also to assess if rates of falls declined with ILR implantation, in a similar manner to syncope[271].

The investigational device collected background cardiovascular data and activity levels (including posture change) to be discussed and analysed in Section 4.

Chapter 11: Methods

11.1 Study Design

A prospective, single centre, proof of concept study of use of ILR in unexplained fallers was undertaken. Eligible participants were >50 years and were referred to a specialised falls unit with at least 1 unexplained fall and a history of another fall or syncope within the previous 3 years. Participants were excluded if they were unable or unwilling to perform the study protocol requirements, if they were cognitively impaired (Mini Mental State Exam[338] score </= 20), currently had implanted cardiac device (pacemaker, ILR, defibrillator), a known intolerance to any constituents of ILR, a life expectancy <12months or any significant disease or disorder that may either put the participants at risk because of participation in the study. A fall was defined as "*an event which results in a person coming to rest inadvertently on the ground or floor or other lower level*"[20]. An "unexplained fall" is a fall for

which no cause has been identified following a multifactorial assessment that "cannot be explained by a failure to adapt to an environmental hazard or by any other gait or balance abnormality"[21]

A cardiovascular assessment was performed on all potentially eligible participants in line with European Society of Cardiology Syncope (ESC) guidelines. This included a 12-lead surface electrocardiogram (ECG), cardiac auscultation, an active stand comprising of phasic blood pressure and heart rate measurement on changing posture from supine (following a 10-minute rest period) to upright for 3 minutes. Further investigations such as a head up tilt table test and/or carotid sinus massage were performed when indicated.[23] If it was deemed that the participant required an ILR to investigate unexplained falls, potential recruitment to the study was discussed and they were provided with the participant information leaflet (PIL).

Participants provided written informed consent following detailed education including reading the PIL (see Appendix C for PIL and Informed Consent form). Each participant was followed for 12 months. During this period, participants were asked to complete 3 monthly falls diaries, accept a phone call from the study team every 2-3 weeks to enquire about falls or other issues. Finally, prior to commencing the study, each participant would have an implantable cardiac monitor embedded with a triaxial accelerometer placed.

11.2 Data Collection

Data generated for this clinical investigation was collected through 2 primary sources: clinical assessments on a three-monthly basis and data generated through the ILR (accelerometer data and cardiac data).

11.21 Clinical Assessments

A comprehensive set of tests for common fall risk factors was performed in the Falls and Syncope Unit (FASU) at St James's Hospital.

The complete set of data and assessments collected at study baseline was as follows:

1. Demographics (gender, age)
2. Mini Mental State Exam (MMSE): to ensure baseline cognitive state
3. Medical history

4. Medications
5. Frailty assessment: using the SHARE Frailty Instrument
6. Physical exam
7. Timed Up and Go Test (TUG)
8. Gait assessment: this assessment was performed with the GAITRite system. This is an electronic measurement system with a 4.6m computerized mat that provides objective and quantitative gait and balance assessment data including walking speed, cadence, step time, step length, double support time, swing and stance.
9. Falls history and details (time of day of fall, injury, loss of consciousness, prodrome, etc.)

11.22 Follow Up Assessments.

Participants were followed up for a period of 12 months, with visits to site occurring at months 3, 6, 9 and 12 for full clinical assessment. During each of these in-clinic follow up visits, the same assessments performed at baseline were repeated (except for demographic information and the Mini Mental State Exam). In addition, participants underwent an additional gait assessment on the GaitRITE. Participants were asked to walk 6 lengths of the sensored mat while wearing an external Holter and activating the Reveal LINQ™ Holter mode allowing for all the axes of the triaxial accelerometer to be activated.

11.23 Implantable Loop Recorder

Consented participants underwent ILR implantation under aseptic conditions with the supervision of a consultant cardiologist. All ILRs were inserted in the left parasternal region. Participants were advised to activate the device in the event of a fall, syncopal event, dizzy spell or if they experienced palpitations. ECG data was downloaded daily and interpreted using the CARELINK system. Any cardiac arrhythmias detected during the study duration were treated as appropriate.

11.24 Falls Records

At baseline, participants were provided with fall diaries to prospectively collect details of any falls and symptoms (dizziness, unsteadiness, near faints and near falls or falls). These were

collected at follow up visits. Regular biweekly telephone contact was also undertaken to optimise compliance and collect information on fall events.

Whenever a patient manually activated the Reveal LINQ™ following a fall or due to symptoms, each stored potential arrhythmic event was analysed and appropriate interventions took place, per standard clinical practice.

Details of any fall events were collected, including prodromal symptoms, presence of transient loss of consciousness, injuries sustained and whether medical attention was sought. When a fall was identified, the information was added to a falls log. The cardiac data was also assessed to see if there was an arrhythmia at the time of the fall.

11.25 Implantable Loop Recorder Data

Data generated through the Reveal LINQ™ Falls Prediction System was transmitted through the Medtronic's MyCareLink™ monitoring system and the standard cardiac parameters of the device were accessible in FASU via the secure CareLink™ network as per standard care.

Standard Cardiac Data

Cardiac data was generated in 2 ways. Firstly, the ILR would pick up automated recordings in the event of an arrhythmia this would be reviewed retrospectively. Secondly, in the event of a participant experiencing symptoms (fall, blackout, dizzy spells or palpitations) the participant would use the patient activator to essentially put a time stamp on the ECG readings allowing for a retrospective analysis of the reading in order to correlate patient symptoms to the cardiac rhythm. The study team would then analyse the ECG data in conjunction with a discussion with the patient to clarify the circumstances of the activation.

Investigational Data

The data generated from the investigational sensor features was only accessible in the CareLink™ network by the Medtronic research team and was not available clinically. The Medtronic R&D team converted the raw investigational data generated by the Reveal LINQ™ FP Research System from a proprietary format into .mat and .json format for the purposes of this clinical investigation.

The processed data (also referred to as converted data) was made available to the study team every week through Microsoft Teams file storage. Data was subsequently managed and extracted from Matlab to Excel databases, as well as being subjected to signal processing for analysis. The parameters that were collected and considered for the study are listed and described in Table 4 below.

Data variable name	Description
Parameters from Investigational Software	
Active minutes	Sum of the number of 1 minute activity counts that are greater than an Activity Threshold (hourly data)
Posture change count	Number of posture changes (Z axis only) in 5 minutes
Average activity count	Average of 1 minute activity counts (Z-Axis only) over 5 minutes
RR interval median	The median RR interval taken from the RR interval histogram (over 5 minutes)
Accelerometer x axis	Raw accelerometer data from the x-axis
Accelerometer y axis	Raw accelerometer data from the y-axis
Accelerometer z axis	Raw accelerometer data from the z-axis
Day and night average ventricular rate	Day and night heart rate. Day is defined as the 12-hour period between 8:00 AM and 8:00 PM, and night as the4-hour period between 12:00 AM and 4:00 AM as indicated with the Reveal LINQ™ clock.
Activity per day	Measurement for activities of daily life, including walking at a slow pace. A single axis is used to capture patient motion as an electric signal. The number of minutes a patient is active per day is counted, where a minute is considered active if a threshold is reached that incorporates both the number and magnitude of deflections in the accelerometer signal.
Heart rate variability	The device measures each ventricular interval and calculates the median ventricular interval every 5 minutes. It then calculates a variability value (in milliseconds) for each day.

Table 4. ILR parameters collected for study.

The investigational data collected was used to determine potential early physiological changes that may herald a fall, this is discussed in Section 4 below.

11.3 Outcomes

The primary outcome of interest in this section was to assess the relationship between cardiac arrhythmia and falls in unexplained fallers, particularly at the time of a fall.

The secondary outcome measures were a) other significant arrhythmias and b) falls rates following implantation.

Chapter 12: Results

12.1 Baseline Characteristics

The mean age of this cohort was 68 (±9.3). 19 participants (63.3%) were female, while 22 had a history of cardiovascular disease (defined as at least one cardiovascular condition present in medical history (e.g., ischaemic and valvular heart diseases, or hypertension)). 7 participants were deemed to have a high falls risk at baseline based on their Timed Up and Go test (>13.5 seconds)[300]. 8 participants were adjudged to be frail and 4 pre-frail according to the SHARE Frailty Instrument[339].

16 (53.3%) participants had polypharmacy (5 medications or more). According to Body Mass Index (BMI), only 6 participants were a normal weight. 1 participant was noted to be underweight, while the remaining 23 participants were noted to be overweight or obese (11 and 12 participants respectively). 2 participants withdrew in the first few months of the study as they were unable and unwilling to follow study protocols. One participant passed away from an unrelated illness.

Variables at baseline assessment		Participants (N=30)
Age, Mean (SD)		68.0 (±9.3)
Sex, n (%)	Females	19 (63.3%)
	Males	11 (36.7%)
History of cardiovascular conditions, n (%) *	Yes	23 (76.7%)
	No	7 (23.3%)
BMI category, n (%)	Underweight (BMI below 18.5)	1 (3.3%)
	Normal (BMI between 18.5 to 24.9)	6 (20.0%)
	Overweight (BMI between 25 to 29.9)	11 (36.7%)
	Obese (BMI above 30)	12 (40.0%)
Polypharmacy, n (%) **	Yes	16 (53.3%)
	No	14 (46.7%)
Frailty status, n (%) †	Non-frail	18 (60.0%)
	Pre-frail	4 (13.3%)
	Frail	8 (26.7%)
Fall risk, n (%) ††	Yes	7 (23.3%)
	No	23 (76.7%)

Table 5. Baseline participant variables

12.2 Timeline of Notable Events

The study began on the 14th of December 2020 and ended on the 28th of November 2022. 22 participants were followed up until the final assessment visit (12th month) and completed the study. The following participants were withdrawn early from the investigation:

- FINV009, FINV013, FINV017, FINV021, FINV030: significant arrhythmias were detected necessitating pacemaker implantation. ILR's were removed. **NOTE: FINV = Falls Investigation (participant number)**
- FINV001: loop recorder was explanted and participant withdrawn from the study due to mental health issues.
- FINV023: participant was admitted to hospital due to Covid-19 on 23rd December 2021. Participant passed away on the 14th of January 2022 due to Covid 19 complications.
- FINV025: withdrawn due to lack of adherence to study protocol.

In some cases, assessments were not conducted exactly three months apart, to accommodate for participants needs and availability. This was noted as a protocol deviation.

12.3 Arrhythmia Detection

16 participants (57%) demonstrated significant arrhythmia on ILR. Arrhythmia detection occurred at a mean of 101.6 days (SD+/-82.37, range 1-290 days).

Participants with significant arrhythmia N=16/28 (63%)	**Mean age +/- SD**	**Description of arrhythmia ***	**Issue Classification**
4 (14%)	67+/- 10.11	Asystole RR interval pause> 3 seconds	1
4(14%)	64+/-10.36	Bradycardia < 40 bpm for >10 sec	2
9(32%)	67.5+/-12.42	SVT/AF >140bpmfor 15 secs	4

Table 6. Arrhythmia detection using ISSUE Criteria *Note: Does not account for every arrhythmia detected, rather the first significant arrhythmia detected per participant.

During the 12 month follow up period 9 participants (32%) required intervention due to arrhythmia. 5 participants (18%) required pacemaker insertion with a mean age of 69. The mean time to pacing event was 99.4 days (SD+/-77.06, range 9-204). Significant arrhythmias captured during the study are summarised according to ISSUE classification[340] in table 6.

12.4 Falls and Arrhythmia

13 participants (46%) experienced at least one fall during the follow up period. Seven of these participants had a significant arrhythmia detected at some point of the study while the remaining 6 fallers had no arrhythmia detected. In total, there were 32 individual reported fall events during the course of the study. For 24 of these falls the investigators had sufficient information provided to identify the precise cardiac rhythm at the time at the time of the fall event. Only three falls had a significant arrhythmia at the time of a fall event: one asystole, one bradycardia and one tachycardia.

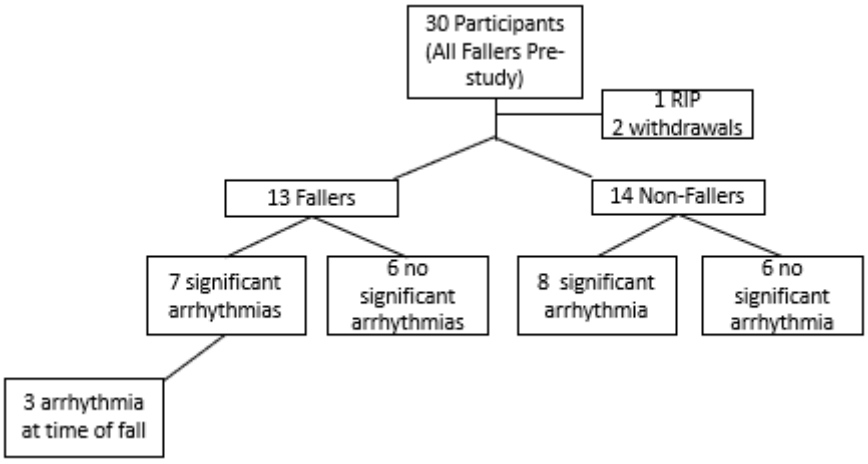


Figure 19. Study flow diagram: Falls and Arrhythmia.

12.5 Falls and ILR Insertion

The number of falls in the year prior to ILR insertion experienced by the cohort was 77 (2.85 falls per participant). These data exclude the participant who passed away and the 2 withdrawals. For the year following ILR insertion there was a total of 32 falls (1.18 falls per participant). See figure 20 below.

11/27 participants had some form of medical intervention initiated by the study team during the study in an effort to reduce falls. 5 participants required PPMs, 2 required medication to control arrhythmia, 3 required medications to elevate blood pressure and 1

participant ceased antiepileptic medication. Of the remaining 16 participants who had no meaningful interventions, 15 had fewer fall events in the year following ILR implantation. See histogram below for graphical depiction of falls rate reduction.

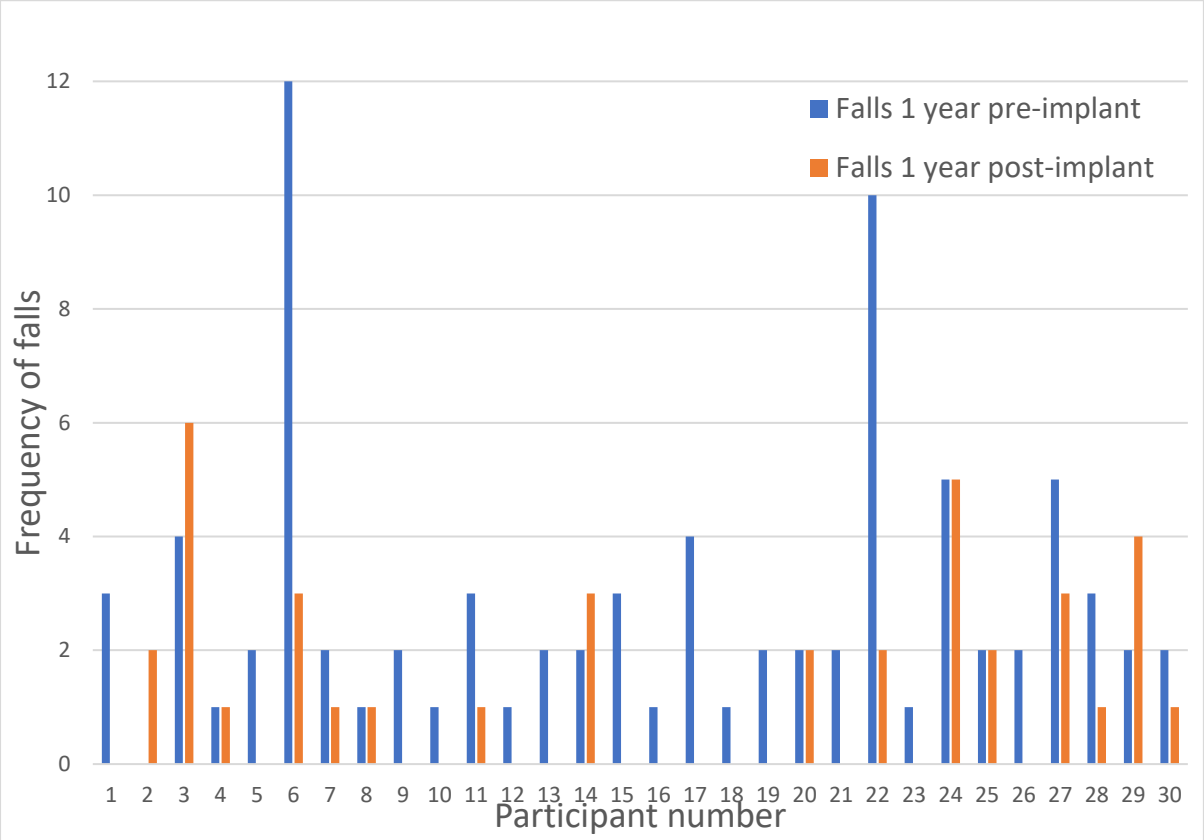


Figure 20. Falls pre and post ILR implant.

Chapter 13: Discussion

This study demonstrates the value of ILRs in unexplained fallers. All participants in this study were recruited following a detailed cardiovascular assessment in a specialised falls and syncope unit where no clear cause of their falls was identified. The diagnostic yield of participants requiring pacemaker insertion is similar to previous work[49].

ILRs have proven to be a revolutionary tool in syncope management. The ability to continuously monitor cardiac activity over extended periods has changed the nature of our understanding and management of syncope. The utility of ILR in falls diagnosis has also become apparent in recent years [289,290]. This has led to both the European Society of Cardiology and the recently published World Falls Guidelines advocating for ILR use in cases of unexplained falls[21,23].

There is a well-established overlap between falls and syncope[50,52,53]. This is a complex relationship as it can be difficult to distinguish between the two based on history alone[53]. This is partly due to the amnesia that is often associated with syncope and also due to the unwitnessed nature of many falls affecting older people[54]. Of note, syncopal events have a significant injury burden with 33% of patients with VVS reporting injuries, 4-13.8% of these being classified as severe (fractures, burns or joint damage)[48,55].

The results of this study demonstrate a high arrhythmia burden amongst this group of unexplained fallers with over half the group having a significant arrhythmia detected during the 1 year follow up. Most importantly the study demonstrates that an ILR was responsible for diagnosing a potentially modifiable risk factor for falls in 1/3 of participants. These were then treated with either a pacemakers or anti-arrhythmic medications which should reduce their falls risk.

This trial adds to the literature on arrhythmia and falls and has several strengths. The sample consisted of “unexplained fallers” meaning that conditions like orthostatic hypotension and valvular heart disease as the cause of falls was out ruled based on detailed cardiovascular assessment prior to enrolment. Falls diaries were used to ensure the most accurate information surrounding fall events could be captured. The falls diaries were supplemented by bi-weekly telephone calls by the study team to extract as much precise temporal information about fall events as possible.

The main weakness of this study is the limited number of participants, meaning that it is underpowered to identify statistical associations. The patient cohort was also quite heterogenous with varying ages, comorbidity profiles and frailty states accounted for. It would perhaps be more instructive to focus on an older frailer cohort to identify the group at highest risk.

An interesting observation is that participants implanted with an ILR and no medical or cardiovascular interventions tended to have less falls following implantation. Early ILR research appears to show a decline in syncope rates and an improvement in quality of life for people with ILRs inserted[272,341]. More recently a paper published in 2021 demonstrated a survival benefit in patients with ILR insertion for recurrent unexplained syncope compared to an age and comorbidity matched cohort[342]. Although a Cochrane review published in 2016 did not demonstrate a mortality or quality of life benefit, it did show higher rates of diagnosis and a reduction in syncope recurrence compared to control groups[295].

Similarly, a body of research examining the utility of pacemaker implantation to reduce falls in patients with carotid sinus hypersensitivity demonstrated efficacy in decreasing falls[232-234]. All three studies demonstrated a reduction in falls following the implantation of a device, including an active dual-chamber pacemaker, an inactive (temporarily switched off) dual chamber pacemaker or an ILR (subcutaneous device for monitoring heart rate and rhythm). While these studies were underpowered, they suggest that there may be a neuropsychological contribution to falls associated with certain falls. This area certainly warrants further exploration.

Chapter 14: Conclusions

ILRs are proving to be an important tool in the diagnosis and management of unexplained falls by providing physicians with a direct correlation between symptoms and cardiac activity. This data can then be used to identify abnormalities or irregularities responsible for the fall, syncopal event or symptoms, thereby guiding therapeutic approaches and preventing future occurrences.

One of the key advantages of ILRs is their ability to capture asymptomatic or infrequent arrhythmias that may be missed during conventional diagnostic methods. By continuously monitoring the heart, ILRs can detect and record transient arrhythmias that may occur without presenting symptoms. This capability is particularly valuable in patients who experience infrequent or unexplained falls or syncope, as it helps to diagnose underlying rhythm disturbances that would otherwise remain undetected. Thus, the study further strengthens the case for prolonged cardiac monitoring in the case of unexplained fallers.

SECTION FOUR: EARLY PHYSIOLOGICAL PREDICTORS

Chapter 14: Introduction

This section addresses the possibility of using changes in physiological parameters to potentially predict falls. The investigational device can record a number of physiological parameters using specialised software developed by Medtronic. This software allows for recording of accelerometer data, posture change count (based on the z-axis accelerometer values), temperature, activity, RR interval and R-wave amplitude. This software was added to the device at the commencement of the study using a programmer device and removed once the participant exited the study.

Using the data generated, I retrospectively analysed all fall events to evaluate if there were any consistent changes to a number of physiological parameters. The specific physiological parameters evaluated included heart rate, heart rate variability, activity levels, and posture change counts.

I hypothesised that several potential physiological changes could increase an individual's risk of falling. For example, in the context of an infection in an older frail individual. This person may have a urinary tract infection (UTI), without clearly demonstrating the classic features of a UTI (urinary frequency, painful urination). This small infection may not be overly evident to the person, but the presence of a bacterial infection may be enough to disrupt the delicate ecosystem of a frail older person. This may manifest in marginal changes in level of alertness, gait and balance function. Biophysiologically, it could be expected to observe a decrease in activity levels, a slight increase in heart rate and a decrease in heart rate variability (HRV). Ultimately in the presence of this external stressor the person may fall due to several acquired subtle impairments to their physiology.

Using a similar logic, I assessed "nocturnal restlessness". I hypothesised here that in the event that a person did not have a good night's sleep that this may lead to cardiovascular instability and a lack of physiological resilience to overcome gait and balance issues or other stressors. This could lead to an increased likelihood of falling.

Over the following pages I will outline the processes and present the exploratory data generated. The results and discussion section have been combined.

Chapter 15: Methods

15.1 An Exploration (plotting and data visualization) of Cardiac and Gait Parameters

The following section outlines the many approaches taken to uncover physiological patterns that may herald a fall event. This process was exploratory in nature.

Data gathered with the ILR was investigated to assess whether changes in heart rhythm and/or activity per day could be observed in time periods preceding a fall. First, histograms of activity per day and cardiac variables from the ILR were produced to assess the normal distribution of the data (Appendix D) . Possible relationships or patterns between HRV, heart rate (day and night), activity per day and falls were explored in a number of ways:

- Plotting variables before and after the time of falls
- Comparing values on the day of the fall with average values
- Comparing values on the day prior to the fall with the week before the fall

Line graphs for heart rate variability and activity per day were plotted for the week before a fall and three days following the fall. Data for all captured falls are included in Appendix E. A selection of results are presented and described in chapter 16 below.

Scatterplots of heart rate variability and activity per day were produced taking a time window extending three weeks before and a week after a fall. Data for all captured falls are included in Appendix F with selected examples in chapter 16 below.

Similarly, a number of comparisons were made with the purpose of identifying any patterns of heart rate leading to a fall, as well as any unusual differences that could arise between day and night heart rate values. Average day and night heart rate values corresponding to the days when falls occurred were extracted and compared with the corresponding total averages of day and night heart rate from each faller accordingly (Figure 25). Additionally, average heart rate of the day (and night) prior to a fall was contrasted with the average of the week (day and night) prior to the fall (Figure 26).

For each faller the HRV value on the day of the fall was compared with the total average of HRV values for the entire period of data collection (Figure 27). Alternatively, a comparison between average HRV values between the previous day of a fall and previous week of a fall was also conducted (Figure 28).

15.2 Hypothesis Tests

For each of the 32 fall events recorded during the study, heart rate, heart rate variability, activity levels and posture change counts were calculated for each fall. This data formed the basis of the “subclinical infection” and “nocturnal restlessness” hypotheses.

15.3 Calculation of Variables

The Investigational software takes the RR Median interval from the RR interval (over 5 minutes), therefore producing 12 values per hour, every hour. Heart rate variability is calculated by the investigational device in the following manner. The device measures each ventricular interval and calculates the median ventricular interval every 5 minutes. It then calculates a variability value (in milliseconds) for each day.

The patient activity level measurements were designed to assess activities of daily life in patients, including walking at a slow pace. A single axis from the embedded accelerometer was used to capture patient motion as an electric signal. The number of minutes the patient was active per day was counted, where a minute was considered active if a threshold is reached that incorporates both the number and magnitude of deflections in the accelerometer signal up to a maximum of 1440 max active minutes. This approach has been validated and used in prior research [334,335,343]

Chapter 16: Results and Discussion

The novel nature of this element of the study made interpretation of data quite challenging. Given the lack of published data on this topic, we as a study team used common sense and clinical acumen to consider what were ultimately some arbitrary concepts and hypotheses.

I examined the data in a number of different ways including visualising trends and patterns in the data. The most pertinent findings are included in this thesis, both in the results section and in the and in the appendix.

Firstly, histograms of cardiac variables showed these parameters were in general normally distributed or in some cases slightly positively skewed, and these distributions were more evident for parameters corresponding to participants with a full dataset (Appendix D).

On review of the line graphs of HRV activity and falls, no clear consistent relationships were evident. See Appendix E for all falls. We hypothesised that activity and HRV would decrease in advance of fall. For example, in the context of a subclinical infection, we could expect a decrease in activity and HRV leading up to a fall event as per the sub clinical infection hypothesis. This did not prove to be the case as evidenced by the wide variety of HRV and activity patterns. There was no clear relationship evident evidenced in any metrics and the falls.

However, there are some interesting figures to elaborate on with some clinical background history, for example, Figure 21. Following this fall there was a marked drop off in activity levels, this fall led to a significant injury that required surgical intervention and a period of rehabilitation.

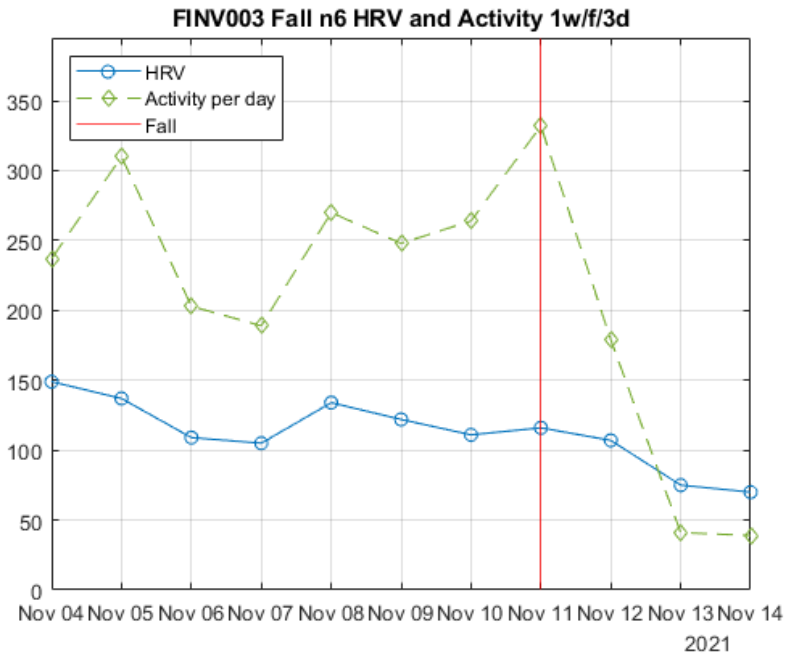


Figure 21. FINV 003 Fall 6. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall.

The x axis represents the date, while the y axis represents HRV (milliseconds) and activity per day (minutes). The solid blue line represents HRV, the dashed green line represents activity per day and the vertical red line represents the fall event.

Similarly, note the very low activity levels in Figure 22. This was the oldest most frail participant in the cohort and the lack of physical activity day to day is quite striking.

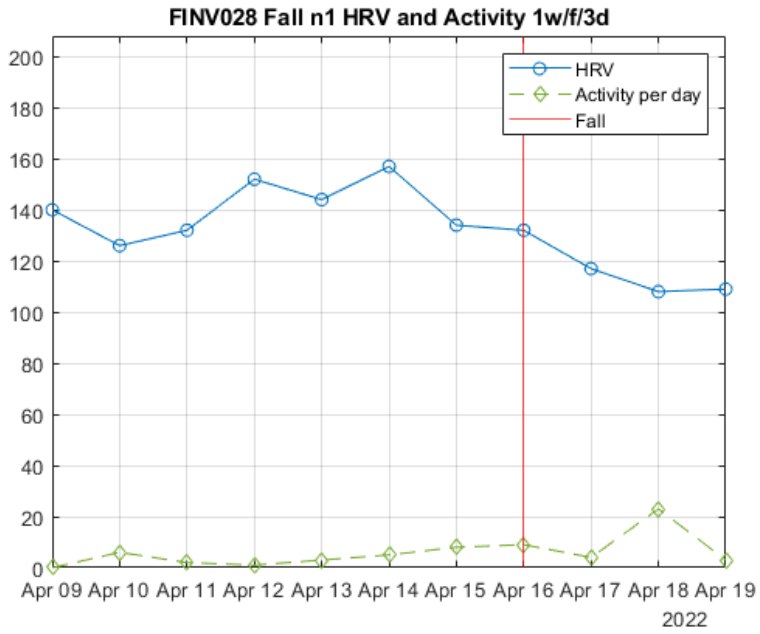


Figure 22 . FINV028 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

The x axis represents the date, while the y axis represents HRV (milliseconds) and activity per day (minutes). The solid blue line represents HRV, the dashed green line represents activity per day and the vertical red line represents the fall event.

Regarding the scatterplots of HRV and activity (Appendix F.), no patterns were discerned during the three weeks before the fall and a week after the fall. The lack of homogeneity in the results can be highlighted by considering some of the the following examples.

Figure 23 demonstrates a fall when HRV and activity levels are at their highest.

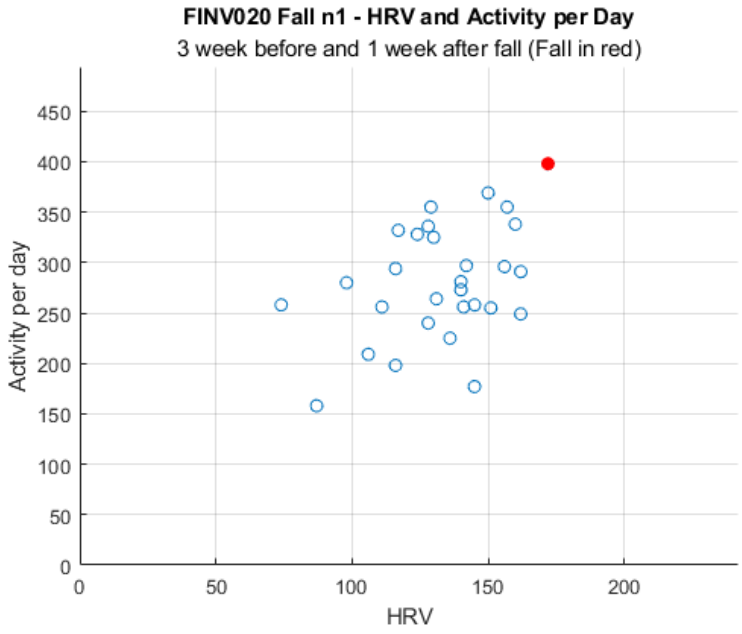


Figure 23. FINV020 Fall 1. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

The x axis represents heart rate variability (HRV in milliseconds) , while the y axis represents activity per day (in minutes). The circles represent days with the solid red circle representing the fall day.

The same participant (Figure 24) also suffered a fall with lower HRV and more moderate activity levels. Overall, there was no clear relationship between HRV and falls.

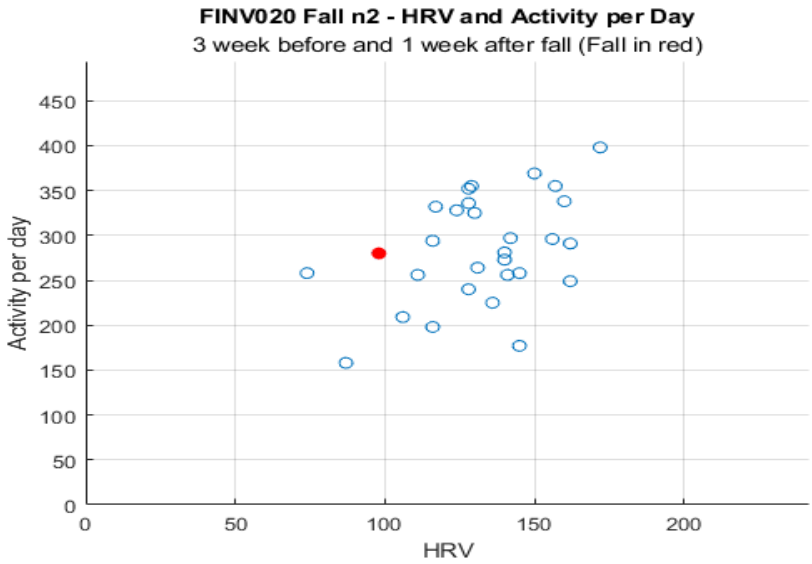


Figure 24. FINV020 Fall 2. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

The x axis represents heart rate variability (HRV in milliseconds) , while the y axis represents activity per day (in minutes). The circles represent days with the solid red circle representing the fall day.

Average day and night heart rate values corresponding to the days when falls occurred were plotted against the corresponding total averages of day and night heart rate from each participant accordingly (total averages encompassed all daily heart rate values available for the given participant). Results are plotted in Figure 25. No clear pattern is evident that may predict a fall event.

Another comparison was explored by plotting heart rate data, this time between the average heart rate of the day (and night) previous to a fall, and the average of the week (day and night) previous to the fall. Results are shown in Figure 26. No differences were apparent between the values compared.

Average HRV on the day of the fall was plotted against the total average HRV during the entire period of data collection (Figure 27). A comparison between average HRV values between the previous day of a fall and previous week of a fall was also conducted (Figure 28). Again, no differences were apparent.

Daytime and Nocturnal heart rate analysis and Falls

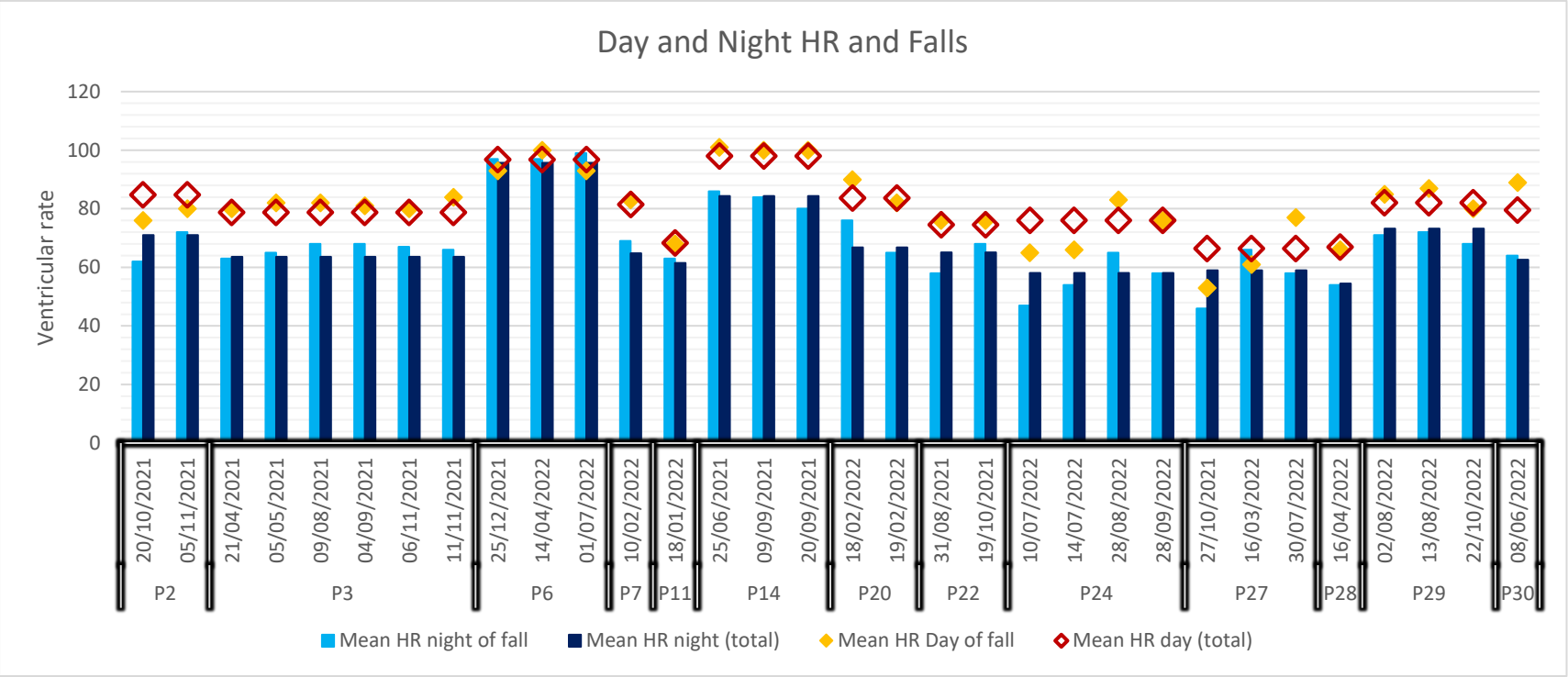


Figure 25. Day and Night heart rate and Falls (X axis = P=participant number. Each date represents a fall).

Each pair of bars and diamonds represent the heart rate values for night and day respectively, and correspond to a fall, with the participant and date of fall on the x axis.

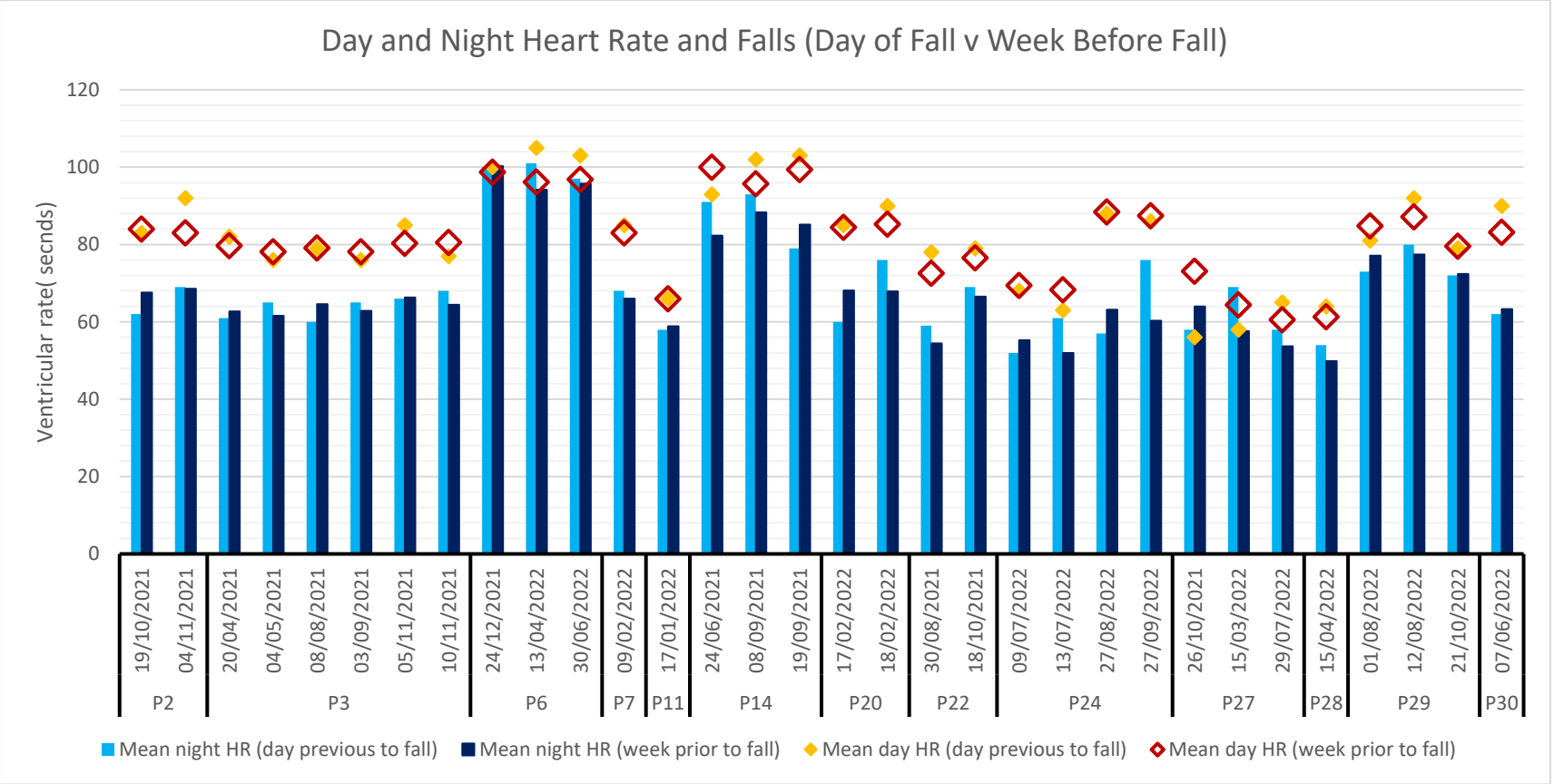


Figure 26. Day and Night heart rate and Falls (Day and Week Before Fall). (X axis = P=participant number. Each date represents a fall).

Each pair of bars and diamonds represent the heart rate values for night and day respectively, and correspond to a fall, with the participant and date of fall on the x axis.

Heart Rate Variability and Falls

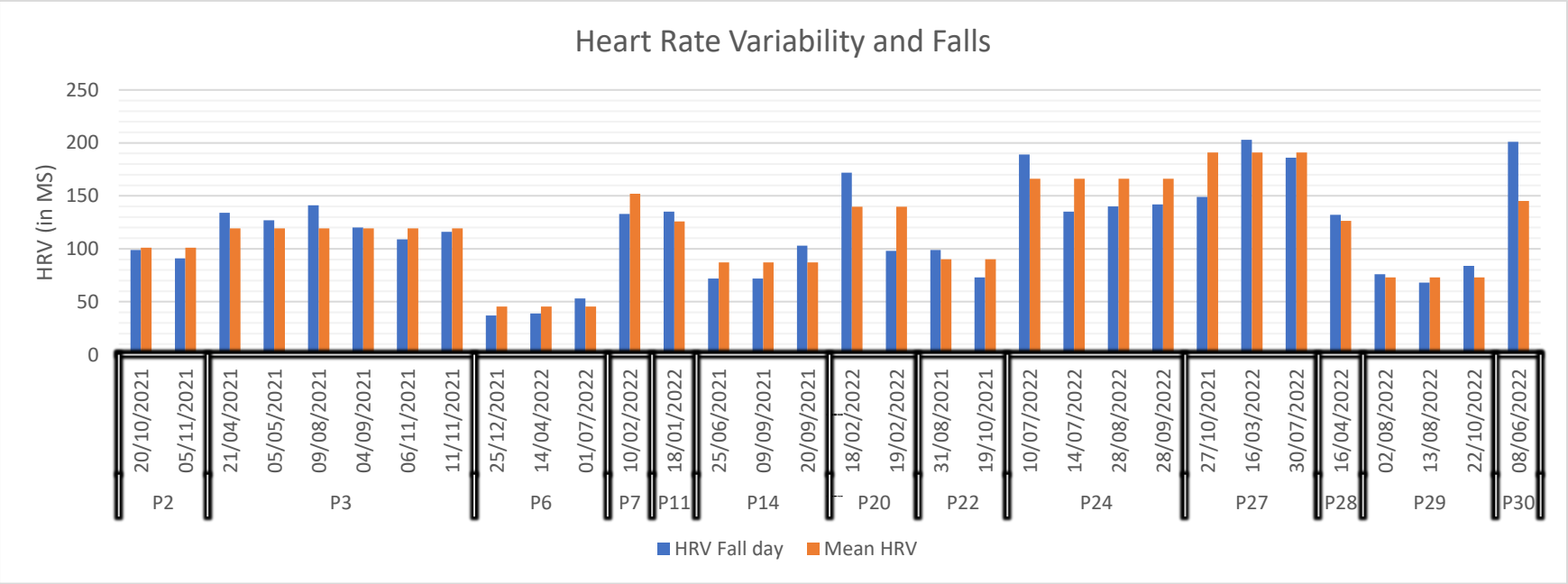


Figure 27. Heart rate Variability and Falls (X axis = P=participant number. Each date represents a fall)

Heart Rate Variability and Falls

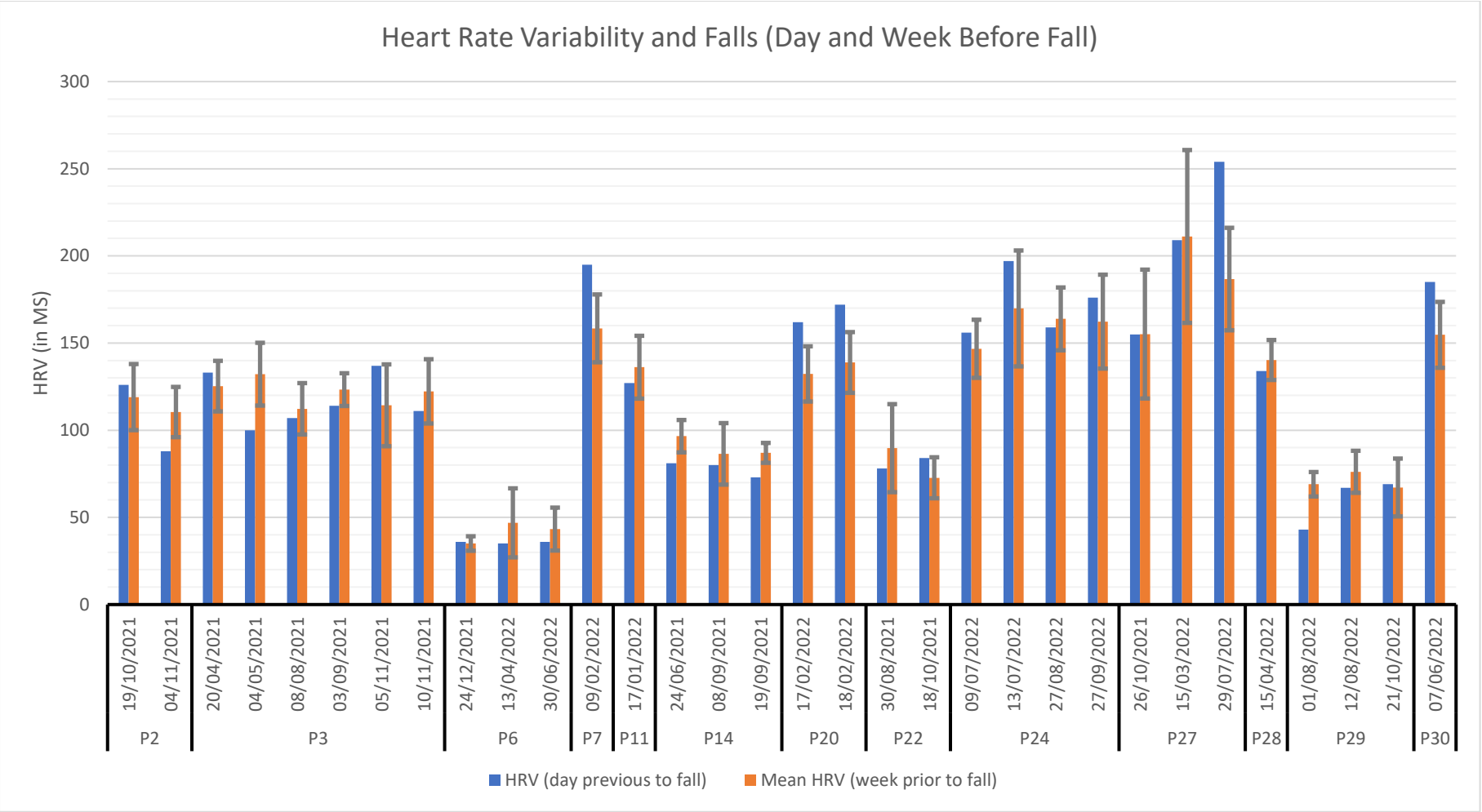


Figure 28. Heart rate Variability and Falls (Day and Week Before Fall). (X axis = P=participant number. Each date represents a fall

Sub Clinical Infection Hypothesis

I visually analysed all fall events, and no pattern was identified in the fallers that fit with the hypothesis. This was extensively tested on all falls by the study team. No reproducible pattern was detected on analysing these metrics. All line graphs and scatterplots are included in the results section in the Appendix E and F respectively.

Nocturnal Restlessness Hypothesis

This hypothesis considered the effect that sleep quality might have on increasing the risk of falls. Poor sleep quality was determined by decreased HRV and increased heart rate as well as increased activity levels and posture change count on the night before a fall event. Based on the analysis outlined below, nocturnal restlessness was not predictive of falls.

Figure 29 and Table 7 represent the results. Table 7 details the numerical differences between both data points. Figure 29 offers a more granular overview. From visual inspection of Figure 29, no consistent pattern is present.

	Baseline	Fall	Δ(Fall-Baseline)
Activity	42.1 ± 4.9	41.5 ± 4.4	-0.6 ± 4.6
Posture Changes (per hour)	6.6 ± 3.6	7.2 ±3.5	0.5 ± 3.1
Heart Rate [bpm]	67.5 ± 12.2	67.4 ± 12.9	-0.1 ± 6.6
HRV [ms]	62.6 ± 29.2	62.5 ± 33.5	-0.1 ± 24.8

Table 7. Cardiac and activity values at baseline (average of 4 days in preceding month), day of falls and difference.

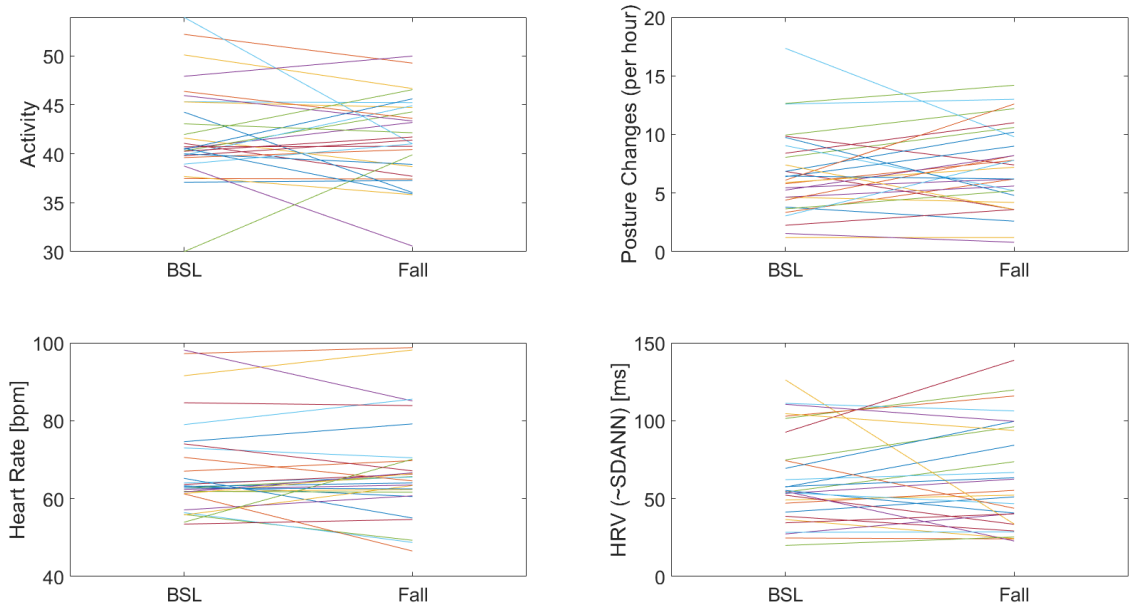


Figure 29. Nocturnal Restlessness hypothesis

Each coloured line represents a fall. Each line has 2 data points. BSL represents the baseline calculated as the average of 4 days in the preceding month. The endpoint on the right of each line represents the fall event. The coloured lines therefore represent the difference between values at BSL taken as the average of 4 days prior to fall and the values on fall day in cardiac and activity parameters.

Our use of these hypotheses makes theoretical sense to me as a physician however they have not been supported by the data. It is possible that similar methods may prove more fruitful if a larger sample size was used and a more homogonous patient cohort, particularly an older frailer group.

A note on battery life: Similar to pre-trial testing undertaken by Medtronic, the use of the investigational software did not appear to have a meaningful impact on battery life.

Chapter 17: Conclusion

An observational analysis of the investigational data including heart rate, HRV, posture changes and activity levels and how these metrics are related to falls did not demonstrate any consistent associations in this small cohort. Furthermore, postulations including the sub clinical infection hypothesis and the nocturnal restlessness hypothesis also did not demonstrate any consistent relationship to fall events. This may have been because the study participants were a heterogenous group in terms of age, co-morbidity profile, and functional status. The sample size was also small (n=30), meaning that the study was always likely to be underpowered. Of note, almost all data analysis was univariate, i.e., looking at the association between a single variable and the occurrence of falls, except for the explorative analysis of HRV and activity (appendix E and F). As falls are usually multifactorial, a multivariate analysis may be more successful in predicting falls. As the number of usable events (falls) was relatively small in this study, however, this approach was not pursued due to the risk of overfitting.

This element of the study was completely novel and this research highlights the potential of this technology and perhaps guide future research.

SECTION FIVE: OVERALL CONCLUSIONS

Chapter 18: Summary Conclusions

Section 1 outlined the current state of the evidence in falls and technological tech. The recently published systematic review and meta-analysis[22] which was used in the synthesis of the world falls guidelines[21] demonstrates the importance of a comprehensive cardiovascular falls risk assessment in all unexplained fallers. The remainder of this section introduced the potential new technology available to clinicians in an attempt to measure different variables that may increase falls risks.

In Section 2, I sought to better understand the potential of embedding a triaxial accelerometer within an ILR to assess gait and activity levels. Based on healthy volunteer data, for analysing activity and posture change counts the orientation that the study device was implanted has little bearing on the readings. However, device orientation does have a bearing on gait parameters. I have also confirmed my suspicion that a "posture change" is not strictly measuring changes in the participants posture as a change can be triggered by supine rotational movements, such as an individual rolling over in bed. When both posture change count and activity levels are examined in combination, a better understanding of a participant's actual activity can be gained. The practical applications of my learnings from this process have proven quite useful, for example, if posture changes are registered but activity counts remain < 50, it is very unlikely that ambulation has taken place. The overall protocol helped to inform and characterise some of my hypothesis when considering nocturnal activity and behaviours.

Regarding gait, the acquisition of data from the Reveal LINQ™ embedded accelerometer is a promising tool for monitoring of gait performance. Step times/stride times can be extracted from the signal in the anterior-posterior axis, where the axis reasonably aligns with the anatomical direction. The patient cohort analysed in this study had a wide variation in the orientation of the Reveal LINQ™ as implanted. As such single axis analysis is not reliable for automated extraction of step times.

In Section 3, with respect to cardiovascular outcomes, the clinical investigation builds on prior research demonstrating the benefit of ILR implantation in the detection of arrhythmia in unexplained falls[49]. An interesting finding is the apparent reduction in overall falls in the year following implantation of ILR compared to the year leading up to implantation. This is

similar to previous published research demonstrating a reduction in syncope following implantation of an ILR[272,295]. This is a finding worthy of further investigation.

In section 4 I sought to identify a biophysiological profile that may be associated with falls. Unfortunately, this did not prove to be feasible. However, I have demonstrated that performing a clinical investigation of this type is feasible and this may guide directions for future research.

This research study has several strengths. Firstly, the cardiovascular outcomes are important in terms of strengthening the case for physicians to target cardiovascular causes for unexplained falls, particularly using prolonged cardiac monitoring.

I have demonstrated that implantation of an ILR embedded within a triaxial accelerometer is feasible and potentially useful in fallers. Activity testing has demonstrated how to interpret activity levels and what may constitute posture change counts. I have shown some promising early findings in using the accelerometer data to measure well established spatiotemporal gait variables such as stride length and gait variability albeit in a controlled clinical environment. Further, the accelerometer does not appear to have had any meaningful negative implications on battery longevity at this point nor the ability to record cardiac data.

There were challenges encountered prior to the commencement of the study. The Covid 19 global pandemic made for a challenging work environment. Non-essential activities were cancelled in hospital settings meaning that research activities were curtailed making it impossible to commence the study. Once restrictions were eased there was still some trepidation about coming to hospital appointments and recruiting patients to the clinical trial. There was also a significant staff turnover on the study team.

During the study there were a number of challenges. Firstly, there was a relatively high attrition rate with only 22/30 making it to the final 12-month assessment. One participant passed away, two were withdrawn and five had pacemakers inserted, although pacemaker insertion is an expected outcome, hence the recommendation by the ESC to implant ILRs into unexplained fallers.

Precisely identifying the timing of falls was also a challenge. Compliance with falls diaries was poor with only 9/22 participants who made it to the final assessment completing at least 3/4 diaries. The research team had accounted for such issues by incorporating 2-3 weekly telephone contact with all participants in an effort to identify falls and to document timings, but the times given tended to be approximations. This became a challenge during the data analysis phase. We overcame this challenge by analysing the data in several ways, not only considering the apparent precise time of a fall but also by reviewing the biophysiological profile on the night before and days leading up to a fall event.

While data analysis was ongoing throughout the study, once the final participant attended for their final visit, my focus was fully directed toward data analysis. A number of issues made the data analysis quite challenging. Firstly, this is a novel concept and to my knowledge this is the first time that an implantable loop recorder with an embedded triaxial accelerometer has been implanted into participants with a view to capturing accelerometery data and ultimately trying to identify patterns that may herald a fall. I believe we overcame this challenge by leveraging the knowledge base of our bioengineers in both Trinity College and our Medtronic colleagues.

The orientation of the accelerometer (the precise angle at which it was inserted) may also have differed for participants giving slightly different readings although based on the validation studies this did not appear to affect posture change or activity readings. However, this did create problems when interpreting certain gait parameters.

Finally, an important limitation of the investigational device is the battery life and size. The recording protocol was configured to capture data in discrete 5-minute epochs rather than continuous recordings. This episodic recording approach was necessary to optimise the use of available resources and ensure the feasibility of long-term data collection, in particular the cardiovascular data to detect arrhythmia. Due to technical considerations and to maximize device longevity, the accelerometer predominantly utilized a single axis for data acquisition during the majority of the monitoring period. This decision was made by Medtronic during extensive pre-testing to conserve power and storage space while still providing meaningful accelerometer data relevant to the study's objectives.

These constraints influenced the study design and data analysis methodologies, and despite these limitations, the collected data has provided valuable insights. Future studies may benefit from advancements in battery and storage technology that could potentially mitigate these limitations and enable more comprehensive data collection and analysis.

Chapter 19: Future

Future research in this area may be shaped by some of the limitations noted in the previous chapter. Firstly, the sample size was very small making it difficult to truly establish meaningful patterns in the data in such a limited number of participants. Secondly the sample was overly heterogenous. Further research in this area may be better served by focusing on an older cohort, perhaps over 70 with two or more unexplained falls. With an older, frailer participant cohort it is likely that more meaningful inferences could be made from the data generated.

Documenting the precise timing of fall events was certainly a challenge. While attempts could be made to ensure higher compliance rates with falls diaries, it is worth considering that increasing education is unlikely to be beneficial given the extensive education provided by the study team. It is difficult to rely on older, frail people in these circumstances for research studies where some degree of active participation is required. In reality they face more important challenges on a day-to-day basis, and it is probably unfair to add to their burden in this way. Alternative approaches need to be considered with a focus on objective external measurements.

Falls present clinicians with a unique challenge worth considering. Unlike other problems of aging or pathophysiological processes, where there is a gradual accumulation of biomarkers and physiological factors evident prior to the onset of an event, there does not appear to be such a pattern in falls based on this study. This highlights the unpredictable nature of falls and the diagnostic challenges. It is possible that with a larger sample size and a more homogenous cohort of frail older people, a clearer signal may become apparent, however the search for more objective metrics and predictors should be prioritised.

The study attempted to bridge critical gaps in current fall prediction methodologies, offering a promising avenue for pre-emptive interventions and improved patient outcomes. Unfortunately, I have been unsuccessful in creating a falls prediction algorithm based on the variables examined. However, as the scientific community navigate the intersection of cardiology and geriatrics, the potential implications of this novel research extend beyond mere fall prediction, potentially paving the way for a more comprehensive understanding of the intricate relationship between cardiac health and mobility in aging populations.

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Appendices

Appendix A - Protocols for Reveal LINQ™ validation

Location: FASU Gait Lab and MISA corridor (runway) Examiner: Robbie Bourke

Healthy volunteer: Sergio Pérez Quality control: Tim Foran

Overview

1. Program test ILR
2. Place ILR at 45-degree angle on healthy volunteer's chest (left sternal border)
3. Fix ILR in place with adhesive dressing
4. Fix External accelerometer in place with adhesive dressing (alongside and central to ILR)
5. Position volunteer lying supine on bed
6. Program position vector measurements
7. Commence protocol 1
8. Save to disk
9. Repeat steps above with ILR in horizontal position for protocol 2

Protocol 1a

5-minute blocks

1. Commence after 30 seconds - Supine to seat changing posture every 15 seconds for 4 minutes. 30 second rest
2. 5 minutes Supine
3. Commence after 30 seconds - Sit to stand (chest neutral) every 15 seconds for 4 minutes. 30 second rest
4. 5 minutes supine
5. Commence after 30 seconds – Sit-touch toes -stand every 15 seconds-30 second rest
6. 5 minutes supine

7. (Rotations) Commence after 30 seconds Supine in bed.

a. Clockwise rotations- After 30 seconds clockwise to right lying 30 seconds to prone. 30 seconds to left lying 30 seconds to Supine.

b. Counterclockwise rotations - left lying for 30 seconds supine. After 30 seconds right lying after 30 seconds Supine 30 seconds

8. 5-minute rest

9. Supine to sitting (rotational) to right and stand – posture change every 15 seconds. Supine to left to stand- posture change every 15 seconds.

10. 5-minute rest - to include walk to runway

11. 30 seconds rest and commence slow walk for 4 minutes, 30 second rest

12. 5-minute rest

13. 30 seconds rest and commence normal walk for 4 minutes, 30 second rest

14. 5-minute rest

15. 30 seconds rest and commence brisk walk for 4 minutes, 30 second rest

16. 5-minute rest including walk to tilt bed

17. TILT bed protocol 20 and 45 degree

Protocol 1b

As per protocol 1a but with ILR in horizontal position

Protocol 1c:

Location: FASU Gait Lab and MISA stairwell – ground to first floor Examiner: Robbie Bourke

Healthy volunteer: Sergio Pérez Quality control: Tim Foran

Overview

1. Program test ILR

2. Place ILR at 45-degree angle on healthy volunteer's chest (left sternal border)

3. Fix ILR in place with adhesive dressing

4. Fix External accelerometer in place with adhesive dressing (alongside and central to ILR)

5. Position volunteer lying supine on bed

6. Program position vector measurements

7. Commence protocol 1c

8. Save to disk 5-minute blocks

Protocol 1c

1. "RESTLESSNESS" 1 Lying throughout – Switching from right lying to left lying and back every 30 seconds

2. "RESTLESSNESS" 2 Supine to sit x 2. supine to elbow left to reach – right.

3. Bed to bathroom - Walk to bathroom sit to stand walk 6 m – 2m 6 m – stop 9 0 secs

4. Bed to bathroom as above – faster

5. Stairs slow

6. Stairs fast

7. Bed to stairs Sit to stand walk stairs and back

8. Bed to stairs fast

Appendix B - Calculation of vectors – An Explanation

Outputs from the position vectors are given in ADC units. For graphical purposes the outputs across X, Y, Z vectors are scaled such that the root mean square sum of the three vectors for each patient adds to 1(g). This is an approximation to provide some estimation of gravity influence on each axis and in each position (see Figure B1 below). On a broad level the graph illustrates the variety of orientations that the Reveal LINQ™ appears to adopt, as captured at the final clinical session of position vector capture.

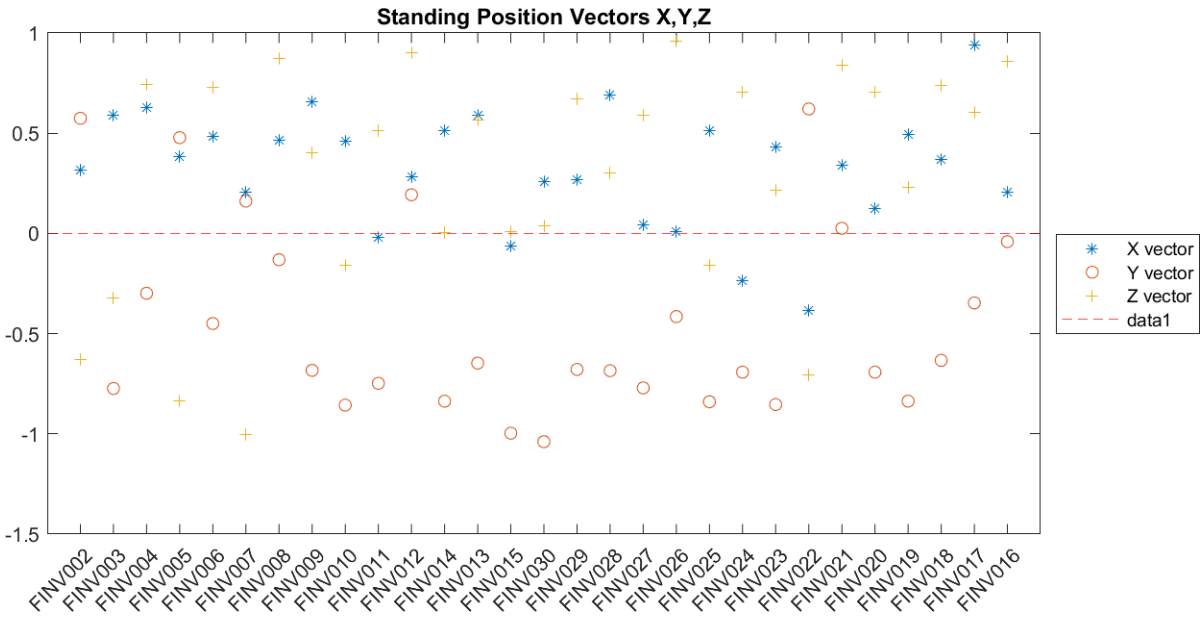

Figure B1 Position vectors Y axis unit=Gs

The influence of gravity varies as the accelerometer is tilted and only when one axis is fully aligned with the vertical (i.e., showing a value of 1g at rest), will it be possible to estimate step length. For example, FINV026 is showing the Z vector is recording ~1g in the standing position, indicating that the Z axis is approximately in the vertical position.

Figure B2 below a plot of values recorded by an accelerometer in various positions to show how the influence of gravity varies as the accelerometer is tilted.

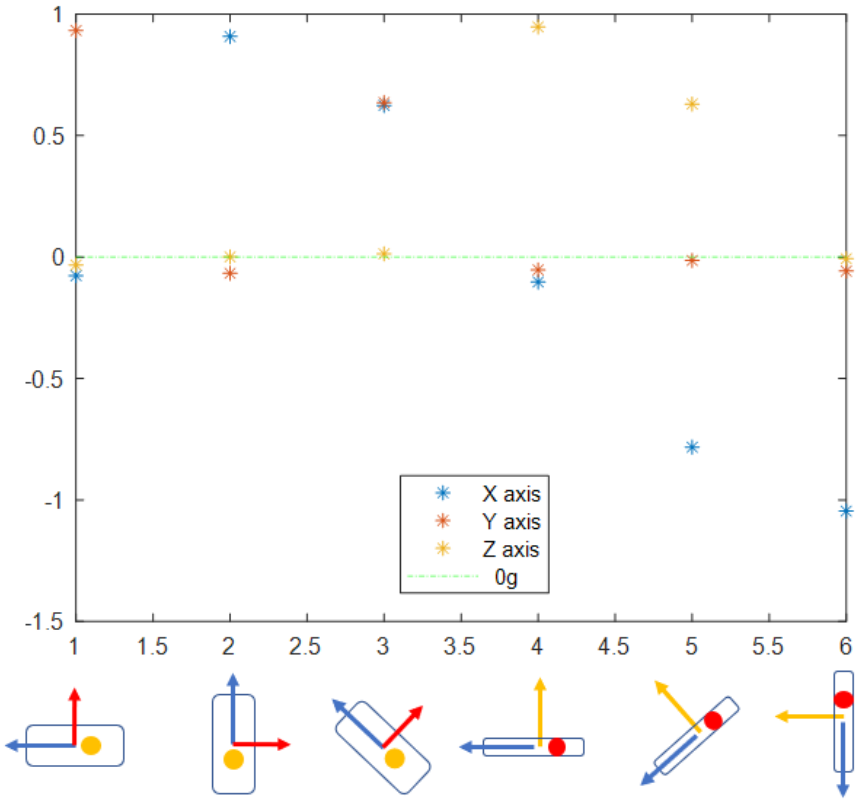

Figure B2 Accelerometer in various orientations Unit = Gs

Appendix C Patient Information Leaflet and Informed Consent form

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Medtronic

PARTICIPANT INFORMATION LEAFLET

Frailty and Falls Implantable System for Prediction and Prevention

FFallS Predictor Clinical Investigation

Principal Investigator: Professor Rose Anne Kenny
Study Site: Falls and Syncope Unit (FASU), St James's Hospital, Dublin 8
Sponsor: Trinity College Dublin
Data Controllers for the Study: Trinity College Dublin and Medtronic
Data Controllers of the medical records: St James' Hospital

You are being invited to take part in this research study which is being carried out at the Falls and Syncope Unit (FASU) at St James's Hospital Dublin, by Prof Rose Anne Kenny of Trinity College Dublin, in partnership with Medtronic.

Before deciding whether or not you want to take part in this study, you should read the information provided carefully. If you wish, please take the opportunity to discuss it with your family, friends or GP. Please take time to ask any questions you may have, and to talk to a member of the team if there are any aspects of the study that you would like further information on.

Don't feel rushed or under pressure to make a quick decision. You should have a full understanding of the study and what it involves so that you can make a decision that is right for you. Thank you for taking the time to read this leaflet.

PART 1 – THE STUDY

Why is this study being done?

The purpose of this study is to see if the data from a small implantable monitoring device in this case The Reveal LINQ™ with updated research features could be used to monitor and detect potential changes in certain body measurements that may predict a non-accidental fall.

Background

Falls account for a large proportion of visits to the Emergency Department. The Irish Longitudinal Study on Ageing (TILDA) has shown that almost 1 in 4 people fall each year. Research has also shown there is a link between being frail and having a fall. For this study

we are particularly interested in 'non-accidental' or 'unexplained' falls- that is falls which are not clearly due to a slip or a trip. Our previous research shows that a high number of these non-accidental falls may be due to changes in heart rate and irregular heartbeats (heart - rhythm). There may also be other changes associated with falls such as changes in posture or step count. Identifying these changes may help to predict risk of a fall.
Patients referred to the Falls and Syncope Unit (FASU) at St James's Hospital due to a non-accidental fall, undergo a full clinical assessment, where the medical team aim to identify and treat factors which might contribute to falls. They routinely manage such unexplained falls by implanting a monitoring device, which will measure heart rate and rhythm (known as an implantable loop recorder).

The Reveal LINQ™ (Implantable Loop Recorder)
An Implantable Loop Recorder is a small medical device that is currently used for long-term monitoring of heart rhythms. It is a small device – like a mini-USB stick- inserted beneath the skin in the upper left-hand side of the chest where it can monitor the heart and detect changes in the heartbeat. Irregularities in the heartbeat could cause unexplained falls.

The Reveal LINQ™ device which is made by Medtronic™, is the implantable monitoring device which is used in FASU. It can automatically detect and record abnormal heart rhythms for up to three years. The Reveal LINQ™ is pictured below and a "dummy model" of the device is available to view in FASU.

Patients with the device also use a small hand-held 'Patient Assistant' control, to manually activate data recording if they have any symptoms. The Reveal LINQ™ device transmits data wirelessly (via a bedside monitor) to a secure network called CareLink™ where authorised members of the clinical team can access the data. The Reveal LINQ™ is used in FASU as part of current best practice to monitor patients with a history of non-accidental falls.

The Research Device
The research team at Medtronic™ as part of a collaboration with the Principal Investigator Prof Rose Anne Kenny, have developed a new software update (Falls Prediction RAMware) for the Reveal LINQ™ device that can activate extra sensor features on the device. This update will allow the device to record additional data and new measurements including, step count, walking time, changes in posture and temperature that could be used to predict falls. This updated Reveal LINQ™ is known as the Reveal LINQ™ Falls Prediction Research System.

The Study
This research study will take place at St James's Hospital, Dublin. It is planned that approximately 30 patients will take part in the study. The aim of the study is to see if the Reveal LINQ™ device with the Falls Prediction software update could be used to monitor additional physical changes in the body that may predict increased risk of a fall.

Patients referred to the Falls and Syncope Unit (FASU) as a result of an unexplained fall will be assessed by the clinical team. During the recruitment period for this study, suitable patients will be invited to consider their participation in this study.

Patients will be provided with the approved study information leaflet and will have time to ask questions and decide if they wish to take part or not. If they wish to participate, they will be asked to sign the consent form for the study. This process is known as informed consent. Patients will be screened to ensure they meet all entry requirements and eligible patients will consent to take part. A detailed baseline set of tests will be performed as necessary in FASU. Patients will then attend St James's Hospital to have the Reveal LINQ™ device inserted. Once the device has been inserted, the new Falls Prediction software update will be downloaded to the Reveal LINQ™ device and activated. This will allow the Reveal LINQ™ device to monitor and collect the new research data such as posture change and step count.

Patients will remain in the study for follow up for a period of 12 months and will attend in-clinic assessment visits at 3, 6, 9 and 12 months. As part of the follow up patients will be asked to complete a daily walk (gait) assessment at home and send weekly manual data downloads from their device. Patients will be provided with 'Falls Diaries' to record any falls or symptoms. They will be contacted by phone every two weeks for updates by a member of the study team.

Patients will complete the study after they attend for the 12 Month follow up visit. At the end of the study, the study team will deactivate the investigational Falls Predictor features of the Reveal LINQ™ device, this is done externally using the patient assistant tool.

All assessments and the device implantation and update are explained in more detail in *'What will happen to me if I agree to take part?'* section of this leaflet.

Why am I being asked to take part?

You are being invited to take part in the study as you have been referred to the FASU at St. James's Hospital due to an unexplained fall and you also have a history of falls for which there was no obvious cause.

Do I have to take part? What happens if I say no? Can I withdraw?

No, you do not have to take part in this study. Participation in this study is completely voluntary, it is your decision to take part or not. If you do not wish to take part, you do not have to give a reason and your decision will not affect the care you will receive.

If you decide to take part now, you will still be able to withdraw from the study at any time and you do not have to give a reason for your decision. Withdrawing from the study will not have any effect on the medical care that you receive.

If you withdraw from the study, data collected up to the point of withdrawal will be retained and this data will continue to be used as it would seriously impact on the study to remove it. No further data will be collected after the point of withdrawal.

If at any point you wish to opt out of the study, please contact a member of Prof Rose Anne Kenny's study team at the Falls and Syncope Unit (FASU) on (01) 428 4105 and they will organise this for you.

What will happen to me if I agree to take part?

If you decide to take part in the study, you will firstly be asked to provide your written consent to participate. Your health records will be reviewed by the team to check that you meet the entry requirements for the study.

A comprehensive set of baseline assessments will be performed as needed in the Falls and Syncope Unit. These assessments will take approximately an hour to complete.

Baseline Assessments

- Contact details, age, gender.
- Medical and Falls History
- Medications
- Mini Mental State Exam (Brief questionnaire to measure ability to memorise and concentrate)
- Full Physical Exam
- Measurements of current functional abilities (including hand grip strength test)
- Vision, Walking and Balance Assessment
- ECG (Heart rate and rhythm assessment)
- Blood pressure assessment lying down and standing up, along with a band across the forehead which measures blood flow in the front of the brain.

Implantation Procedure

Once the baseline assessments have been completed you will have a Reveal LINQ™ device implanted. The implantation procedure will take place as per the standard clinical procedure this means that there are no changes to the procedure as part of this research study.

The Reveal LINQ ™ device measures less than 5cm in length – about 1/3 the size of an AAA battery. It is a minimally invasive day case procedure performed by a trained doctor and requires local anaesthetic only. The device will be inserted under the skin on the left-hand side of your chest. You may receive a dose of antibiotic and a small dissolvable stitch. The actual procedure takes less than 15 minutes. The implantation will take place in an appropriate surgical clean room and will follow the routine clinical procedure. You will receive the clinical information leaflet with aftercare instructions.

Falls Prediction RAMware Activation

After the device has been implanted, the study doctor will install the research update (Falls Predictor RAMware) to the device. This is done using the 'Patient Assistant' tool and a small programming computer which will wirelessly transmit the software update to the device. You should not feel any physical discomfort or changes as a result of the update as there are no physical changes to the device or implant site required. The doctor will ask you to change positions from sitting, lying, and standing to program the device to properly collect position measurements. This process should take about 15 minutes.

Education

You will receive education on the Reveal LINQ™ device, and MyCareLink™ Technology from the FASU team. They will show you how to use the 'Patient Assistant' Tool if you have symptoms. They will also show you how to manually transmit a full download of data via your bedside monitor to the Carelink™ system. This is all part of the routine care that you would

receive in the FASU unit. Close family members may also attend this session. You will be provided with the standard clinical information leaflets for the Reveal LINQ™. In addition, the study team will provide you with additional education on the Falls Predictor study requirements and explain how you will perform your daily walk assessment at home. They will also show you how to complete your Falls Diary.

Monitoring
Every night the data from your Reveal LINQ™ device will be transmitted automatically to your bedside monitor and to the CareLink™ system. The standard heart monitoring reports will be received by the FASU team the following morning. If the Reveal LINQ™ device has recorded an alert (for example: an irregular heartbeat) or you have used your Patient Assistant for symptoms the team will then ring you to discuss the alert or symptom activation. They may also ask you to perform a full manual download of the device. If you have not had an alert or a symptom you will not receive a call.

Follow Up
Following implantation of the device you will then enter the follow up period of the study which will take place over 12 months.
During this time, you will be asked to complete some at-home assessments:

- Daily Walk Assessment
  You will be asked to use the Patient Assistant to collect accelerometer data once a day. You will walk for 1-minute to ensure 30 seconds of data collection. This data will be stored and retrospectively analysed to look for changes in your gait (how you walk).
- Weekly Manual Data Transmission
  Once every week you will be required to use your MyCareLink™ monitor to perform a full manual download of the all the data stored on your device.

You will be provided with a study Falls Diary during this time to document any falls, near falls or symptoms. You will also be asked to use the Patient Assistant if you have any symptoms or falls.
A member of the study team will contact you every two weeks for updates.
You will be asked to attend the Falls and Syncope Unit at Month 3, 6, 9 and 12, where the clinical assessments will be performed by the study nurse and doctor as listed as follows.

Follow Up Visits to FASU at Month 3, 6, 9 and 12

- Falls diary review.
- Medical and falls history.
- Medications review
- Full Physical Exam
- Measurements of current functional abilities (including hand grip strength test)
- Vision, Walking and Balance Assessment
- ECG (Heart rate and rhythm assessment)
- Blood pressure assessment lying down and standing up, along with a band across the forehead which measures blood flow in the front of the brain.
- A ‘6 Minute Walk Test’ while wearing an external Holter monitor around your chest to collect data from the Reveal LINQ.

Unscheduled Visits
Should you have a fall during the study, or if you experience any issues you may be asked to attend the FASU for a review.

End of study
Your participation in this study will end after your 12month follow-up assessment or at any time if you wish to withdraw. At this point the Falls Predictor software will be turned off on your Reveal LINQ™ device. Your Reveal LINQ™ implant will remain in place and it will only monitor the standard heart rate and rhythm data from this point. No further data will be collected for the study. You will then be followed up clinically by the FASU team as per the standard of care.

Are there any benefits to me or others if I take part in the study?

There is no direct benefit to taking part in this study, as we do not yet know if the extra information from the Reveal LINQ™ Falls Prediction update will be of benefit in predicting fall risk in patients.

In future, the information obtained may benefit others if the Reveal LINQ™ Falls Prediction System is shown to have the potential to predict the risk of a fall.

Are there any risks to me or others if I take part in the study?

This study has been designed to follow standard clinical procedures to minimise risk from participation.

The assessments performed in clinic during the study will be carried out by a trained study doctor and nurse and will follow the best practice of the unit. It is not anticipated that there would be any additional risks associated with these assessments.
The known risks associated with the study procedures are documented as follows:

Implantation of the Reveal LINQ™ Device
There is no change to the physical properties of the Reveal LINQ™ device that is implanted as part of this study or to the implantation procedures. The implantation of the Reveal LINQ™ device is a well-established clinical procedure in St James's Hospital.
Potential risks or adverse effects from the implantation of the device include:

- Bruising over the insertion site.
- Skin infection at the insertion site.
- Pain at the insertion site after the procedure.

Rare and uncommon potential side effects include:

- Migration of the device – where the Reveal LINQ™ device moves from its location under the skin.
- Device rejection phenomena - a body reaction to the Reveal LINQ™ device as a foreign object.
- Erosion through the skin.

The following effect is considered very low:
Participating in this research may reduce the lifespan of the battery within the Reveal LINQ™ device by up to 6 months due to the additional software that will be added for the duration of the study. This means you may need to have the device removed or replaced by the end of 3 years or earlier.
Your doctors will monitor the functioning of the device even after the study has ended as part of your standard care within the FASU unit.

What will happen if something goes wrong when I'm taking part in the study?

If something goes wrong while you are taking part in the study, you will be looked after by the study team and the clinical team in the Falls and Syncope Unit. You will be referred to the appropriate clinical department if you require any additional care.
You will be provided with contact details for the FASU and the study team so that you can contact them with any concerns.
Appropriate indemnity and insurance will be in place for the study, and the normal claims mechanisms will be available to you should you feel you have been harmed through someone's negligence or as a result of the study device.

What other treatments are available to me?

If you decide not to take part in this research study, you will continue to be assessed in the Falls and Syncope Unit as per standard care. You will still have the option to have an implantable loop recorder such as the standard available Reveal LINQ™ device. This data would only be monitored by your clinical team to assess if there is an underlying abnormal heart rhythm and no additional research activities or assessments would take place.

Will I be told the outcome of the study? Will I be told the results of any tests or investigations performed as part of this study that relate to me?

Any relevant results of clinical tests performed during this study will be communicated to you directly as part of your clinical care.

Any abnormalities identified from the standard clinical monitoring of your heartbeat by the Reveal LINQ™ device will be communicated to you and treated as clinically appropriate.
The data obtained from the new research features of the Reveal LINQ™ Falls Predictor update will not be communicated to you as it will only be analysed and validated at the end of the study.

The results of this research study may be reported in medical journals and may be presented at relevant conferences. The data presented will not contain any personally identifying information.

PART 2 – DATA PROTECTION

Trinity College Dublin is the Sponsor of this study. This study is supported by Medtronic Bakken Research Centre BV, a company with experience in medical technology, including the Reveal LINQ ™ Falls Prediction Research System. The address of Medtronic Bakken Research Centre is: Endepolsdomein 5, 6229 GW, Maastricht, the Netherlands.

The study will be carried out at the Falls and Syncope Unit (FASU) at St James's Hospital Dublin and led by Prof Rose Anne Kenny.

What information about me (personal data) will be used as part of this study? Will my medical records be accessed?

To ensure that you are an eligible candidate for the study, it will be necessary for your clinical team to review your medical records prior to enrolment. If you wish to participate in the study, you will be asked to provide your consent to allow members of the study team to access your medical records for the purpose of the study.

Any relevant information arising from the study assessments will be documented in your medical notes and managed as per standard hospital practice. Only authorised members of the study team will access these records to collect the study data.

You will also be asked to consent to your Hospital Consultant or General Practitioner being informed of your participation in the study if appropriate.

On enrolment, you will be assigned a unique study number. The connection between your Name, Date of Birth and Medical Record Number, will be maintained on a 'Participant Identification Log'. The serial number of your Reveal LINQ™ device will also be documented on this log. Your signed and dated informed consent form will also be maintained as part of the study records.

The data that will be collected as part of this study will include:

- your demographics,
- relevant medical history,
- medication history,
- detailed falls history,
- the data gathered from the baseline assessments,
- follow up assessments and
- your falls diary.

The data transmitted from the Reveal LINQ ™ Falls Prediction Research System will also be analysed and collected as part of the study.

Only the unique study number or your unique device serial number will be used to identify your data collected for the study, this is known as pseudonymisation. Your personal identifying details such as your name will never be used on the study database.

Who will access and use my personal data as part of this study?

The data included in the study from your medical records, study assessments and falls diaries will be entered onto a secure study database by the study Data Manager. This data will only be identified by your unique study number. Only authorised members of the study team at St James's Hospital and Trinity College Dublin will be able to access this database. You will be asked for your consent to allow this.

The data from the Reveal LINQ™ device is processed via the Medtronic CareLink™ Network which is maintained on General Data Protection Regulation ("GDPR") compliant servers managed by Medtronic. The serial number of your Reveal LINQ™ device will be provided to the research team at Medtronic to allow them to access the relevant data from the CareLink™ Network for this study.

Your name or directly identifying personal details will never be provided to Medtronic. Medtronic will be provided access to pseudonymised data from the study database to assist with processing and analysis of the device data.

The clinical team in FASU may access the standard Reveal LINQ™ data (heart rate and rhythm reports) via the CareLink™ system in the department. This is the standard clinical process and you will be asked to provide your consent for this separate to the research study.

All data stored on the study database will be identified by your unique study number or device serial number only.

All study records and data will be kept for 15 years following completion of the study. After this the hard copy documents will be destroyed, and the study database will be deleted.
If required to do so direct access will be granted to authorised representatives from the sponsor, study site and the ethical and regulatory authorities (if required) to allow trial-related monitoring, audits and inspections.

Will my personal data be kept confidential? How will my data be kept safe?

All study records and personal data obtained for the purposes of the study will be kept confidential. The study will adhere to all data protection requirements. The following processes have been put in place to ensure your personal data will be kept confidential:

Pseudonymisation

On enrolment to the study, you will be assigned a unique study number that will be used to identify your study data in place of your name. All data collected in the study database will only be identifiable by the Unique Study Number.

Study Records

Study records that contain your personally identifying information (e.g., name, date of birth, contact details) will be kept to a minimum. They will include the signed consent form and the 'Participant Identification Log'.

The 'Participant Identification Log' will also contain the link to your unique Reveal LINQ™ device serial number. The study records will be kept in a secure locked area with restricted access.

Data Security Arrangements
The study database will be maintained on a secure encrypted password protected server on the Trinity College network. All data collected will be pseudonymised prior to analysis.

Publication of Results
The study results will be published as a review of the overall findings from the study. The results in publications or presentations would be anonymous and it would not be possible to identify specific participants.

What is the lawful basis to use my personal data?

Trinity's lawful basis to use your personal data is that this is scientific research is in the public interest (Article 6(1)(e)) and (Article 9(2)(j) GDPR). In addition, the provision of your 'explicit consent' will allow us to process your data for the purposes of the study as outlined in this information leaflet.

Medtronic's lawful basis to use your pseudonymized personal data as outlined in this information leaflet is your explicit consent (Article 6(1)(a) article 9(2)(a) GDPR).

What are my rights?

You have the following rights regarding your personal data that is included as part of this study unless such requests would seriously impair the research objectives:

- Right to access a copy of the data held about you as part of the study
- Right to restrict the use of the data held
- Right to correct inaccuracies
- Right to have information deleted (up to the point of study analysis)
- Right to data portability

For any of your requests related to the processing of your personal data by Trinity or Medtronic, please contact your study doctor at St. James Hospital Dublin in a written form. As Trinity and Medtronic will only receive pseudonymised data about you, the support of the study doctor is required to execute your requests.

PART 3 – COSTS, FUNDING & APPROVAL

Will it cost me anything if I agree to take part?

There is no cost for participating in the study. You will not be paid for your participation. You will be reimbursed for reasonable expenses associated with the additional follow up visits that are required as part of the study. You must keep all receipts to claim the reimbursement.

Who is funding this study? Will the results study be used for commercial purposes?

This study is being funded as part of a project grant awarded from EIT Health (Innovation by Design). EIT Health is a Knowledge and Innovation Community (KIC) established by the European Institute for Innovation & Technology (EIT), an independent EU body set up in 2008 to promote innovation and entrepreneurship across Europe.

The grant was awarded to Prof Rose Anne Kenny and the Department of Medical Gerontology, Trinity College Dublin as the Activity Leader of the project.

The researchers are not being paid to recruit patients to this study. The grant funding covers only the costs associated with running the study which includes funding to employ staff.

Medtronic™ are the medical device company that are leading the development of the investigational Reveal LINQ™ Falls Prediction software. They are a named collaborating partner on the grant project. Medtronic™ are also supplying the Reveal LINQ™ devices that will be used in the study.

The study results will be available to Medtronic, which may inform their decision to continue development of the Reveal LINQ™ software and device and proceed with further studies that would be required to commercially release the device.

Has this study been approved by a research ethics committee?

This study was submitted to the Tallaght University Hospital / St. James's Hospital Joint Research Ethics Committee (TUH/SJH Joint REC) for review and approval. This is the Ethics Committee that has responsibility for approving research studies involving medical devices that are proposed to take place at St James's Hospital.
The TUH/SJH Joint REC can be contacted via email or phone as follows:
Email: researchethics@tuh.ie
Phone: 01-414 2199

PART 4 – FUTURE RESEARCH

Will my personal data and/or biological material be used in future studies?

Yes, it is anticipated that the data collected for this study may be used by sponsor and Medtronic in future research in the areas of Frailty and Falls with your consent.

PART 5 – FURTHER INFORMATION

Where can I get further information?

If you have any further questions or require further information on any aspect of the study or if you wish to opt out of the study at any point, you can contact any member of the study team and they will assist you.

Further information is also available from the following contacts:

- Principal Investigator:
  Prof Rose Anne Kenny - at 01 4284105
- Data Protection Officer:
  Trinity College Dublin - Email: dataprotection@tcd.ie
  St James's Hospital – Email: dataprotection@stjames.ie , Phone - 01 416 2463
  Medtronic- Email: rs.privacyeurope@medtronic.com

What happens if I wish to make a complaint?

If you have a concern about any aspect of this study, you should ask to speak with a member of the research team who will do their best to address your questions or concerns.

If you remain unhappy and wish to complain formally, you can do this through the Patient Experience Office at St James's Hospital.

They can be contacted via email: patientfeedback@stjames.ie , or phone on 01 4284248 or 01 4103361.

Will I be contacted again?

No, once you have completed participation in this study, you will be followed as per clinical care requirements. It is not anticipated that the study team will need to contact you again.

Thank you for taking the time to read this information.

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Medtronic

CONSENT FORM

Frailty and Falls Implantable System for Prediction and Prevention

FFallS Predictor Clinical Investigation

Principal Investigator: Professor Rose Anne Kenny
Study Site: Falls and Syncope Unit (FASU), St James's Hospital, Dublin 8
Study Team: Trinity College Dublin led by Professor Rose Anne Kenny

To be completed by the PARTICIPANT.

Please carefully read the below statements and tick and initial each one to indicate your consent, please sign and date you name in the section below

Please read and Tick and initial each statement below to indicate your consent.	Tick Box	Initial Box
I confirm have read and understood the Participant Information leaflet Version 3.0 (25-Feb-2021)	☐Yes ☐No	
I confirm I have received enough information about the study, and I have had the opportunity to ask questions and I have received satisfactory answers.	☐Yes ☐No	
I understand that I am free to withdraw from the study at any time without giving a reason and this will not affect my future medical care	☐Yes ☐No	
I agree to allow the study team to use my pseudonymised information (personal data) as part of this study as outlined in the information leaflet	☐Yes ☐No	
I agree to allow the study team to access my medical records as part of this study	☐Yes ☐No	
I consent to information about me (personal data) being used as part of this study by the study team and Medtronic	☐Yes ☐No	
I agree to be contacted by the study team as part of this research	☐Yes ☐No	
I would like my General Practitioner (GP) to be informed of my participation in this study	☐Yes ☐No	
I consent to take part in this research study having been fully informed of the risks, benefits and purpose of the study	☐Yes ☐No	

Future research

I agree that the study data may be used in future research in the area of frailty and falls by Trinity College Dublin	☐Yes ☐No	
I agree that the study data may be used in future research in the area of frailty and falls by Medtronic	☐Yes ☐No	

Signature of Participant:

_____	_____	_____
Participant Name (Block Caps)	Participant Signature	Date

Signature of Delegated Person Obtaining Consent

By Signing below, I confirm I have fully explained the purpose and nature (including benefits and risks) of this study to the participant. I have invited him/her to ask questions on any aspect of the study. I confirm that he/she fully understands my explanation and has freely given informed consent to participate in the study.

_____	_____	_____
Name (Block Caps)	Signature	Date

3 copies to be made: 1 for patient, 1 for hospital records and original for study records

Appendix D– Cardiac data histograms

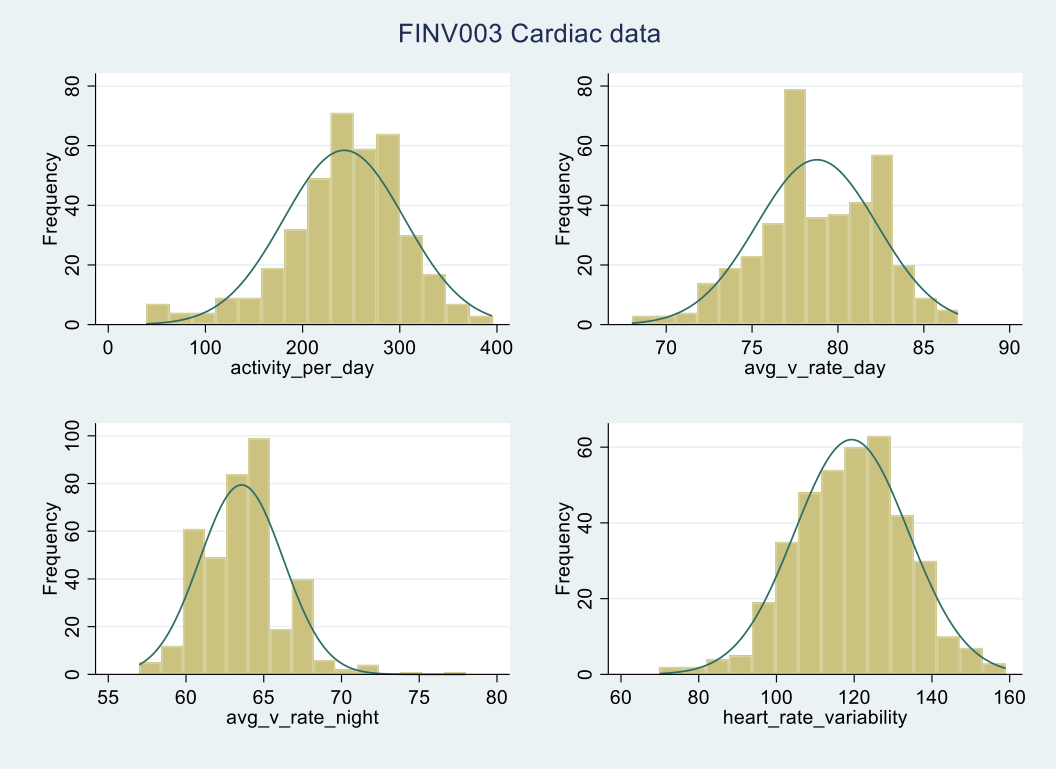

Figure D1. FINV 003. Histograms of activity per day and cardiac variables

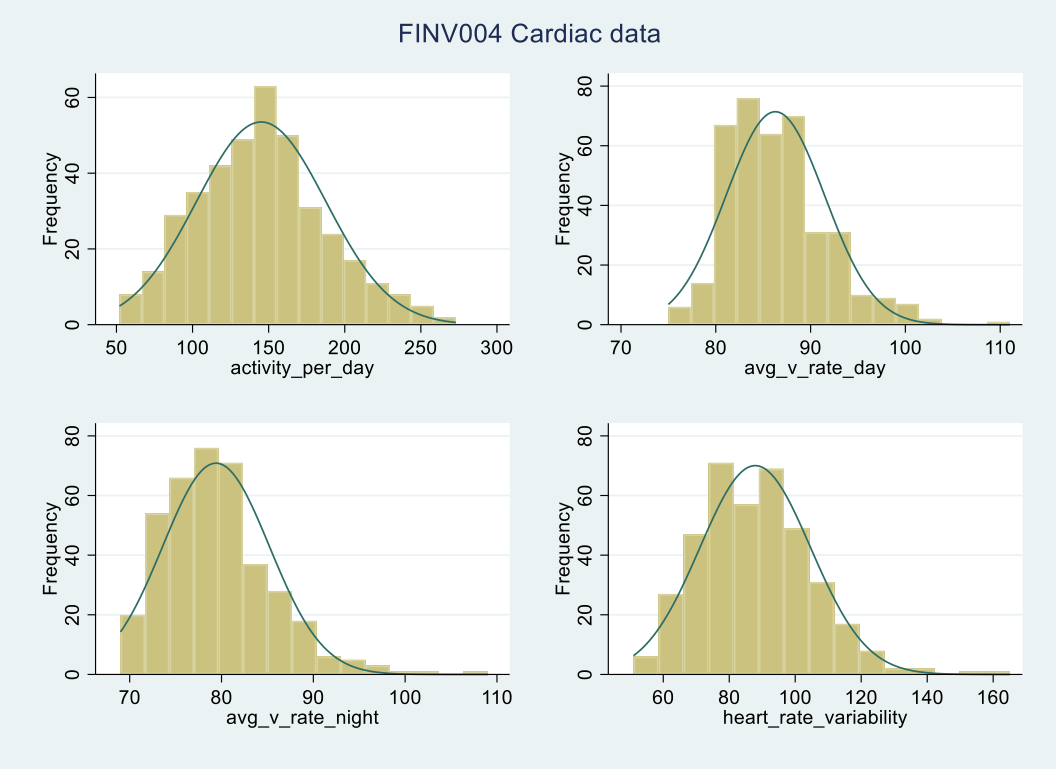

Figure D2. FINV 004. Histograms of activity per day and cardiac variables

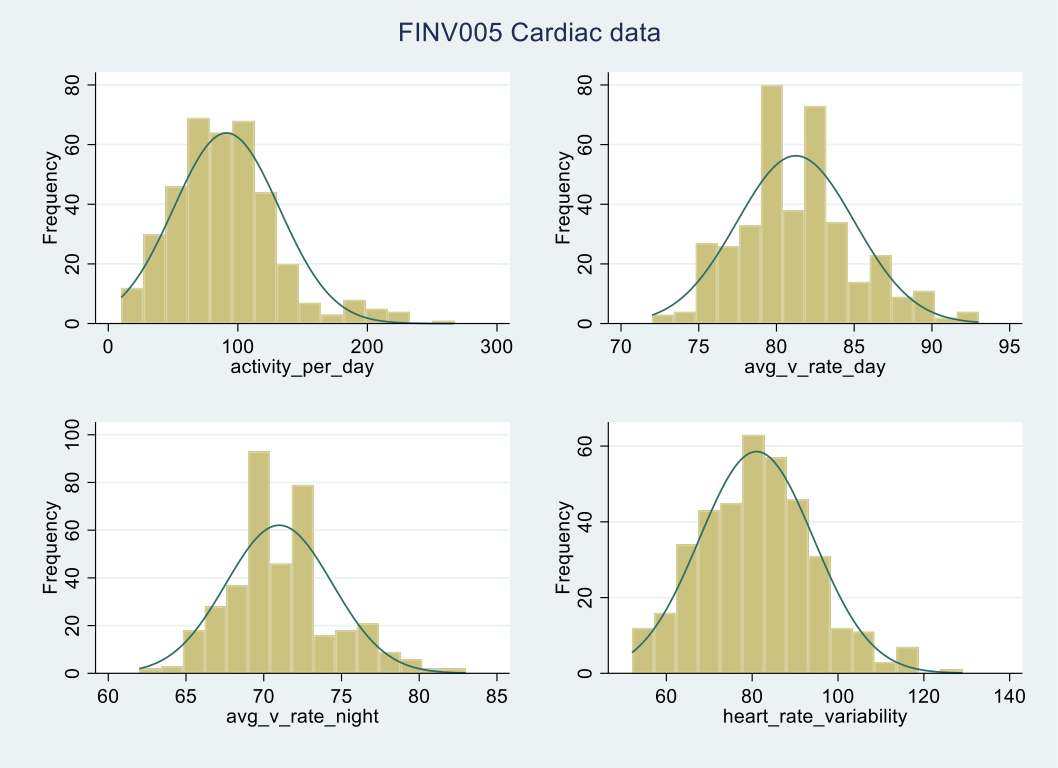

Figure D3. FINV 005. Histograms of activity per day and cardiac variables

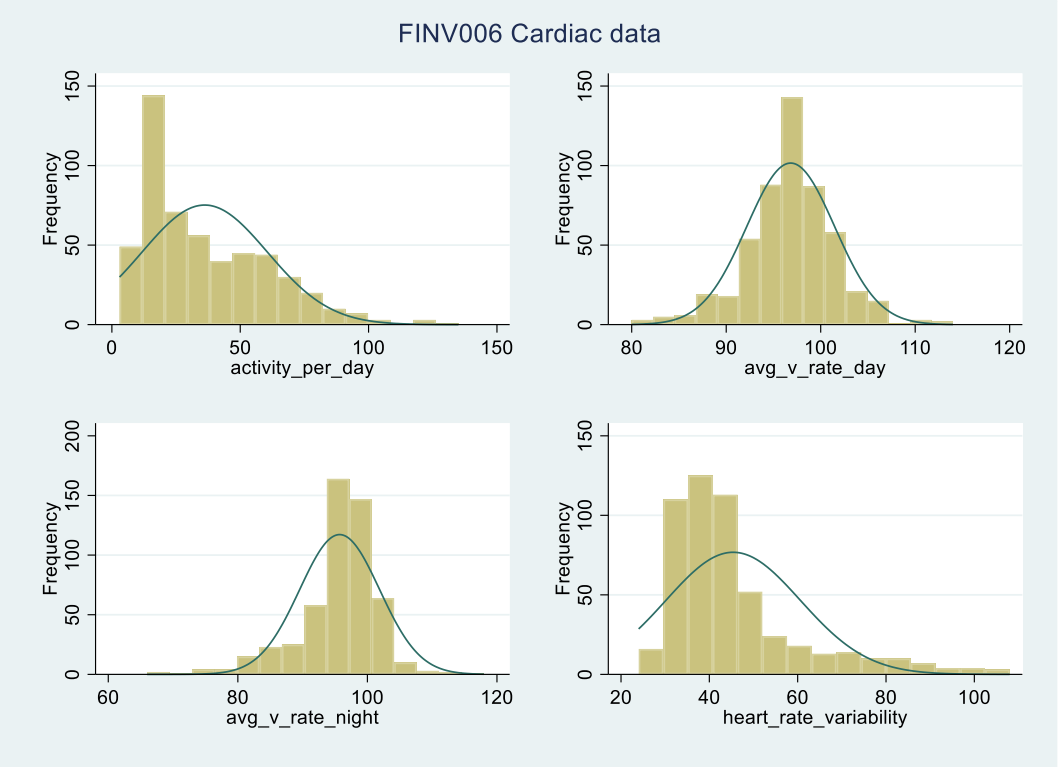

Figure D4. FINV 006. Histograms of activity per day and cardiac variables

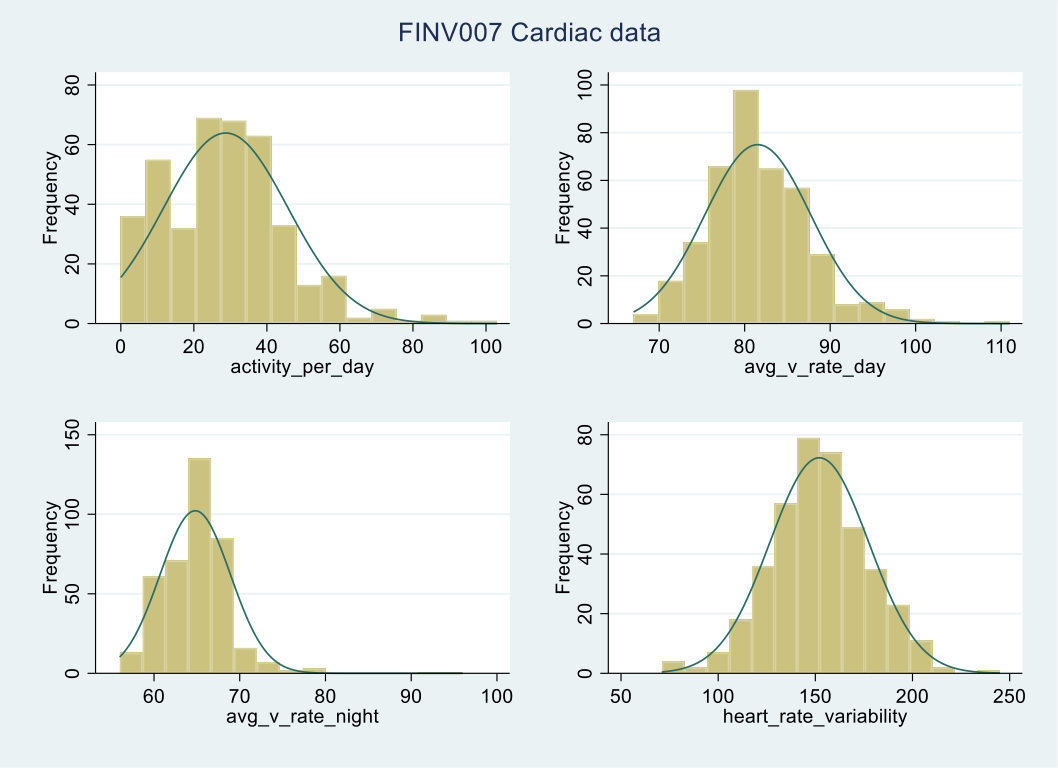

Figure D5. FINV 007. Histograms of activity per day and cardiac variables

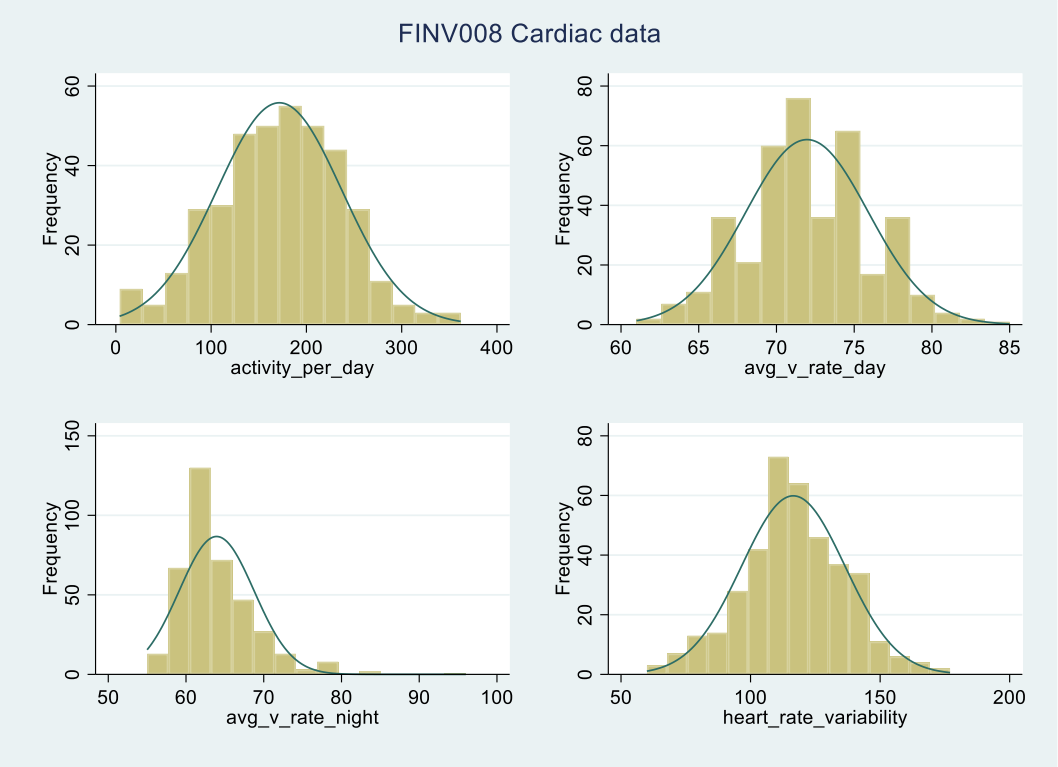

Figure D6. FINV 008. Histograms of activity per day and cardiac variables

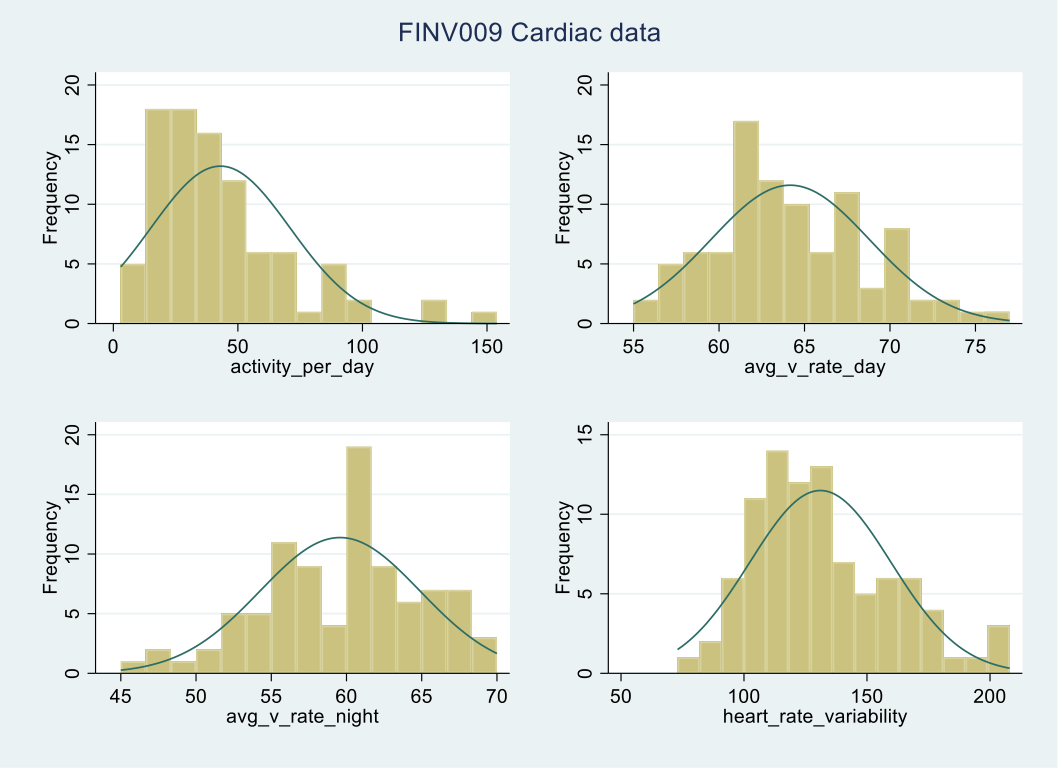

Figure D7. FINV 009. Histograms of activity per day and cardiac variables

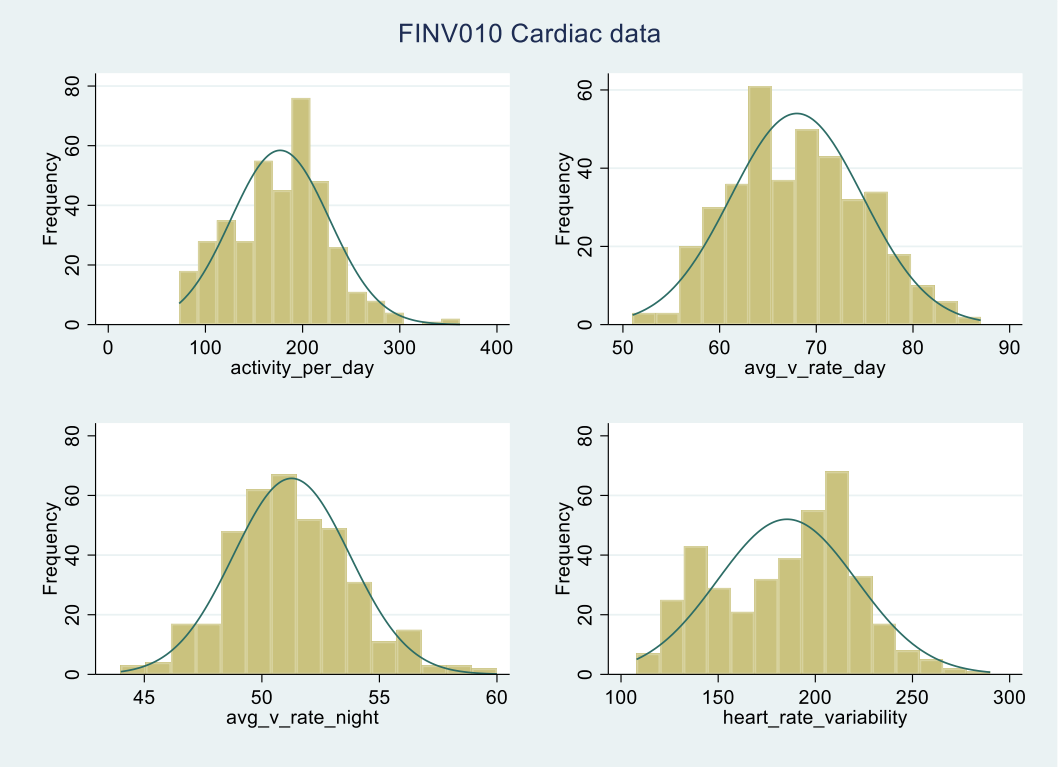

Figure D8. FINV 010. Histograms of activity per day and cardiac variables

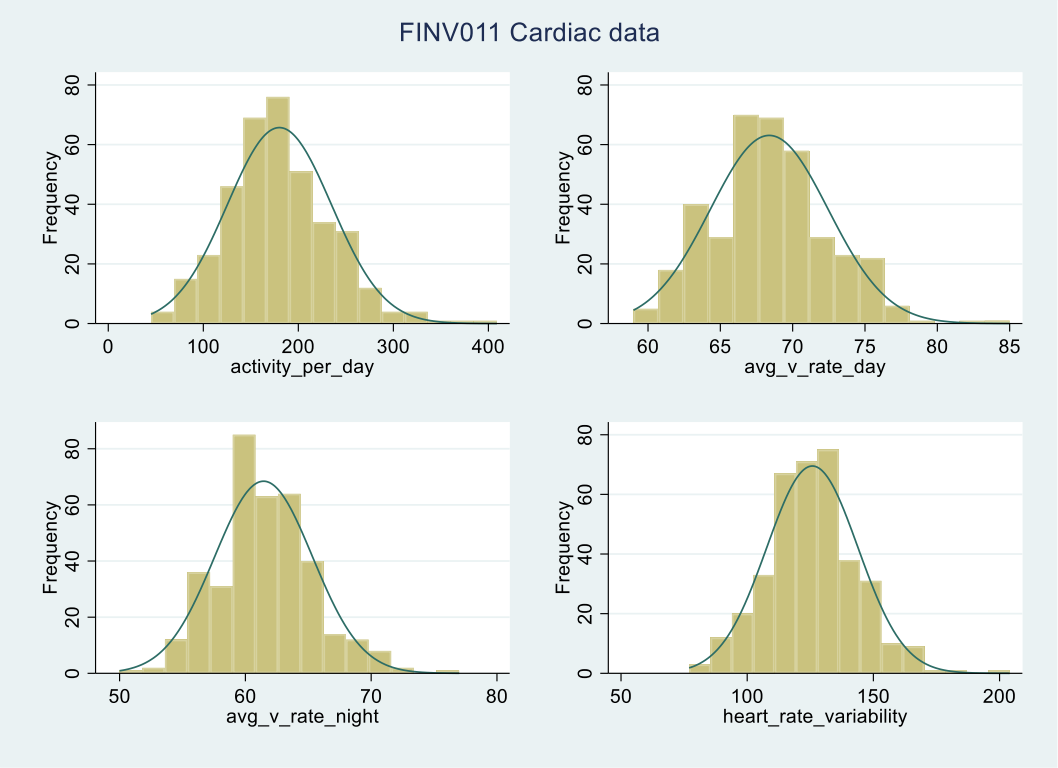

Figure D9. FINV 011. Histograms of activity per day and cardiac variables

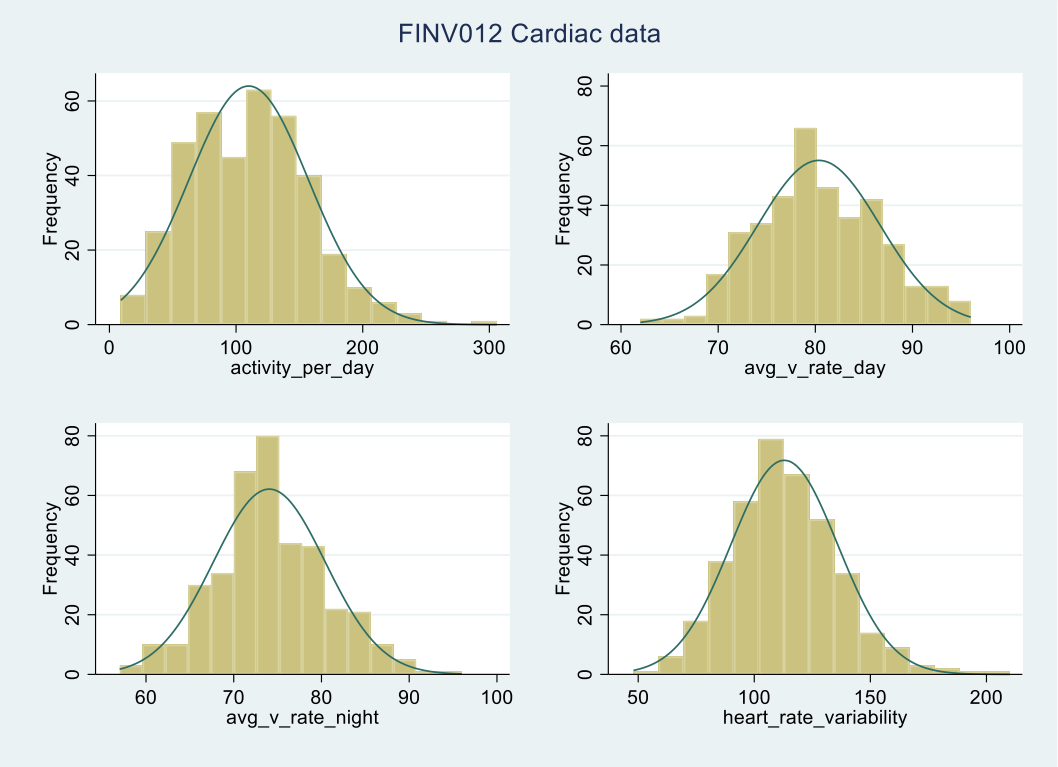

Figure D10. FINV 012. Histograms of activity per day and cardiac variables

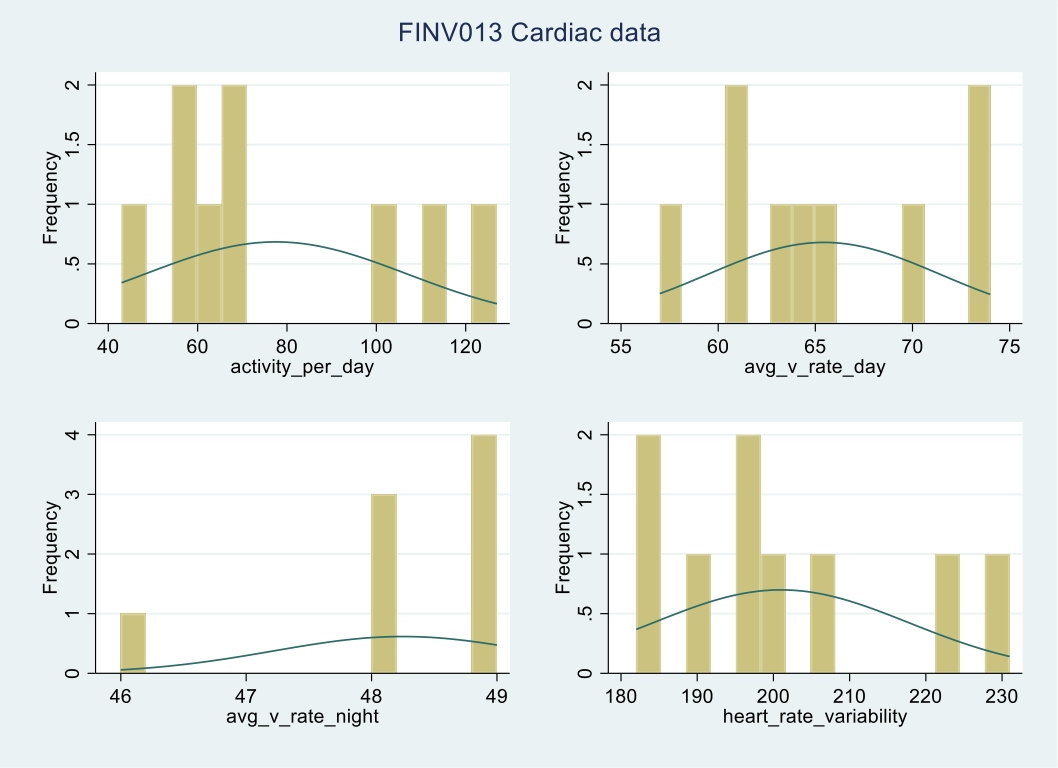

Figure D11. FINV 013. Histograms of activity per day and cardiac variables

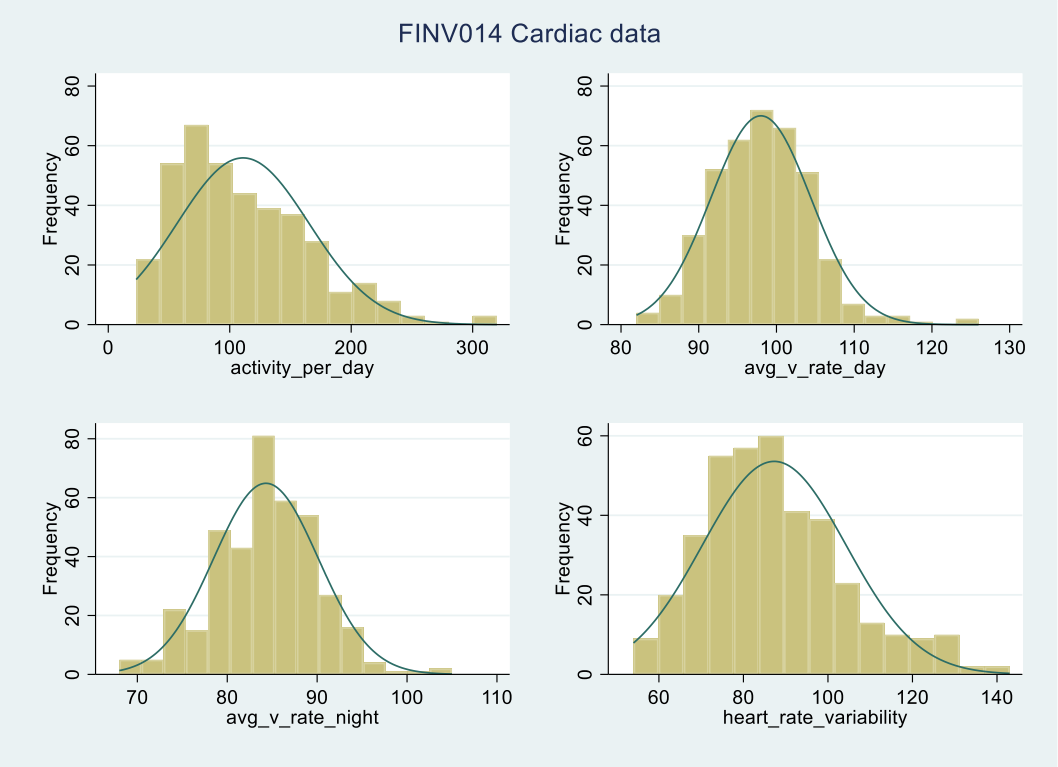

Figure D12. FINV 014. Histograms of activity per day and cardiac variables

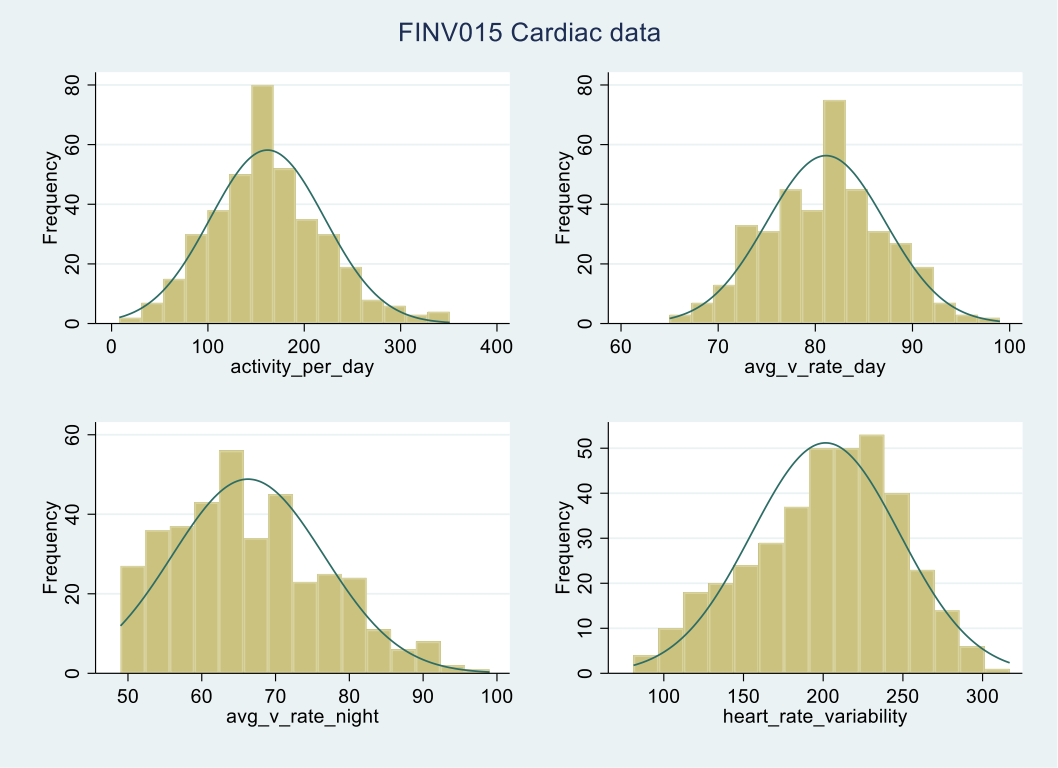

Figure D13. FINV 015. Histograms of activity per day and cardiac variables

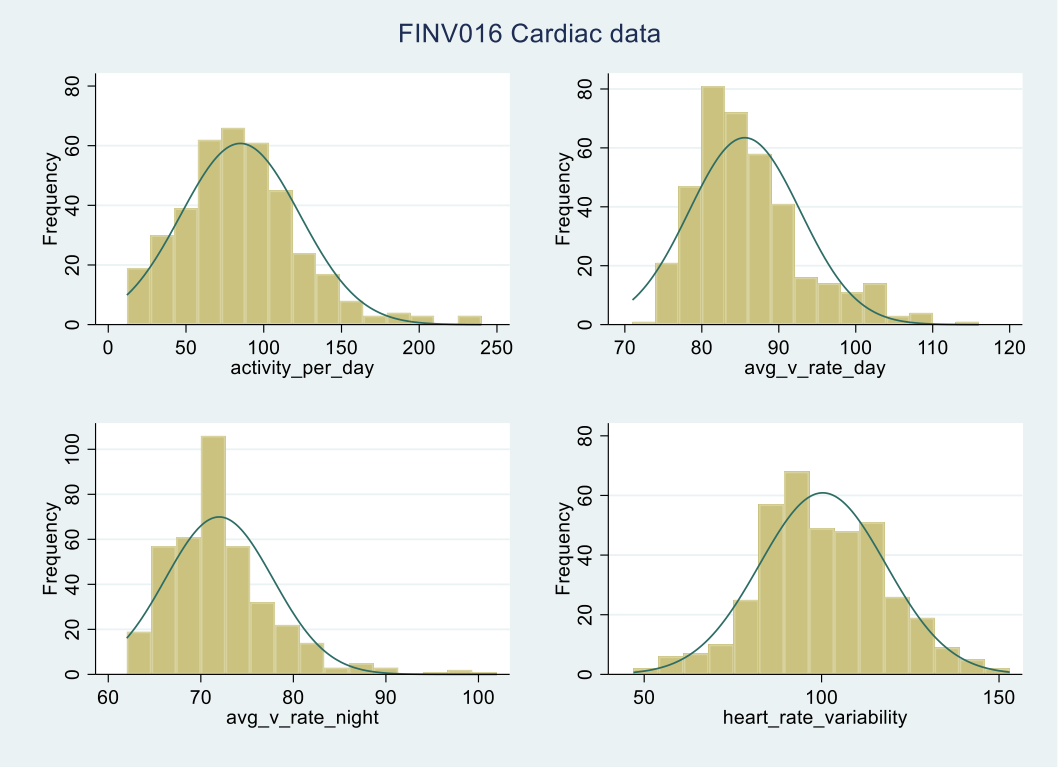

Figure D14. FINV 015. Histograms of activity per day and cardiac variables

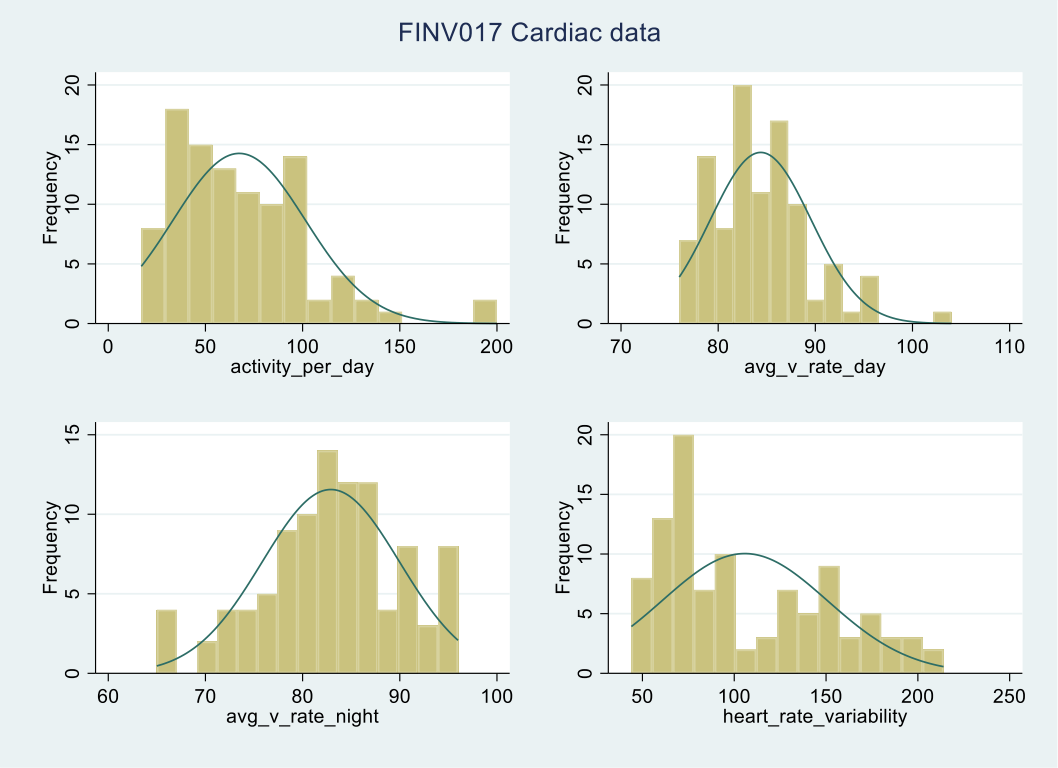

Figure D15. FINV 017. Histograms of activity per day and cardiac variables

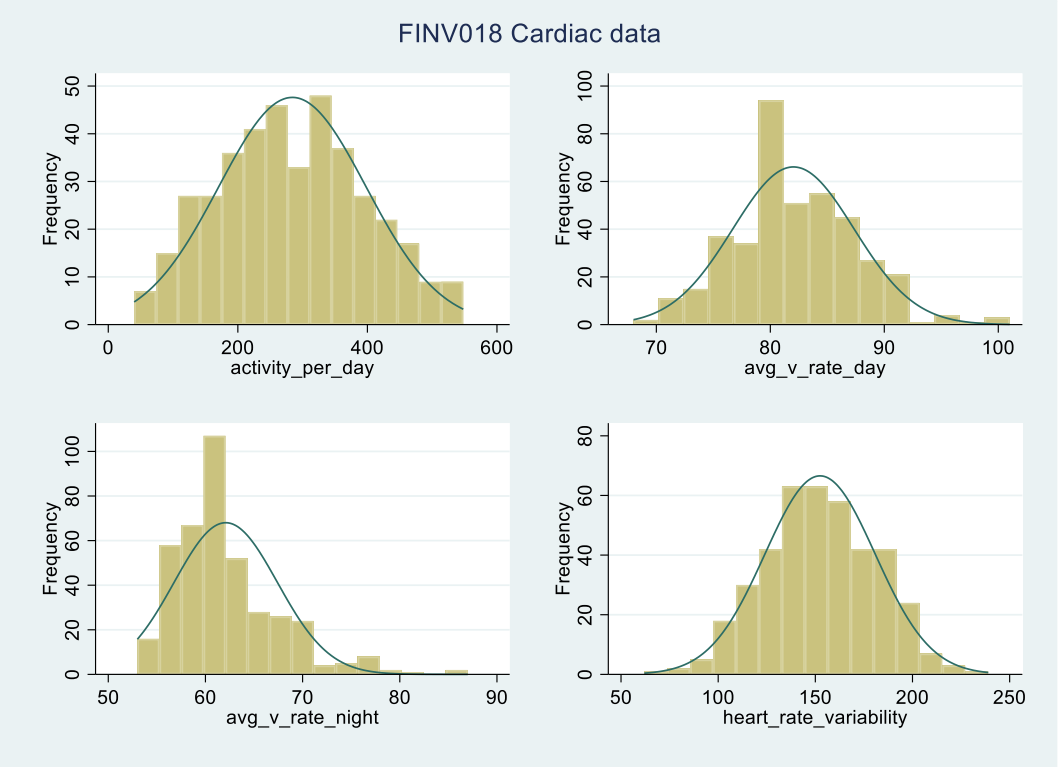

Figure D16. FINV 018. Histograms of activity per day and cardiac variables

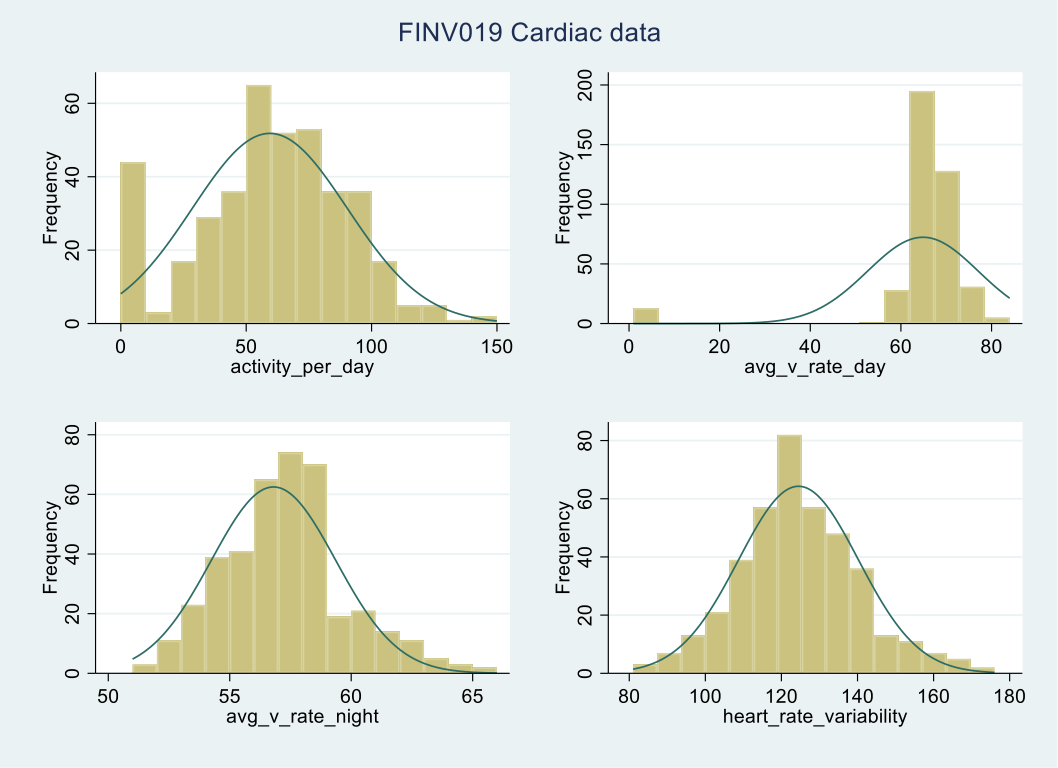

Figure D17. FINV 019. Histograms of activity per day and cardiac variables

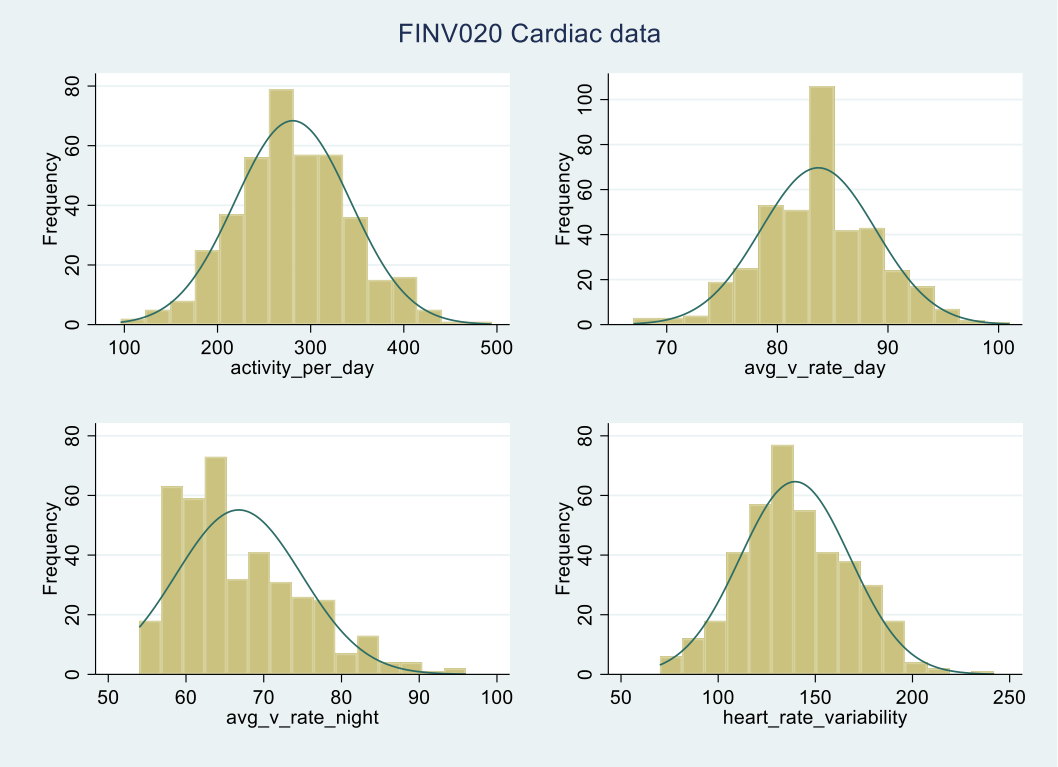

Figure D18. FINV 020. Histograms of activity per day and cardiac variables

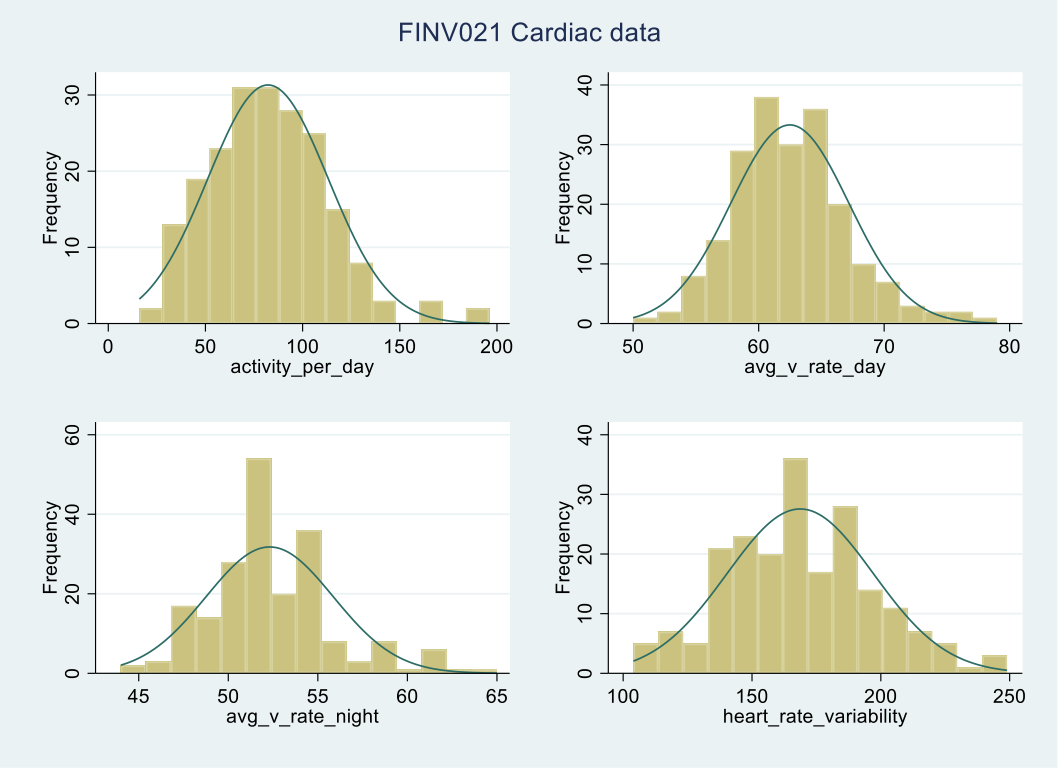

Figure D19. FINV 021. Histograms of activity per day and cardiac variables

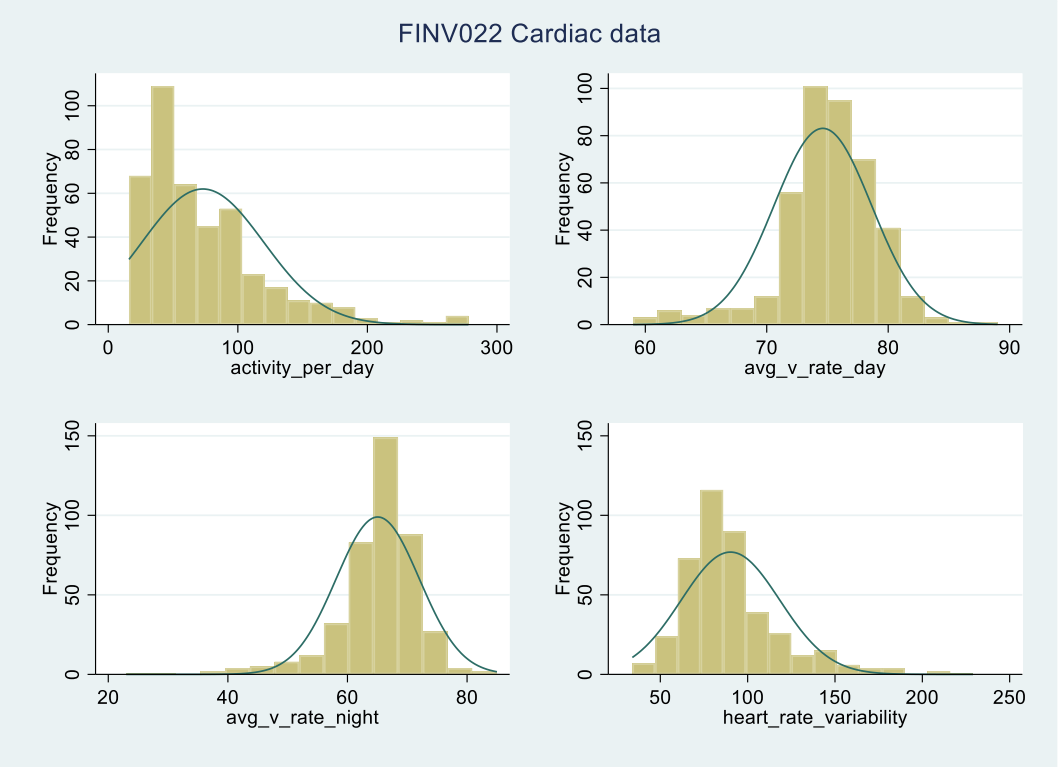

Figure D20. FINV 022. Histograms of activity per day and cardiac variables

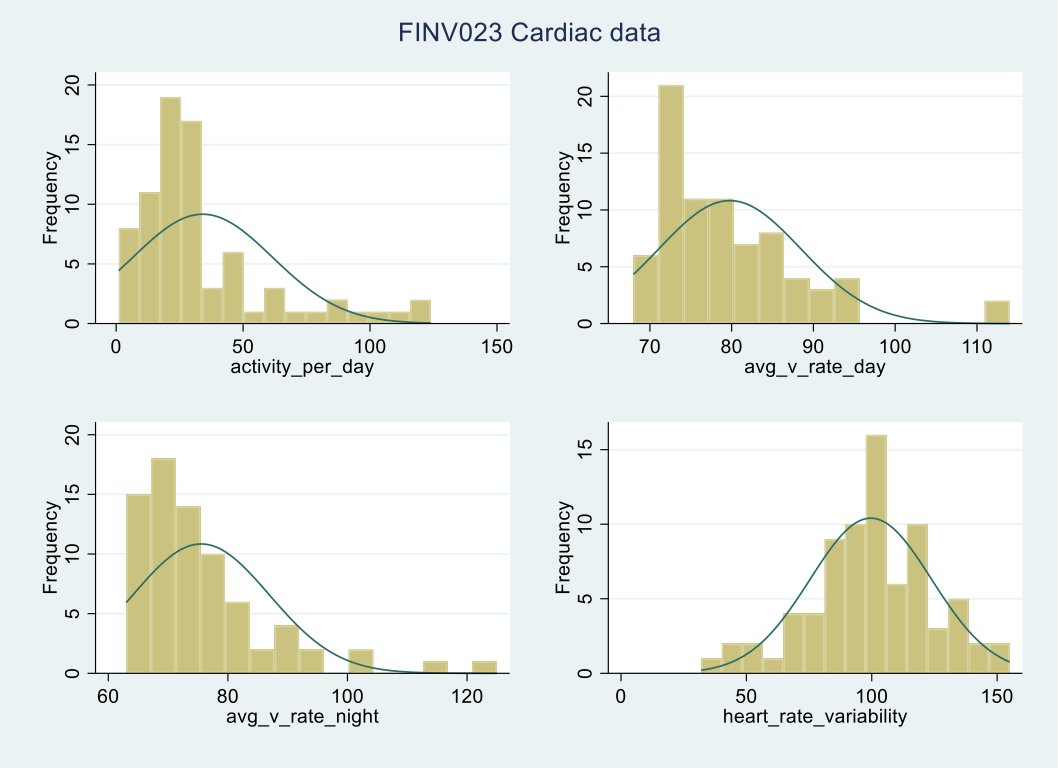

Figure D21. FINV 023. Histograms of activity per day and cardiac variables

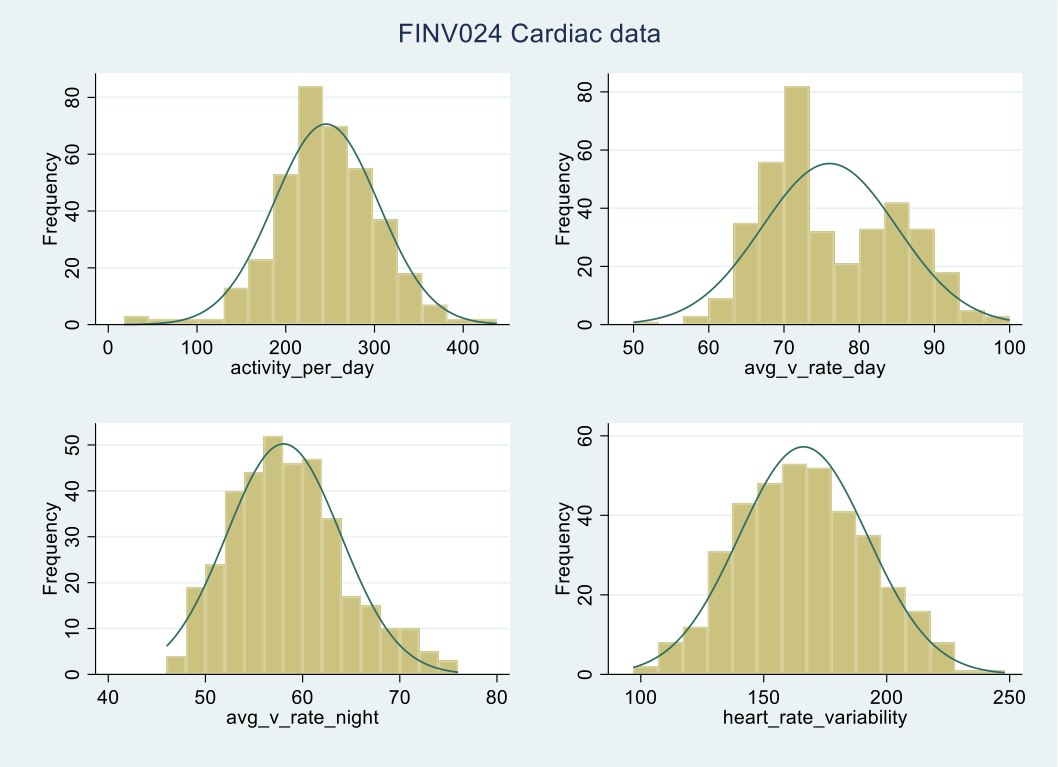

Figure D22. FINV 024. Histograms of activity per day and cardiac variables

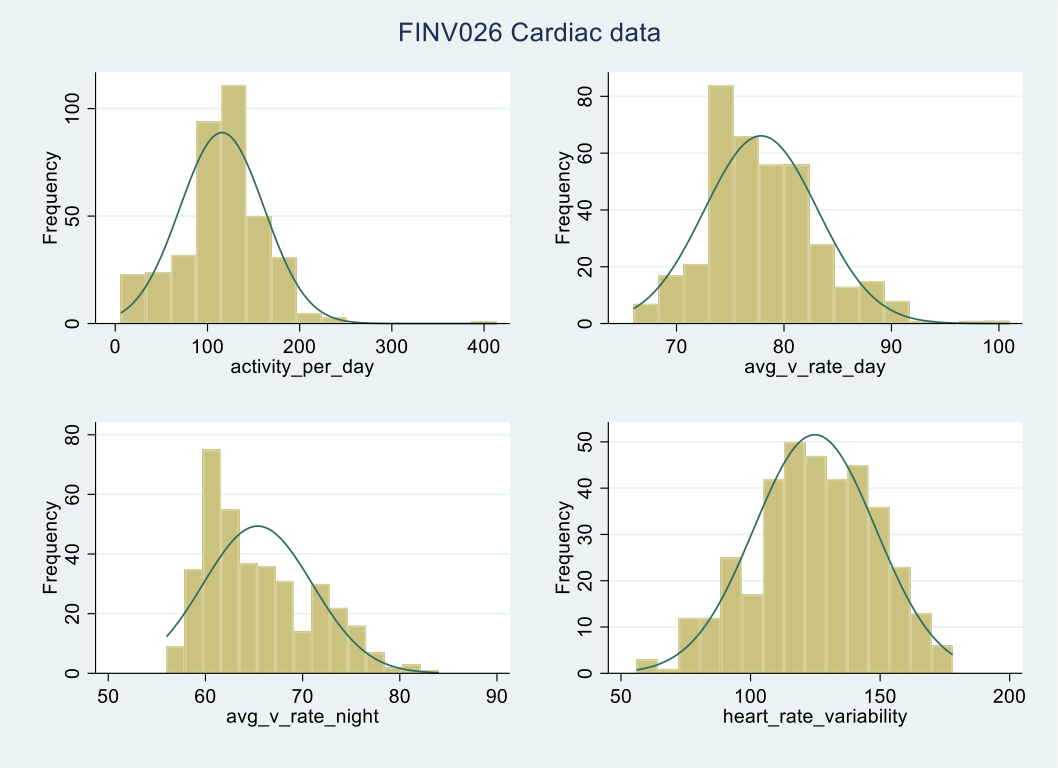

Figure D23. FINV 026. Histograms of activity per day and cardiac variables

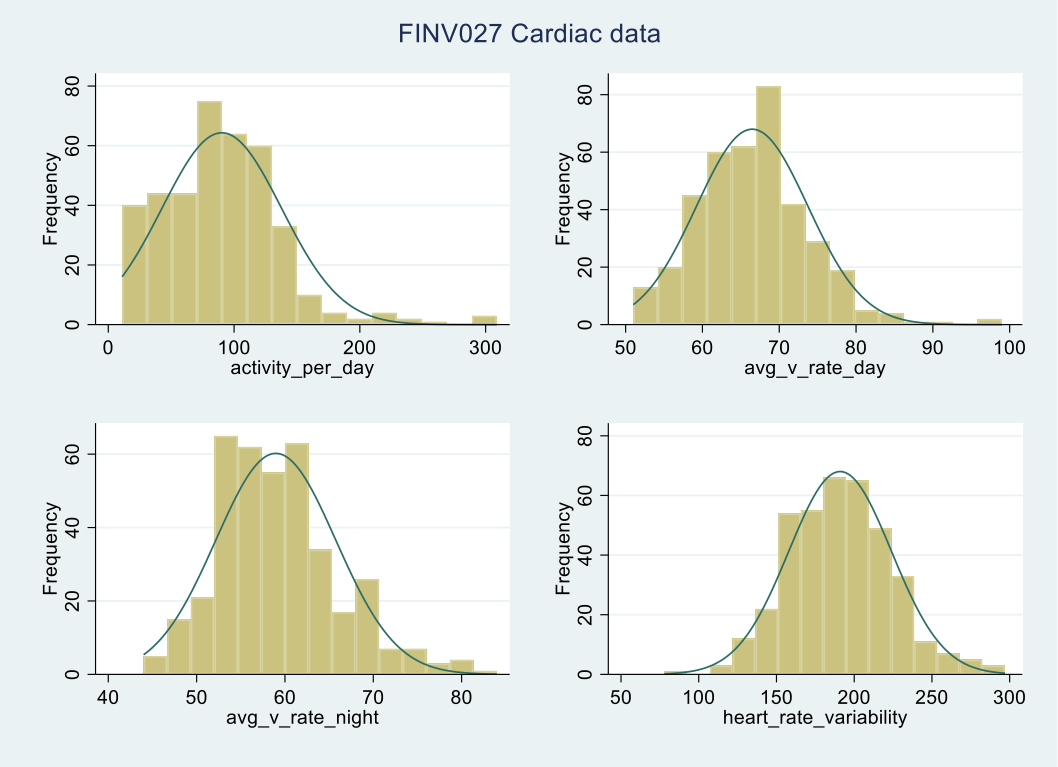

Figure D24. FINV 027. Histograms of activity per day and cardiac variables

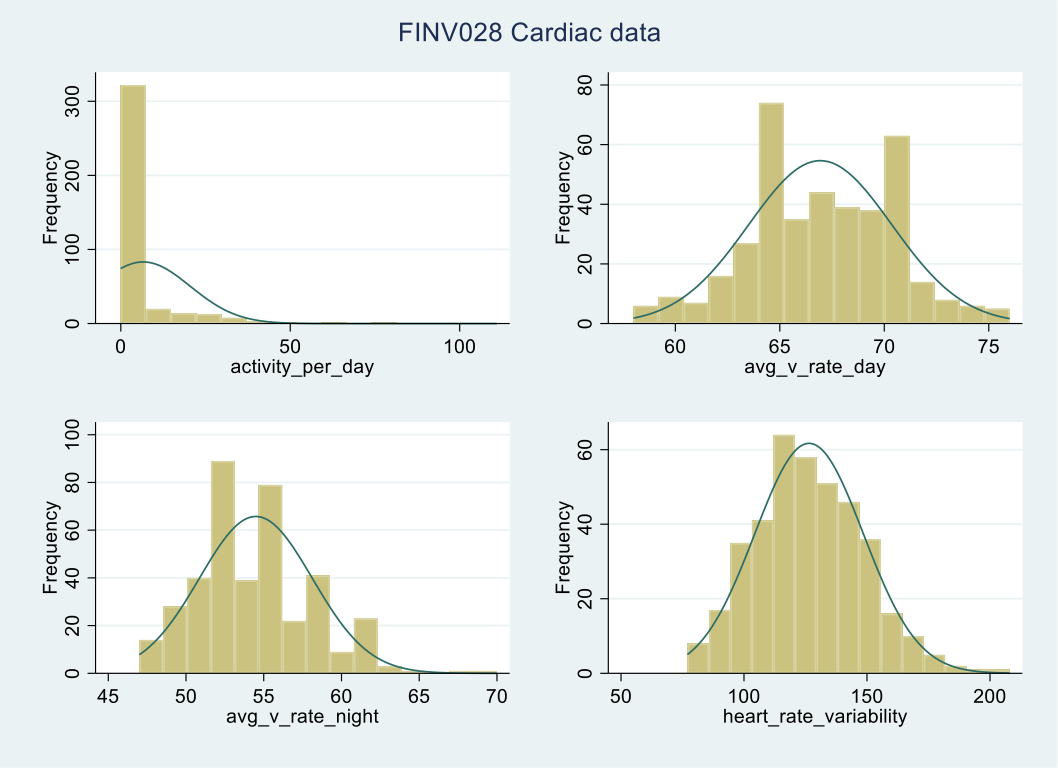

Figure D25. FINV 028. Histograms of activity per day and cardiac variables

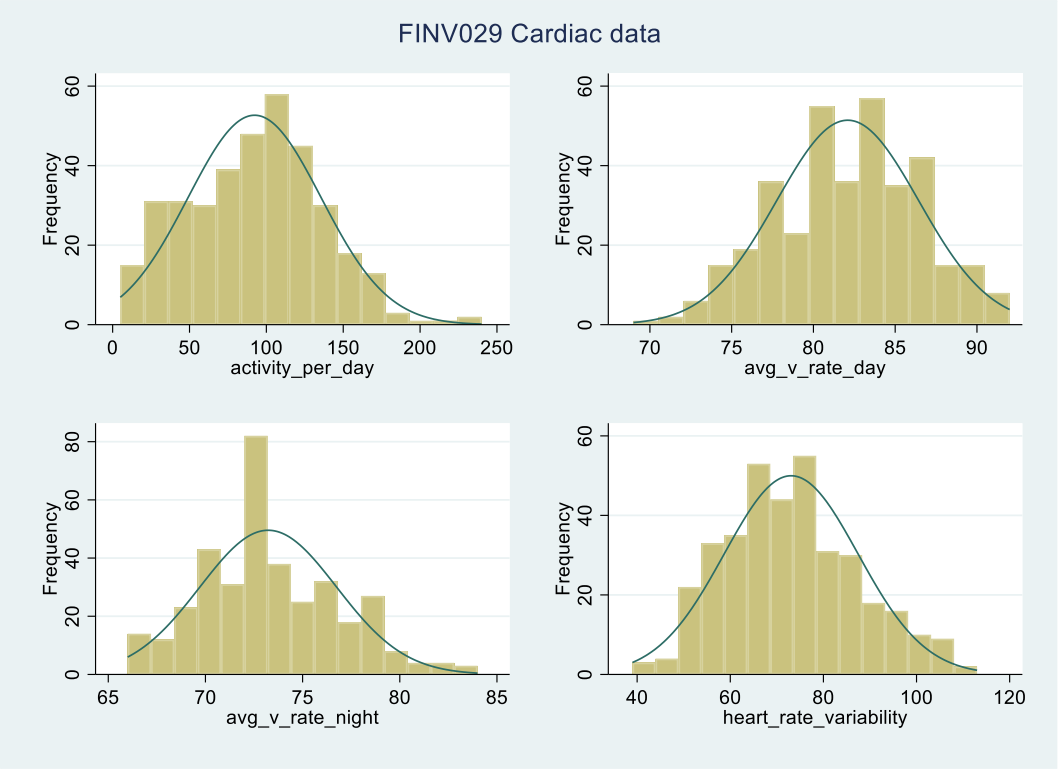

Figure D26. FINV 029. Histograms of activity per day and cardiac variables

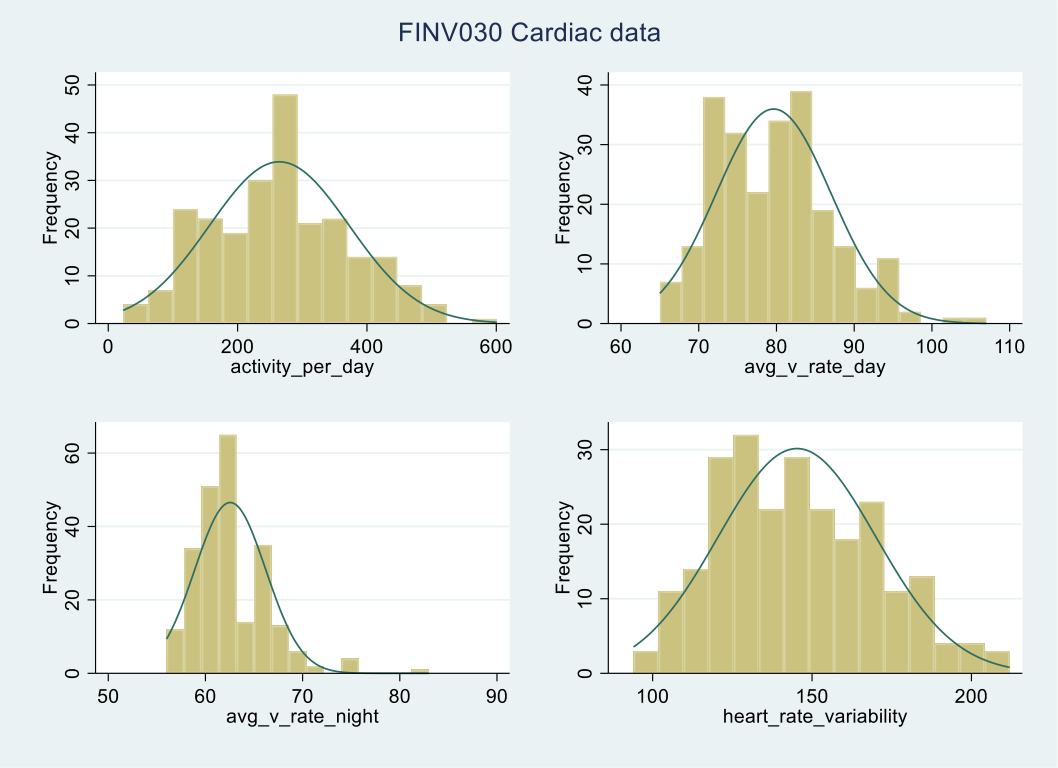

Figure D27. FINV 030 histograms of activity per day and cardiac variables

Appendix E

Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall (1w/f/3d)

For interpretation, the x axis represents the date, while the y axis represents HRV (milliseconds) and activity per day (minutes). The solid blue line represents HRV, the dashed green line represents activity per day and the vertical red line represents the fall event.

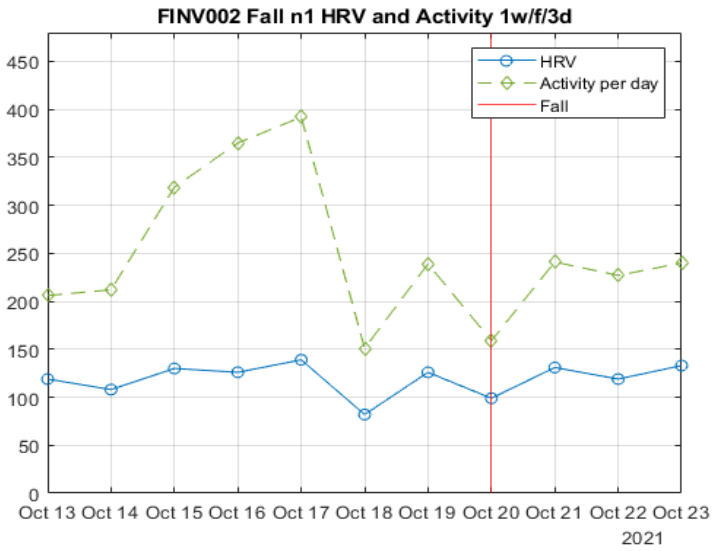

Figure E1. FINV 002 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

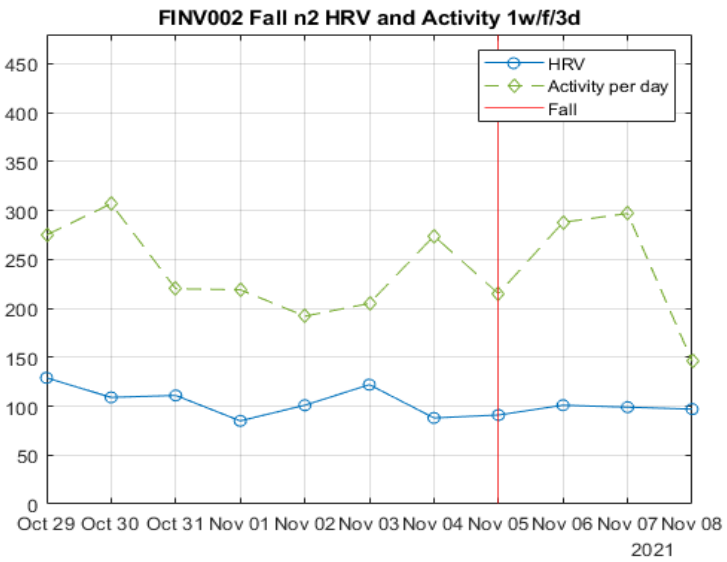

Figure E2. FINV 002 Fall 2. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

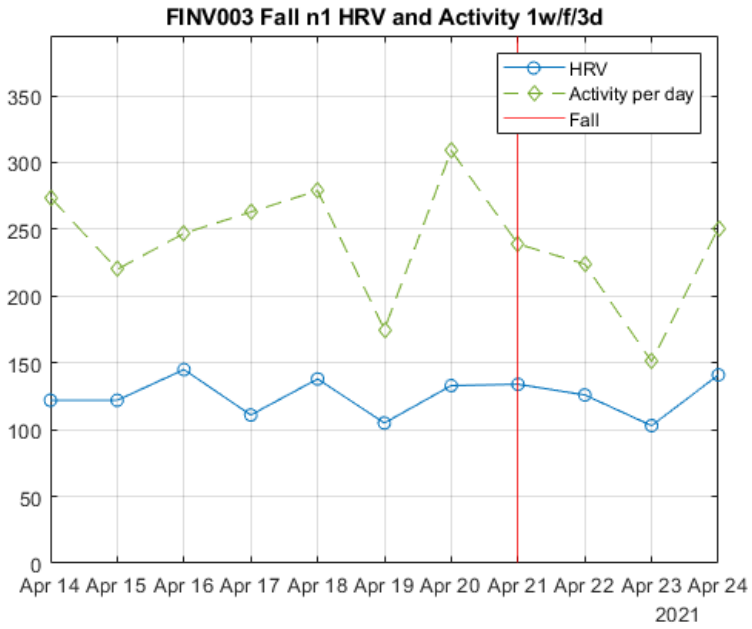

Figure E3. FINV 003 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

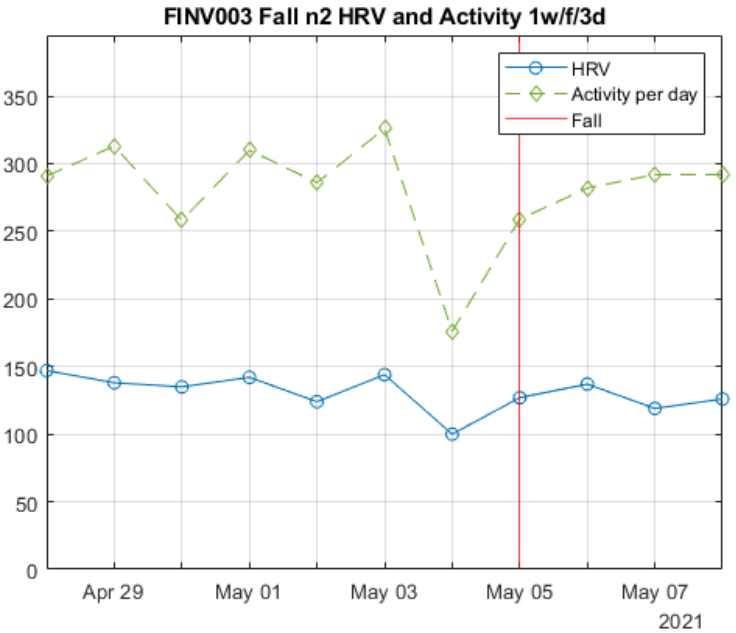

Figure E4. FINV 003 Fall 2. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

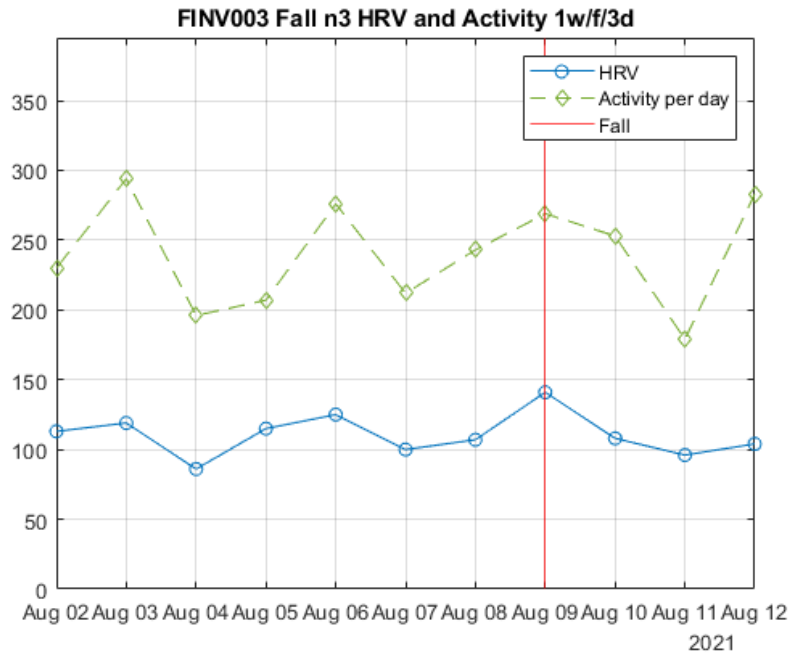

Figure E5. FINV 003 Fall 3. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

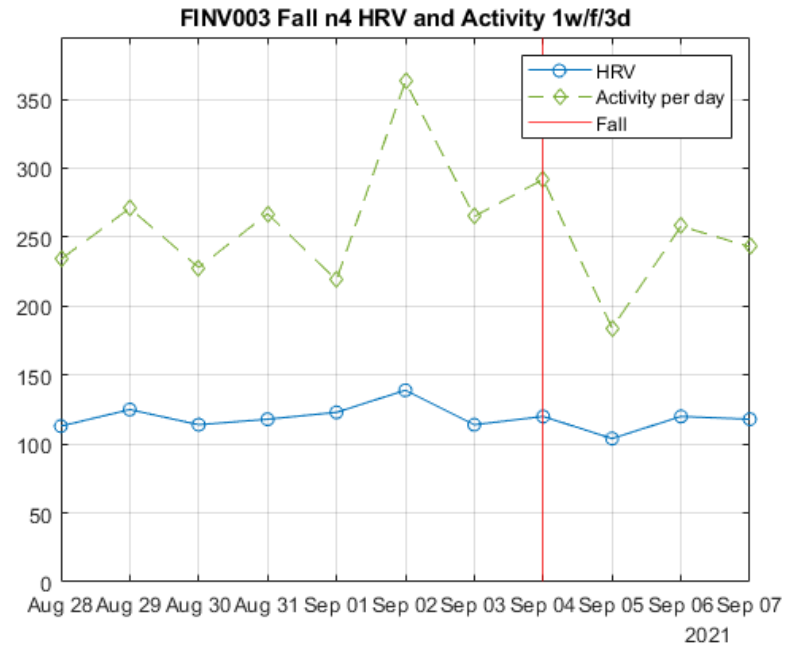

Figure E6. FINV 003 Fall 4. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

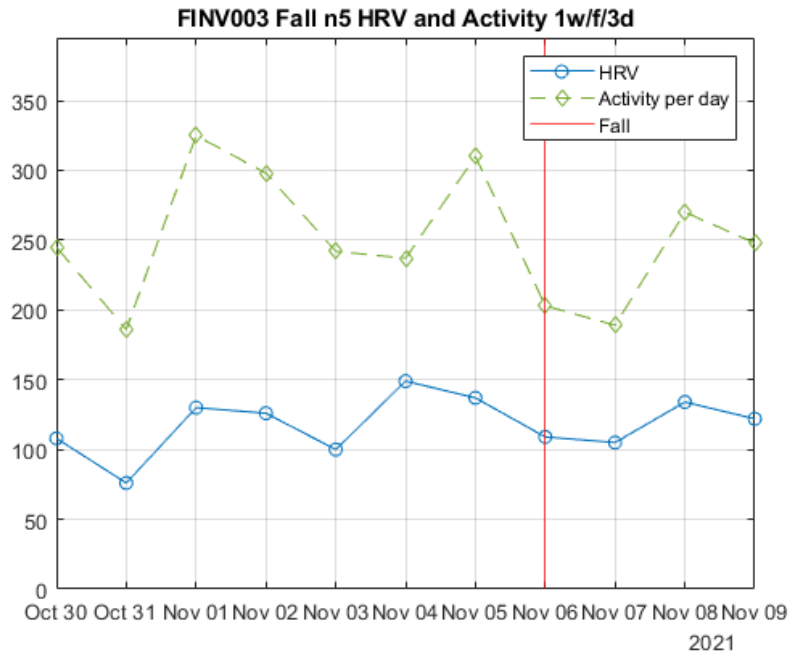

Figure E7. FINV 003 Fall 5. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

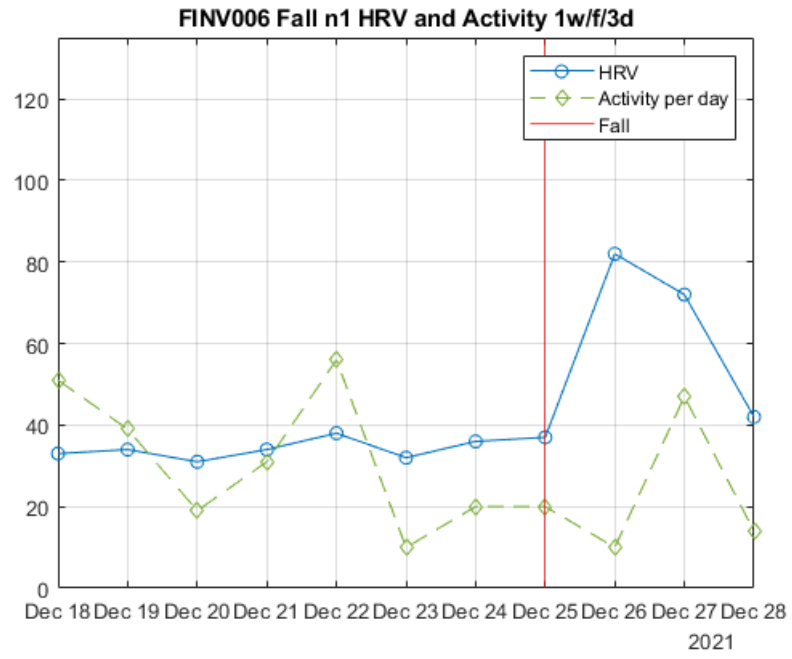

Figure E8 . FINV 006 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

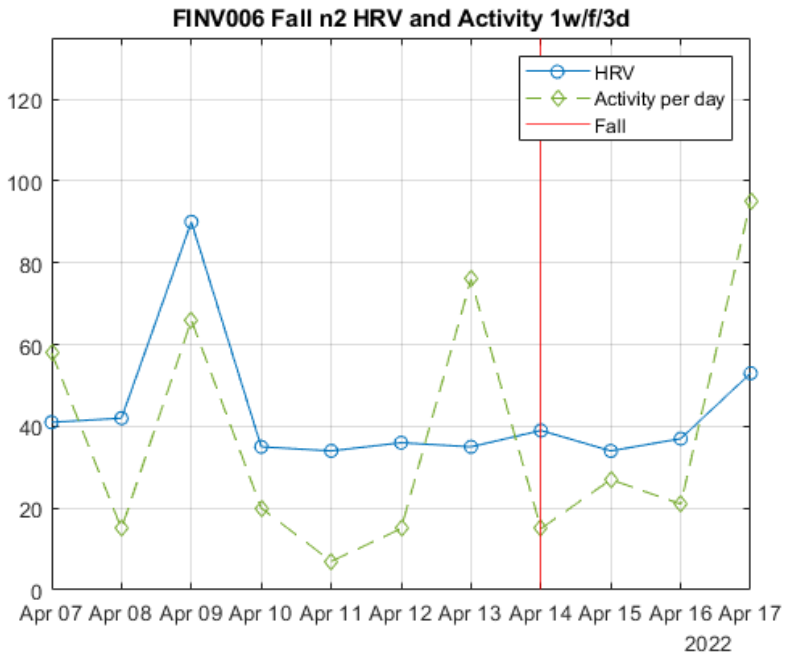

Figure E9. FINV 006 Fall 2. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

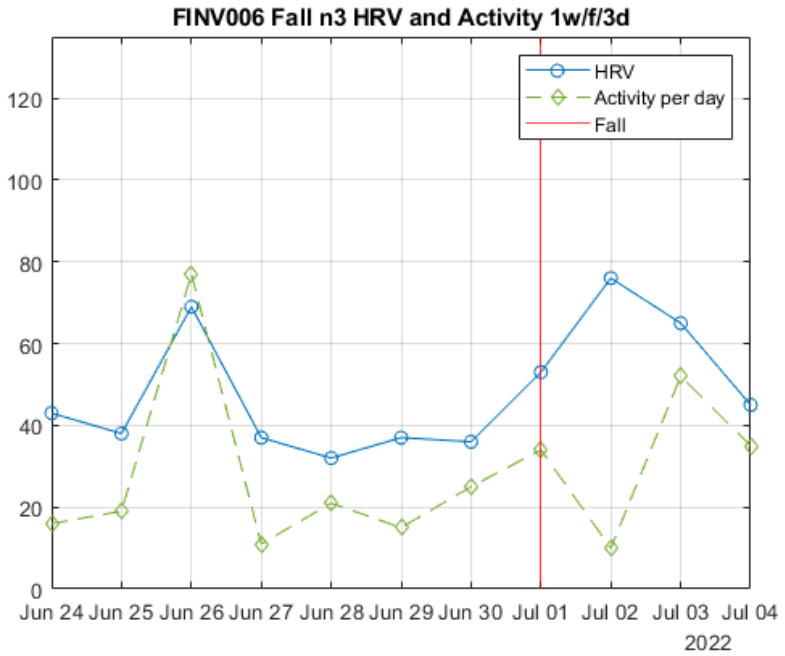

Figure E10. FINV 006 Fall 3. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

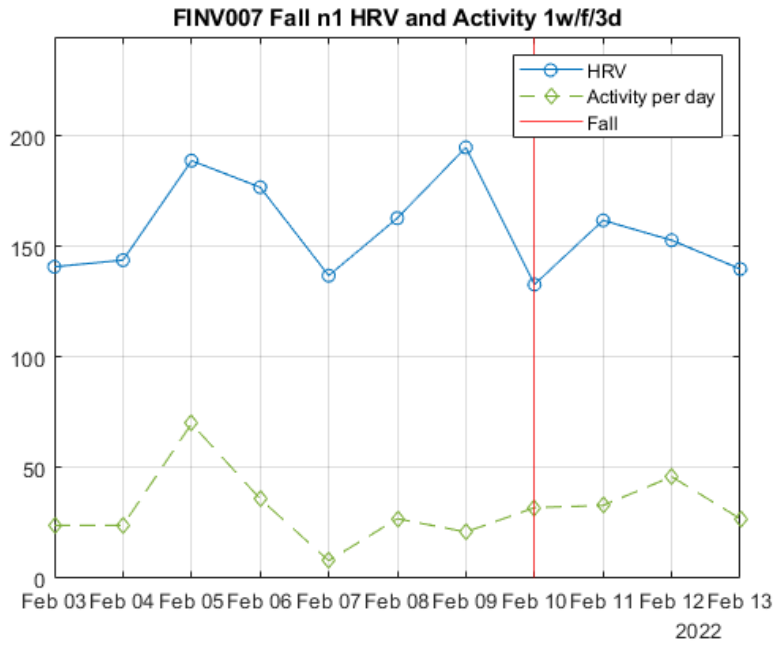

Figure E11. FINV 007 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

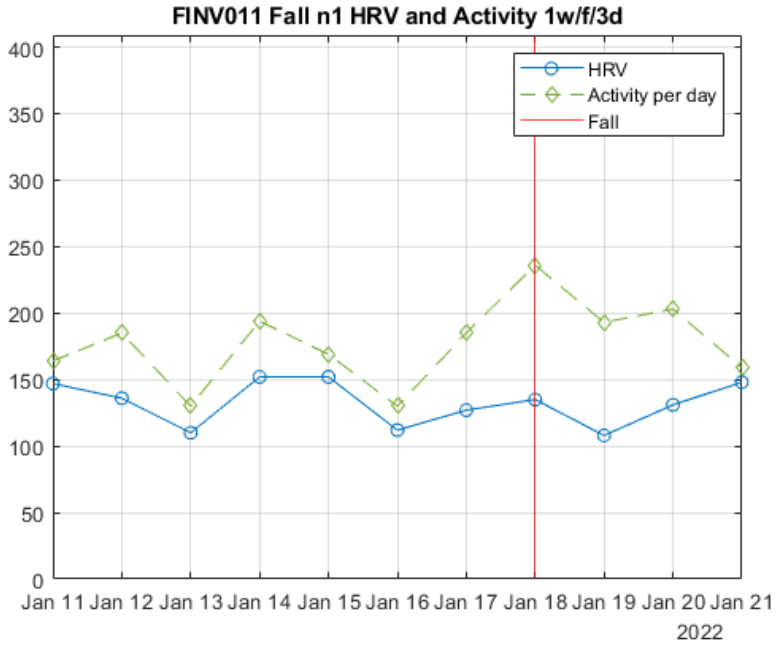

Figure E12. FINV011 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

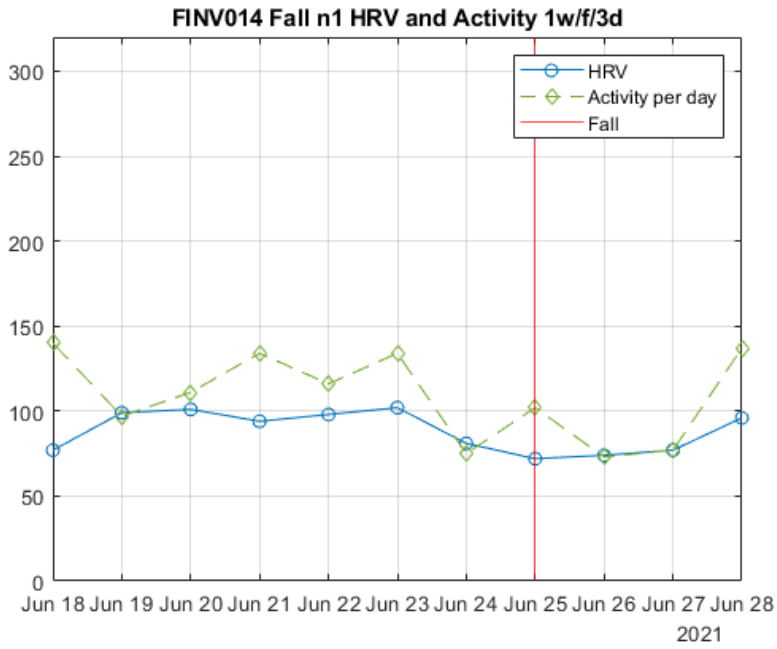

Figure E13. FINV014 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

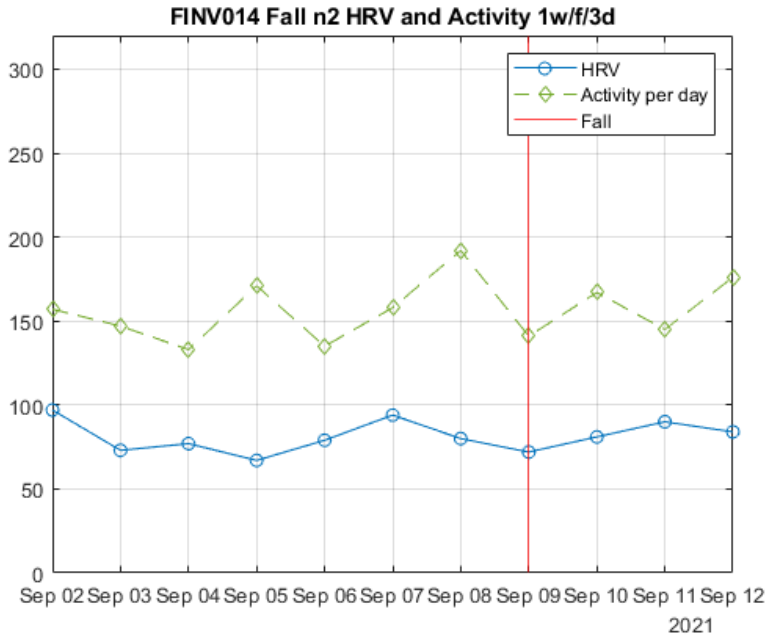

Figure E14. FINV014 Fall 2. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

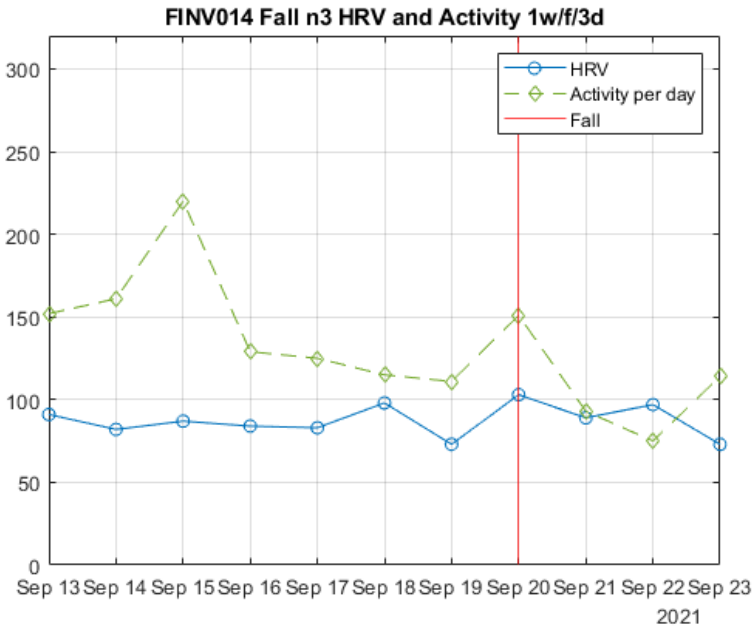

Figure E15. FINV014 Fall 3. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

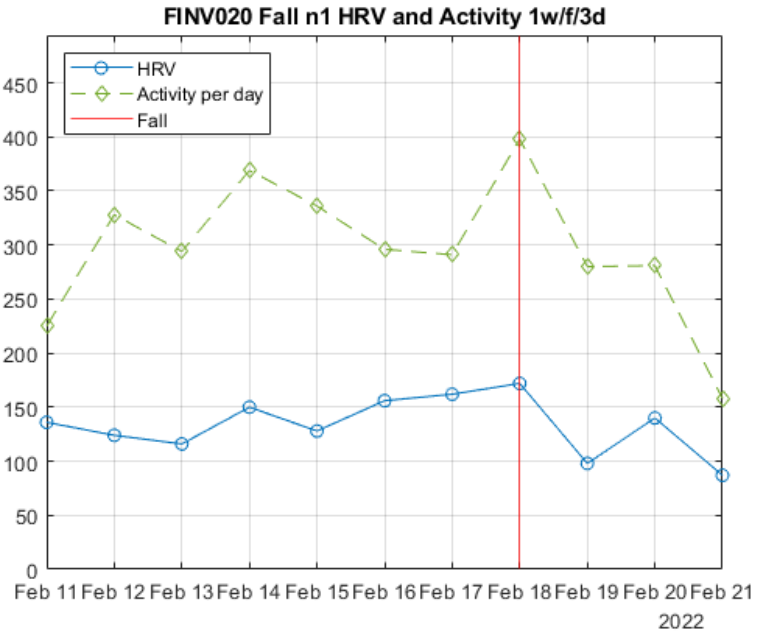

Figure E16. FINV020 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

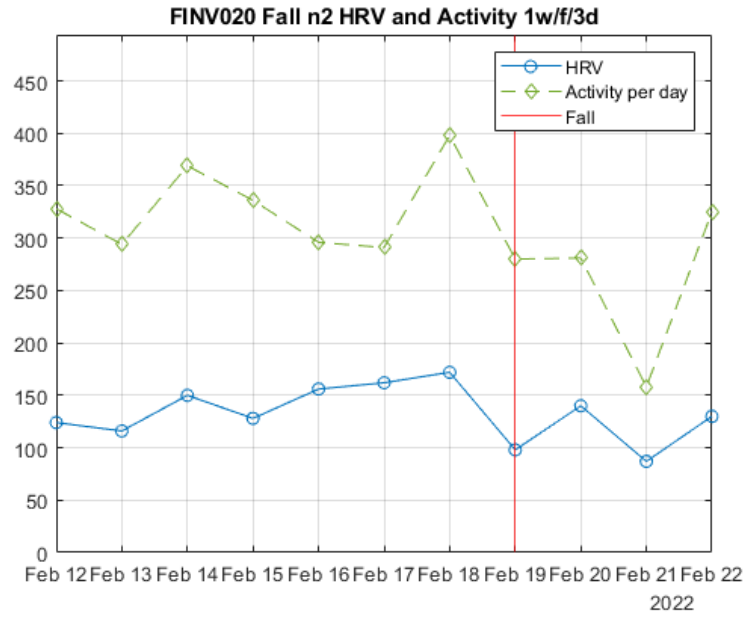

Figure E17. FINV020 Fall 2. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

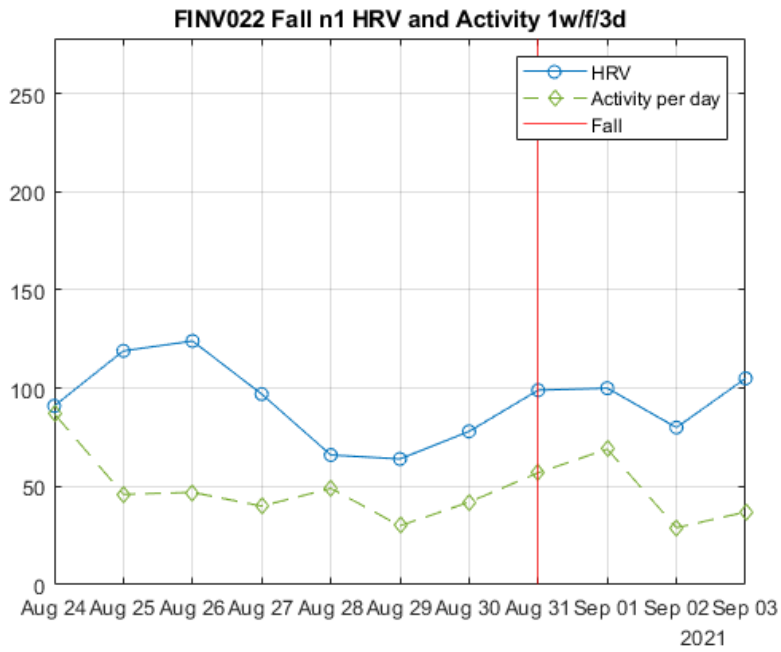

Figure E18. FINV022 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

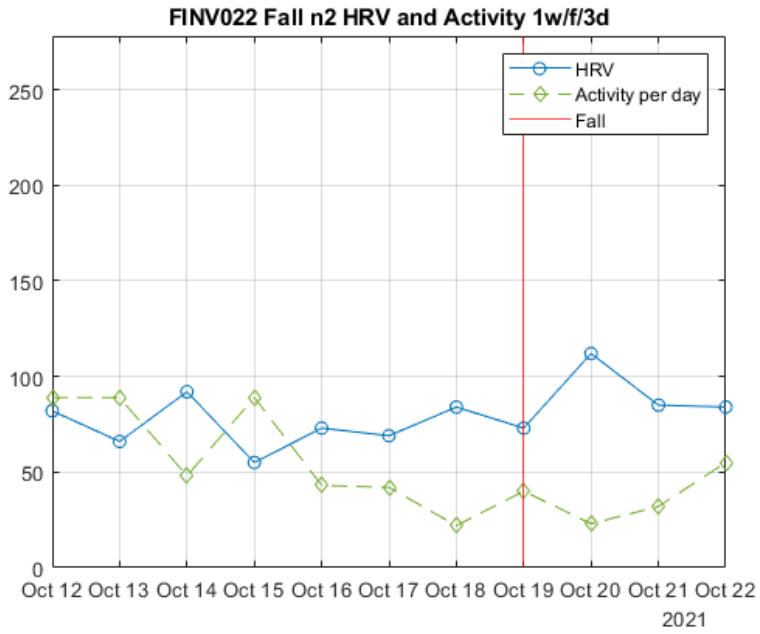

Figure E19. FINV022 Fall 2. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

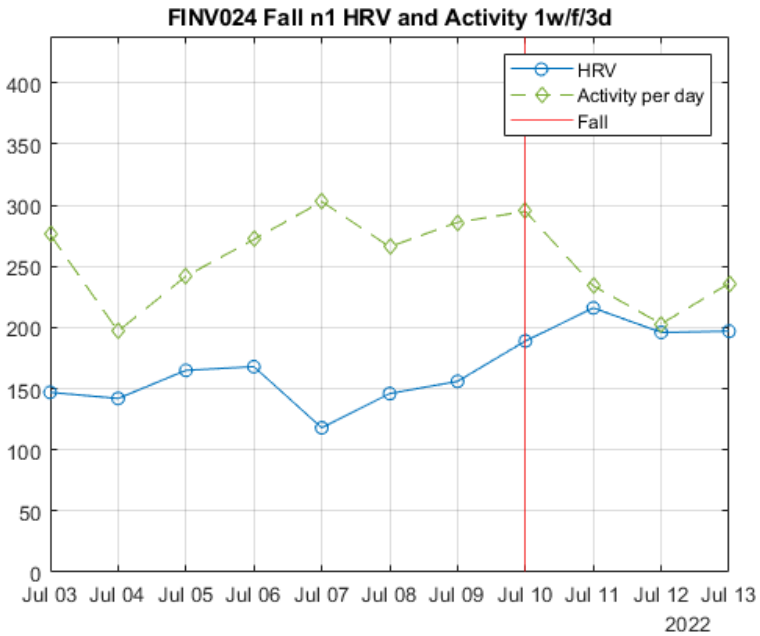

Figure E20. FINV024 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

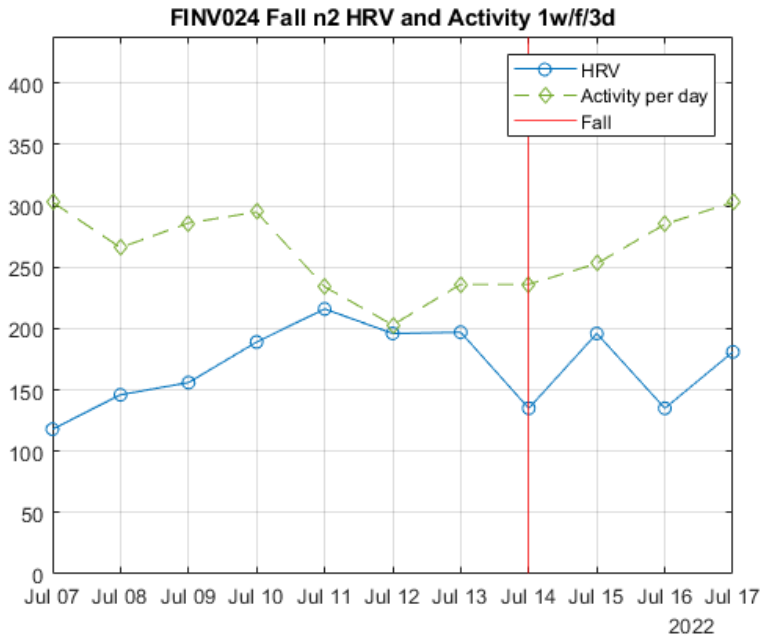

Figure E21. FINV024 Fall 2. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

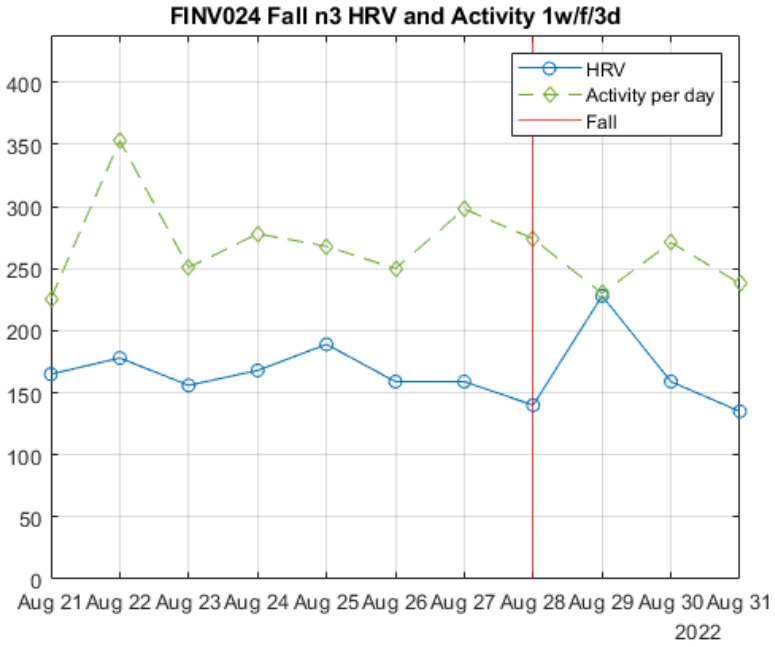

Figure E22. FINV024 Fall 3. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

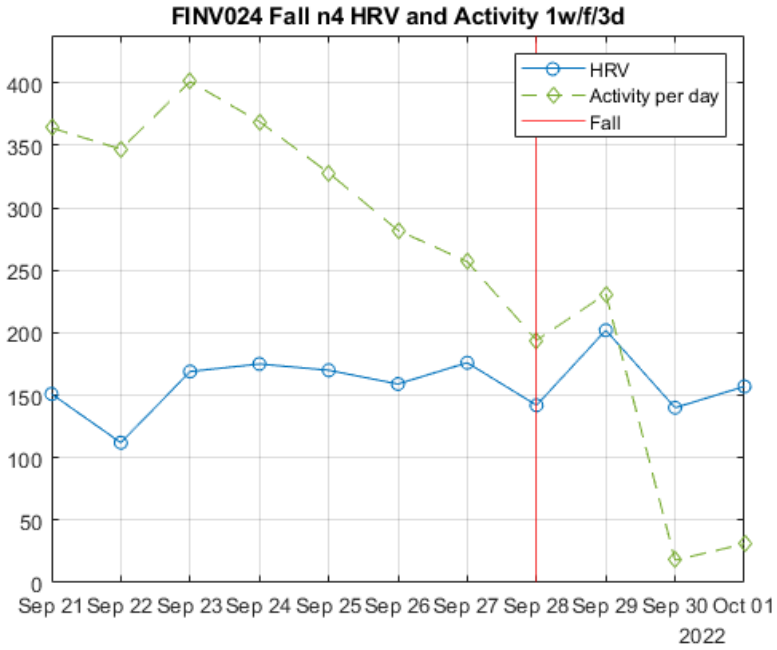

Figure E23. FINV024 Fall 4. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

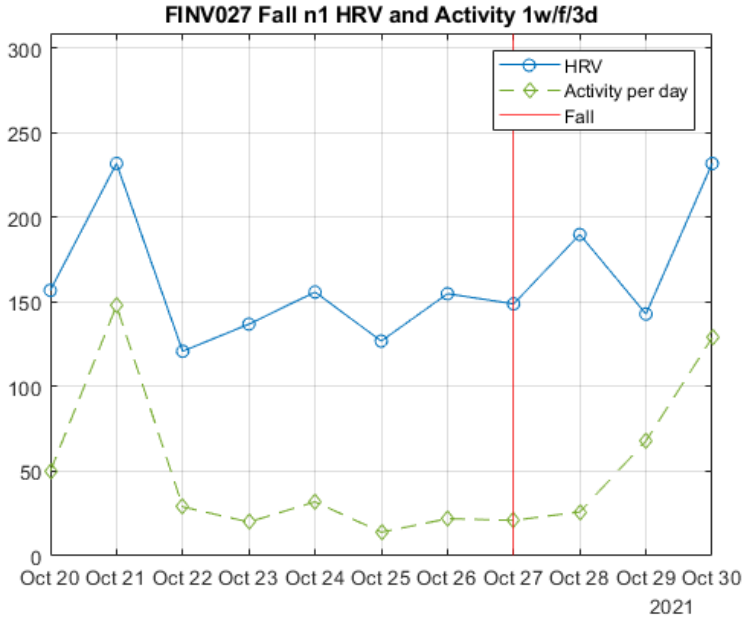

Figure E24. FINV027 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

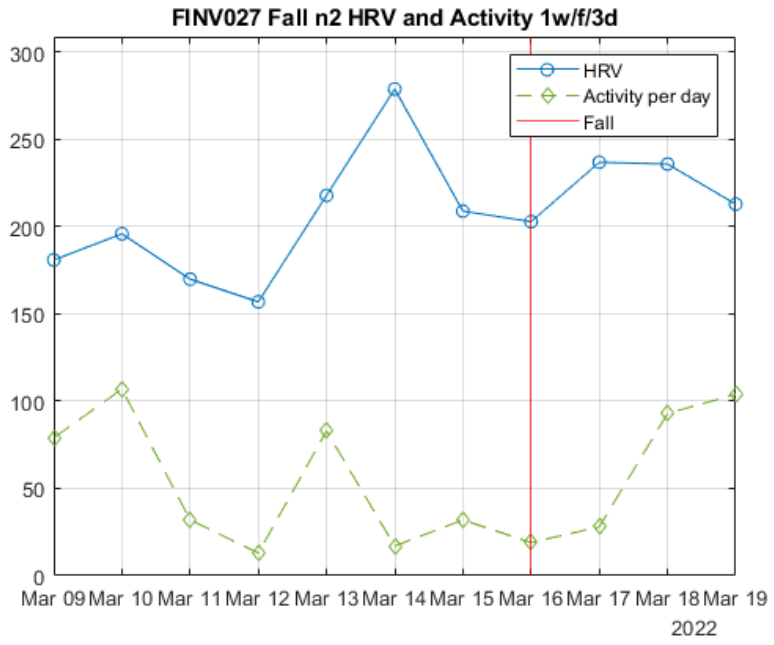

Figure E25. FINV027 Fall 2. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

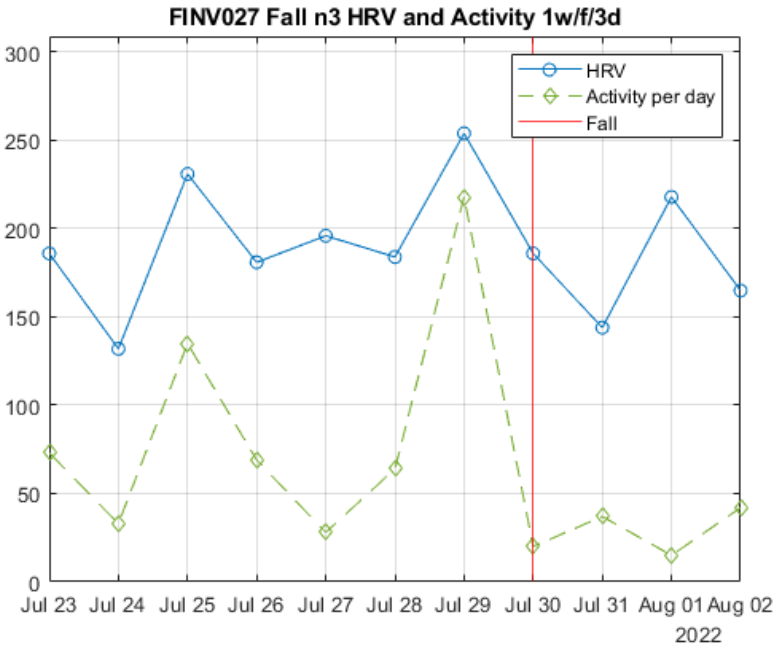

Figure E26. FINV027 Fall 3. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

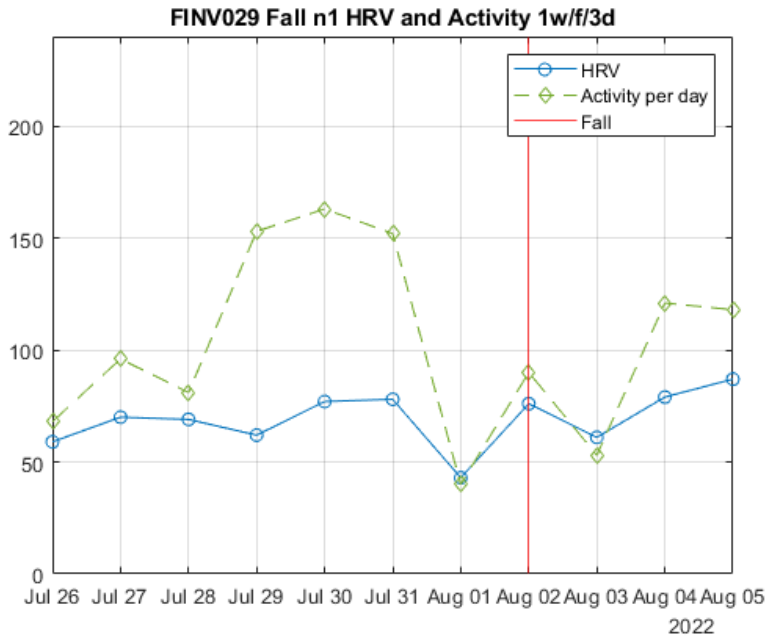

Figure E27. FINV029 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

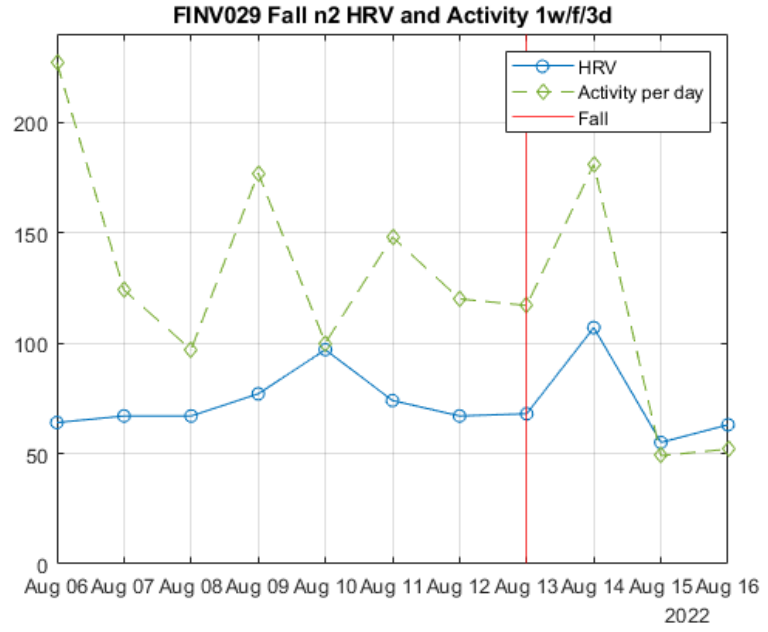

Figure E28. FINV029 Fall 2. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

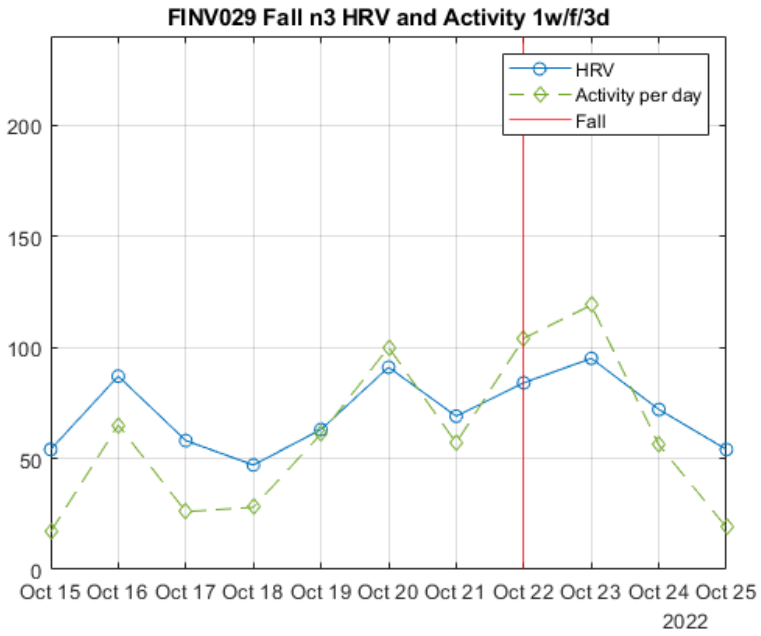

Figure E29. FINV029 Fall 3. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

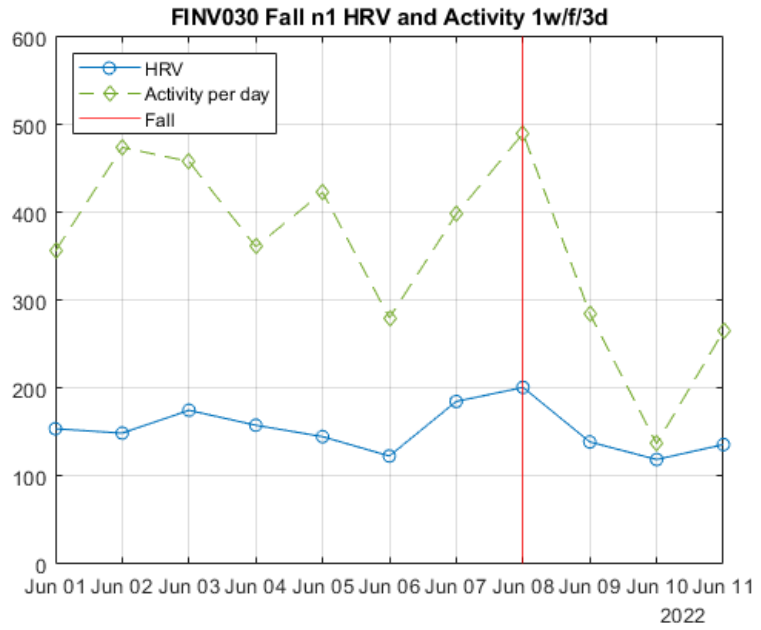

Figure E30. FINV030 Fall 1. Line graphs of HRV, activity, and falls- 1 week before fall and 3 days post fall

Appendix F

Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

For interpretation, the x axis represents heart rate variability (HRV in milliseconds) , while the y axis represents activity per day (in minutes). The circles represent days with the solid red circle representing the fall day.

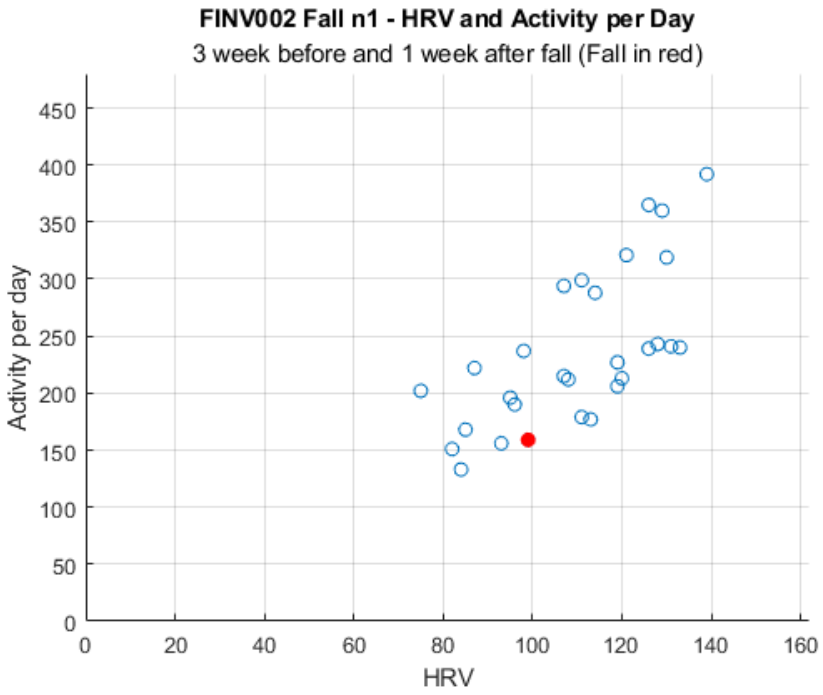

Figure F1 FINV002 Fall 1. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

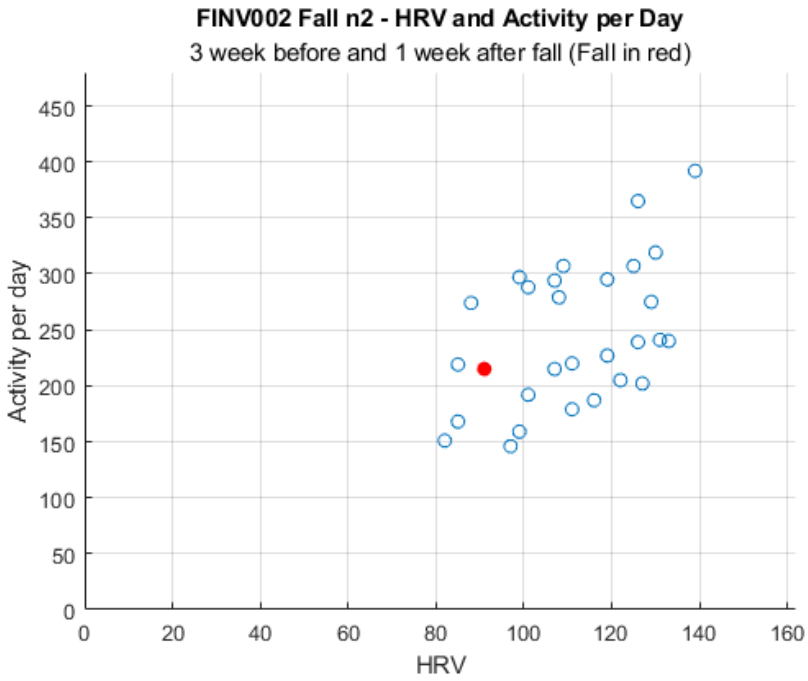

Figure F2 FINV002 Fall 2. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

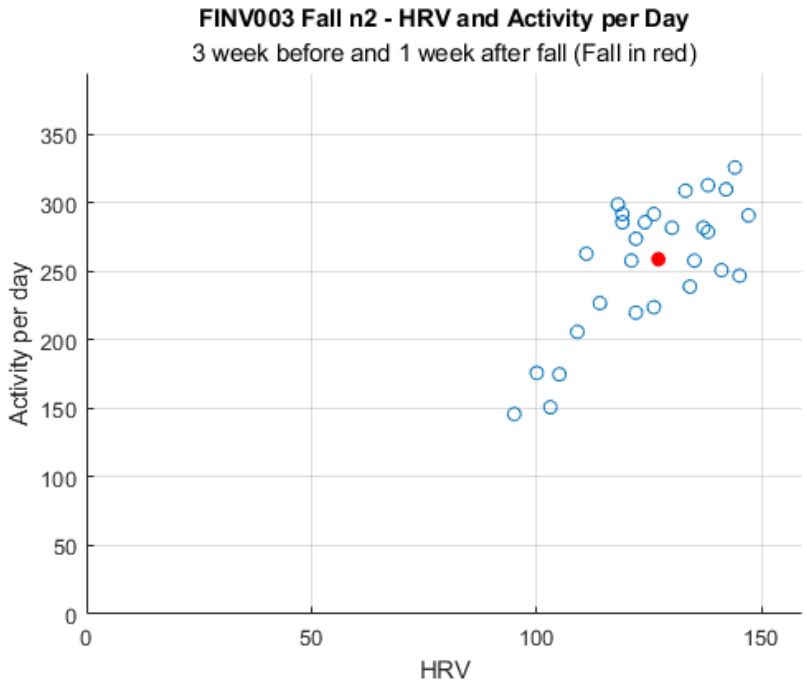

Figure F3 FINV003 Fall 2. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

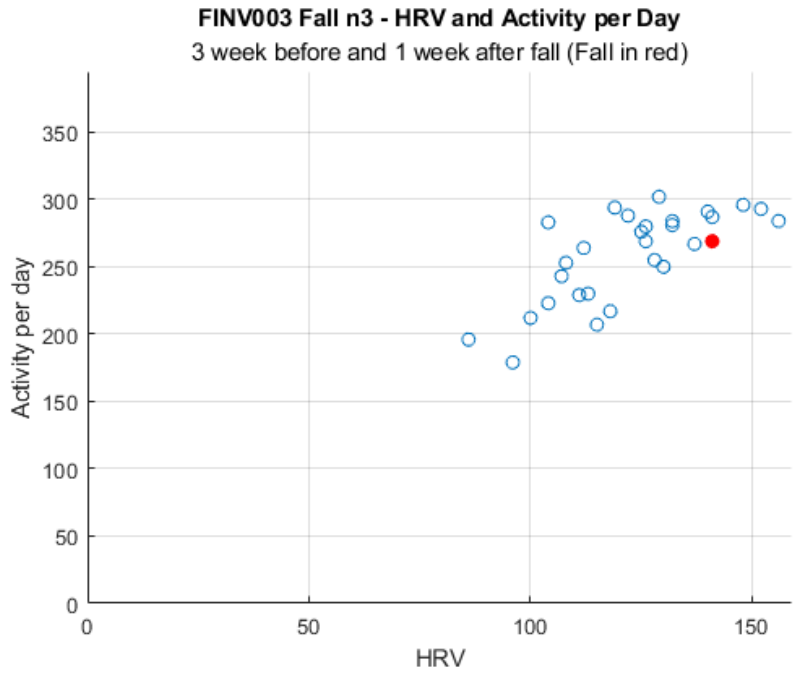

Figure F4. FINV003 Fall 3. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

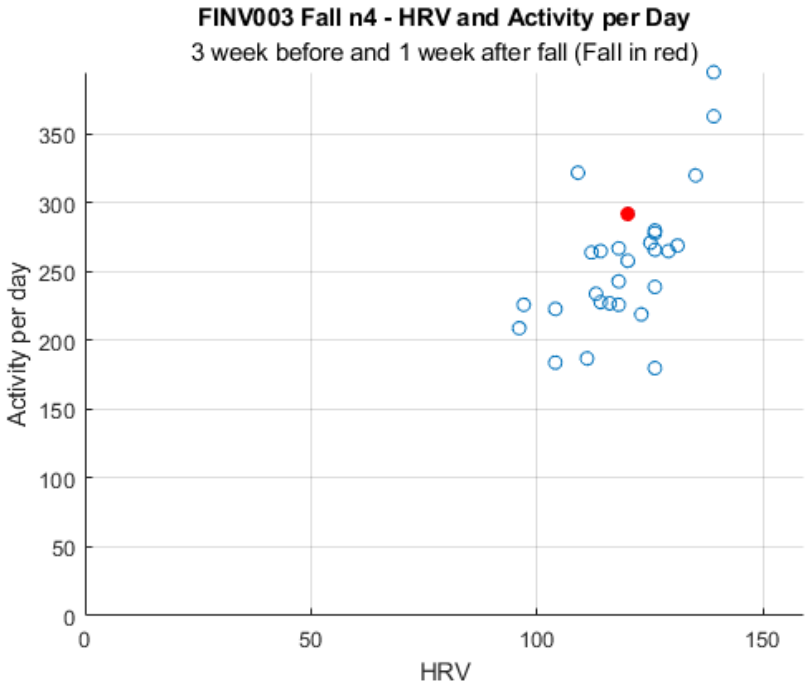

Figure F5. FINV003 Fall 4. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

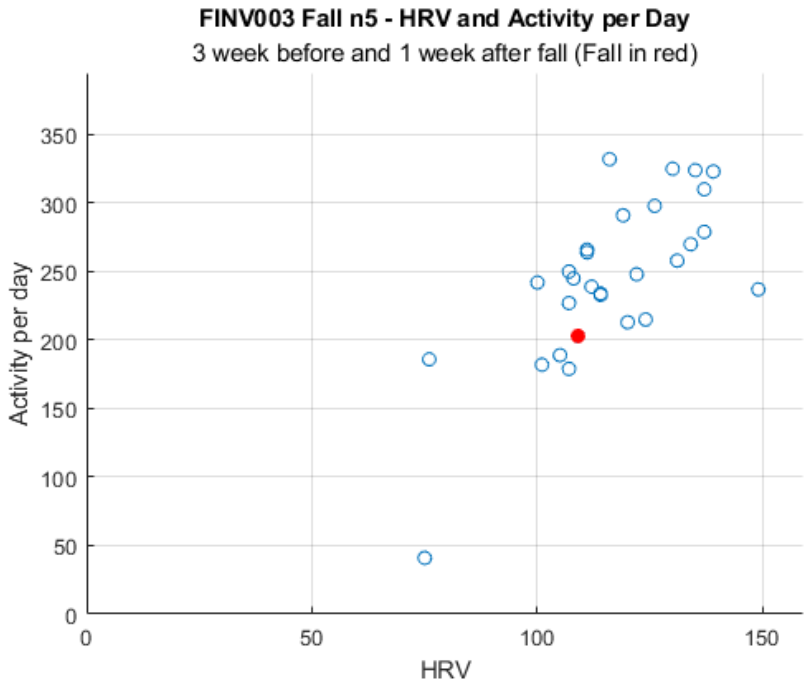

Figure F6. FINV003 Fall 5. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

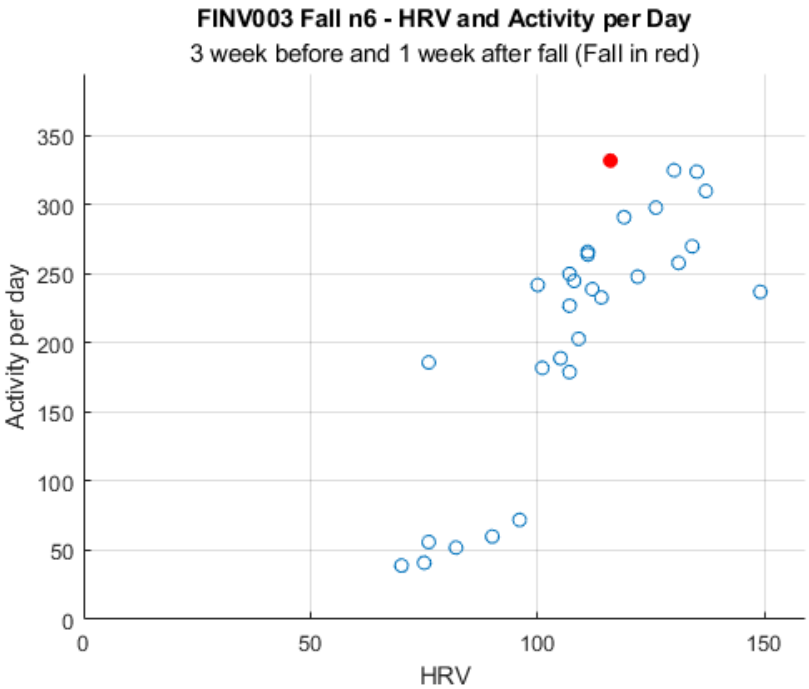

Figure F7. FINV003 Fall 6. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

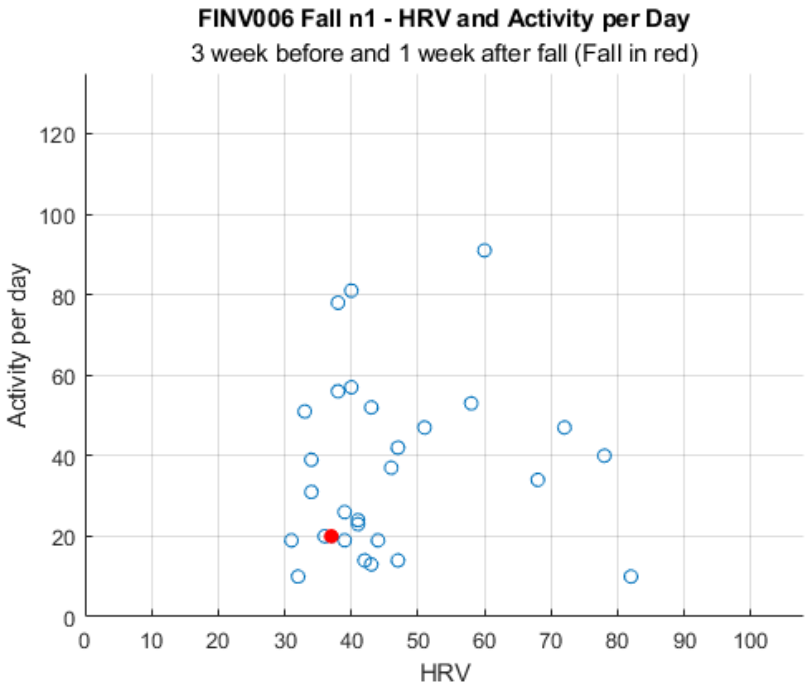

Figure F8. FINV006 Fall 1. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

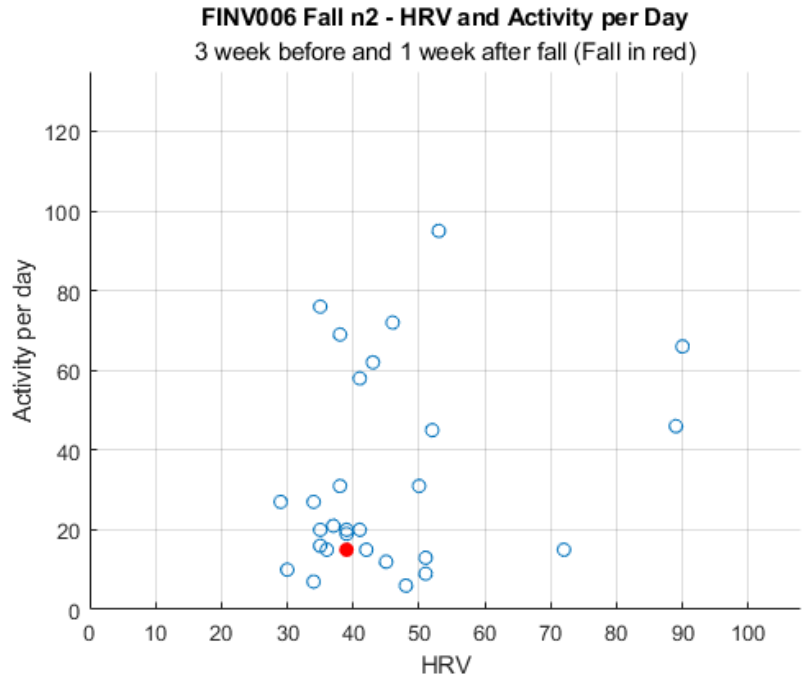

Figure F9. FINV006 Fall 2. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

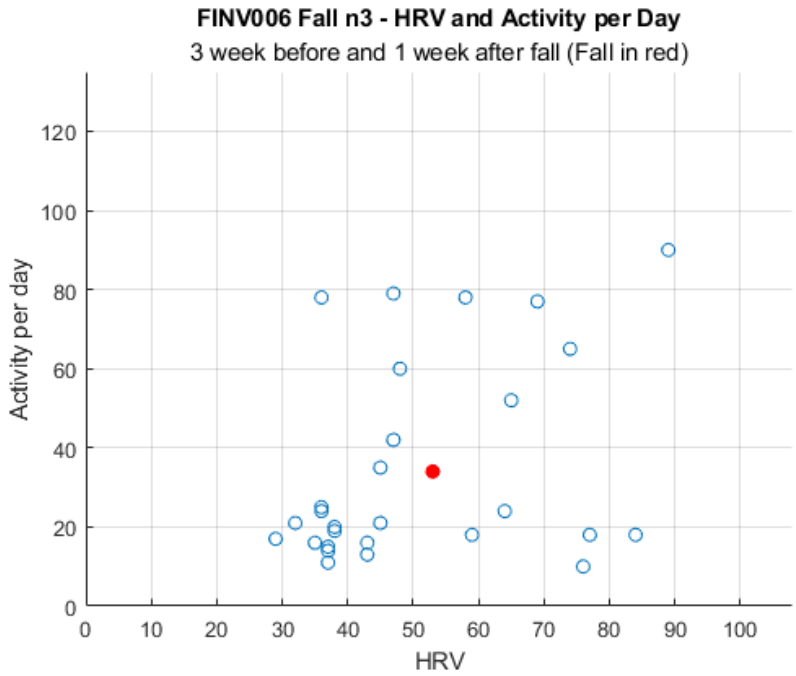

Figure F10. FINV006 Fall 3. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

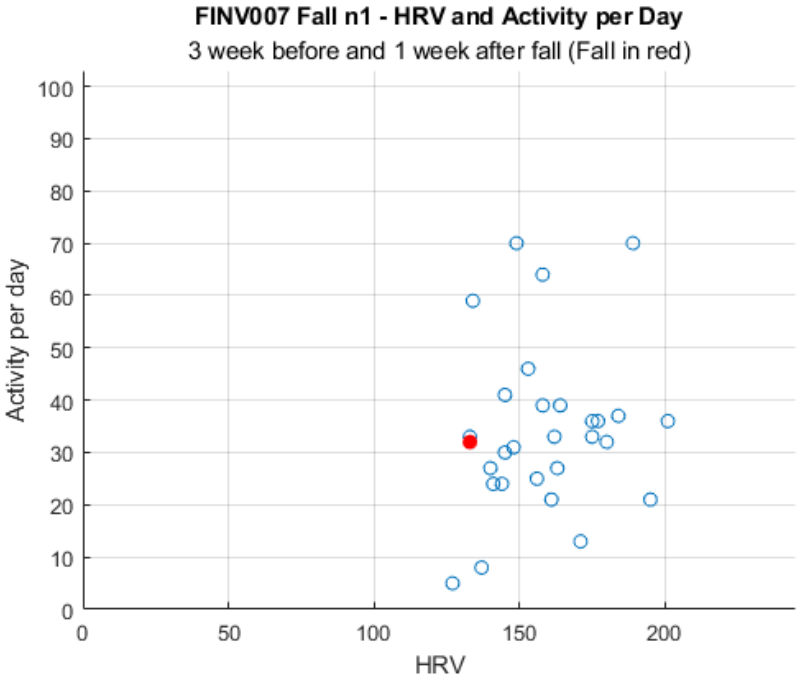

Figure F11. FINV007 Fall 1. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

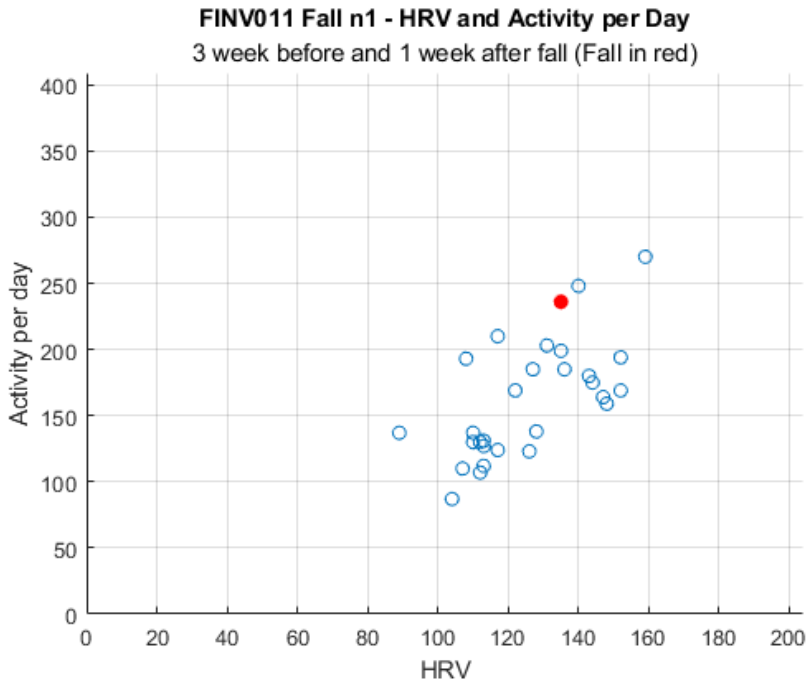

Figure F12. FINV011 Fall 1. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

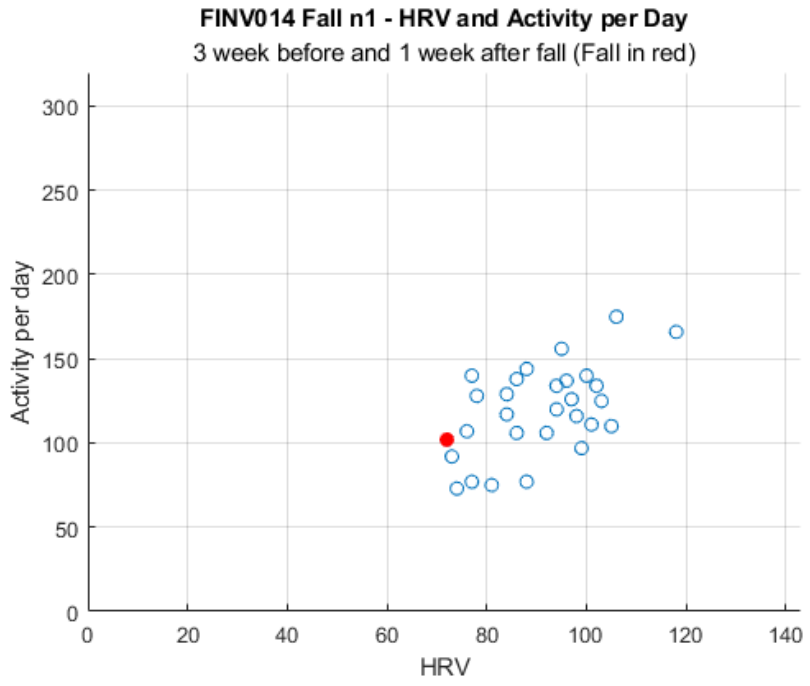

Figure F13. FINV014 Fall 1. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

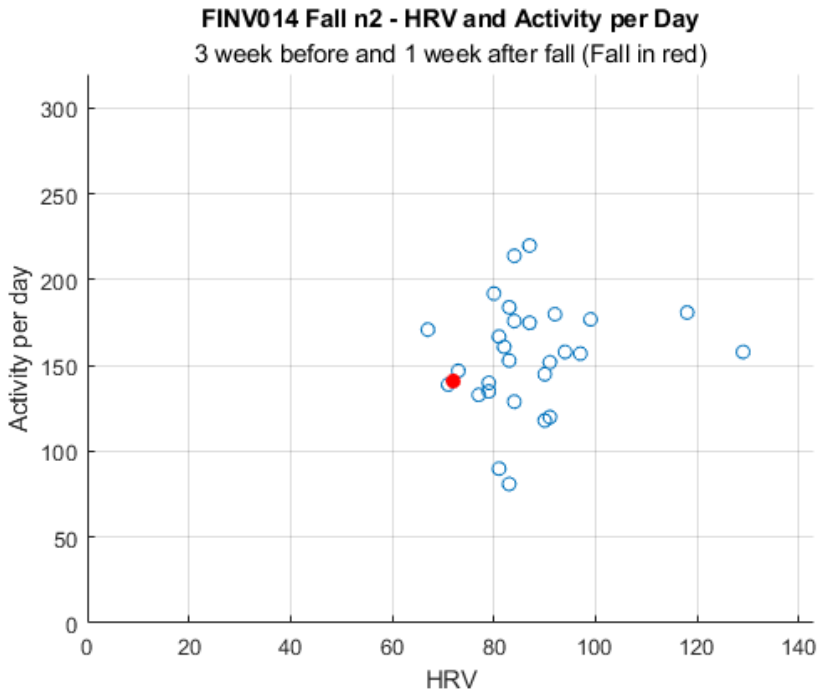

Figure F14. FINV014 Fall 2. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

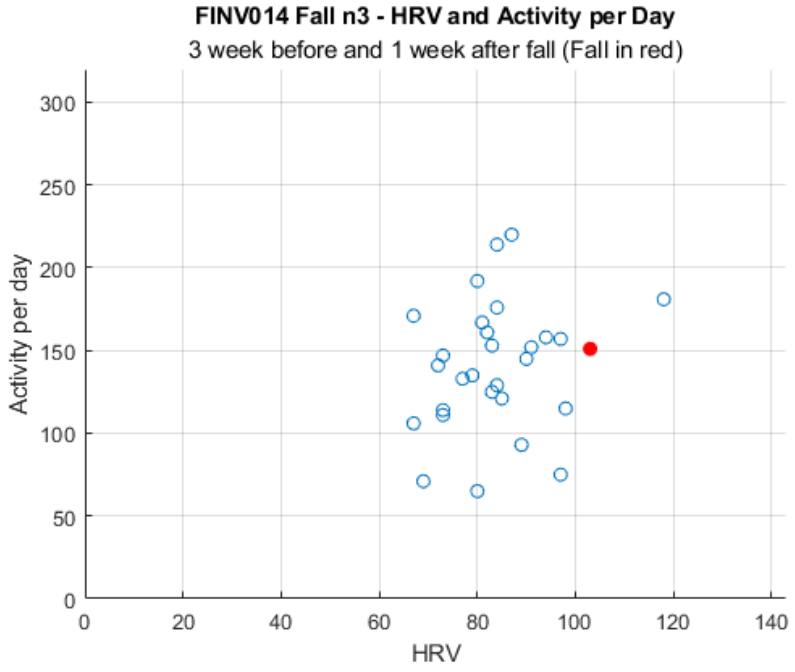

Figure F15. FINV014 Fall 3. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

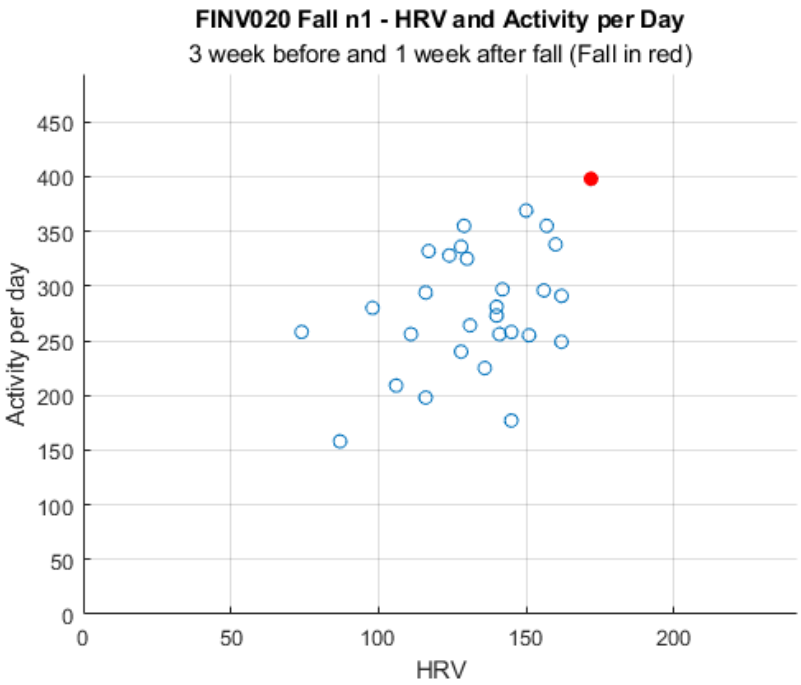

Figure F16. FINV020 Fall 1. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

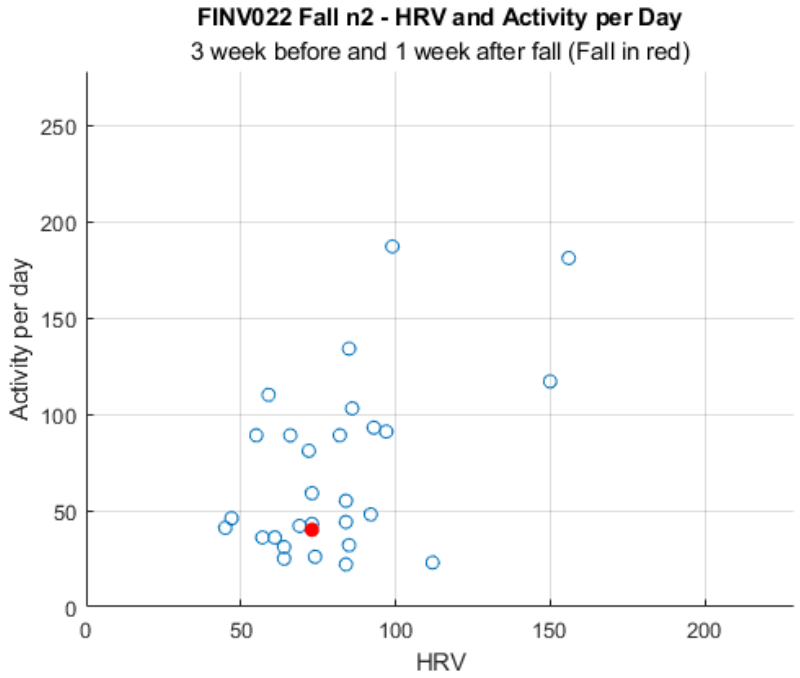

Figure F17. FINV022 Fall 2. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

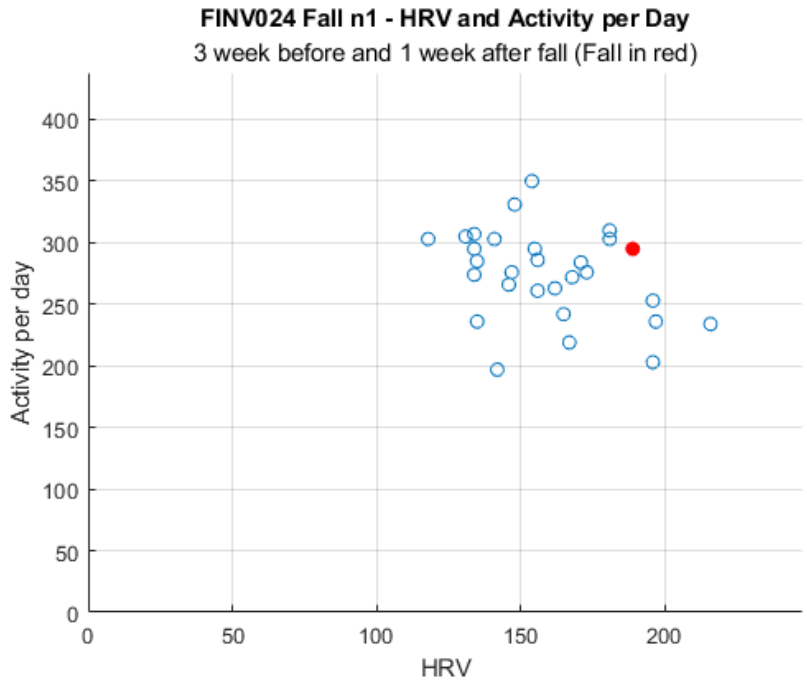

Figure F18. FINV024 Fall 1. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

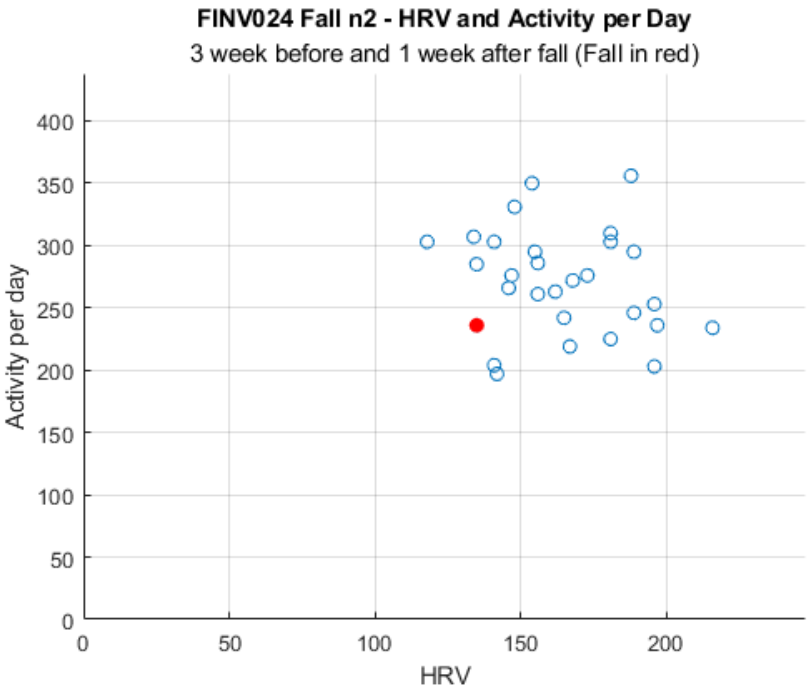

Figure F19. FINV024 Fall 2. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

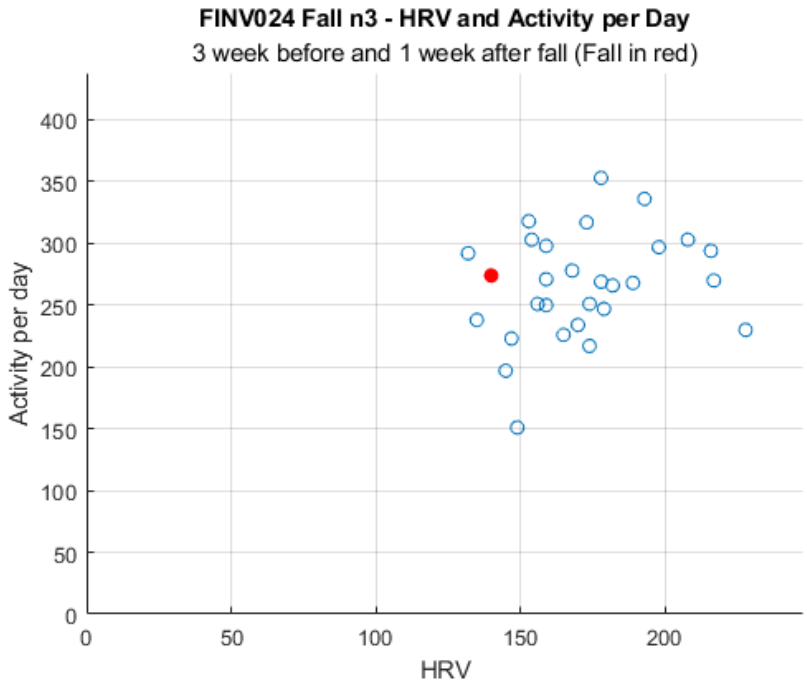

Figure F20. FINV024 Fall 3. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

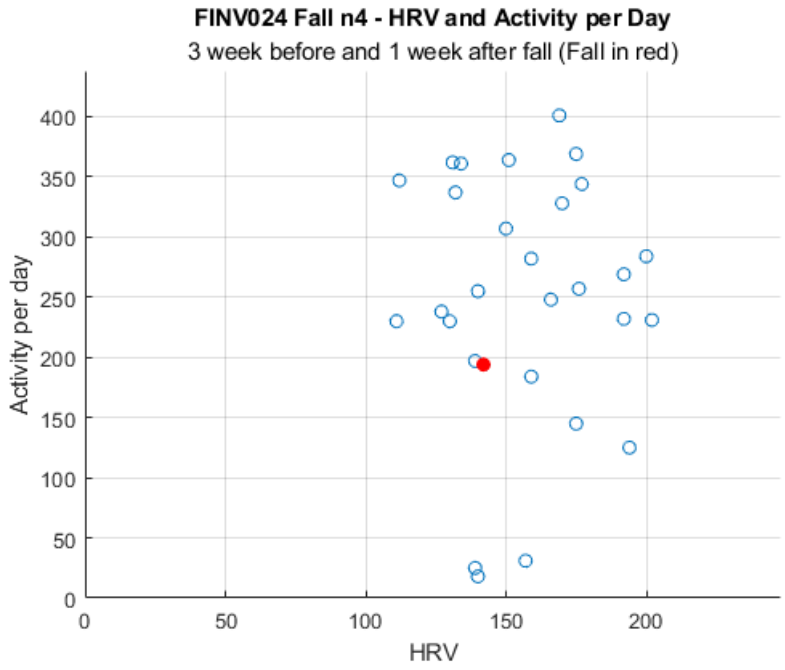

Figure F21. FINV024 Fall 4. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

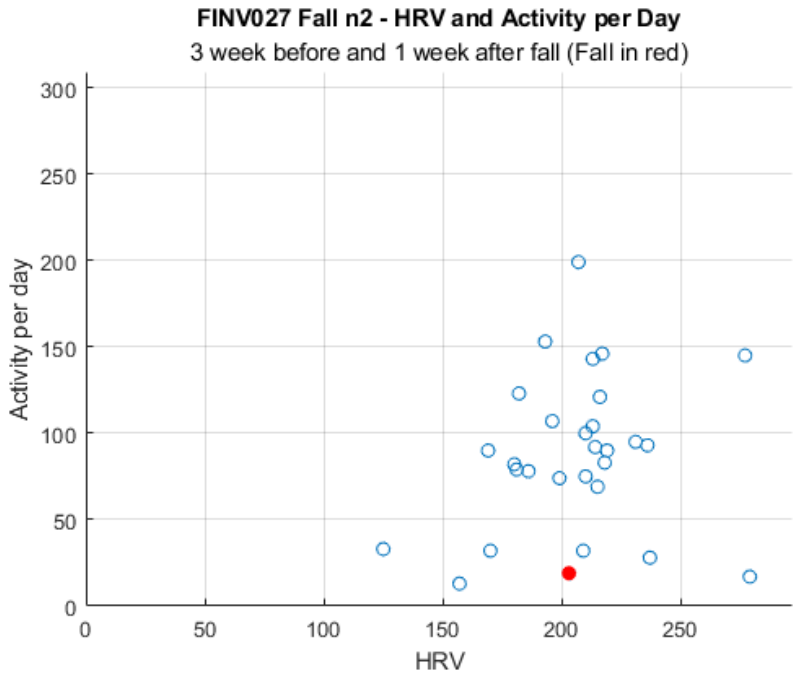

Figure F22. FINV027 Fall 2. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

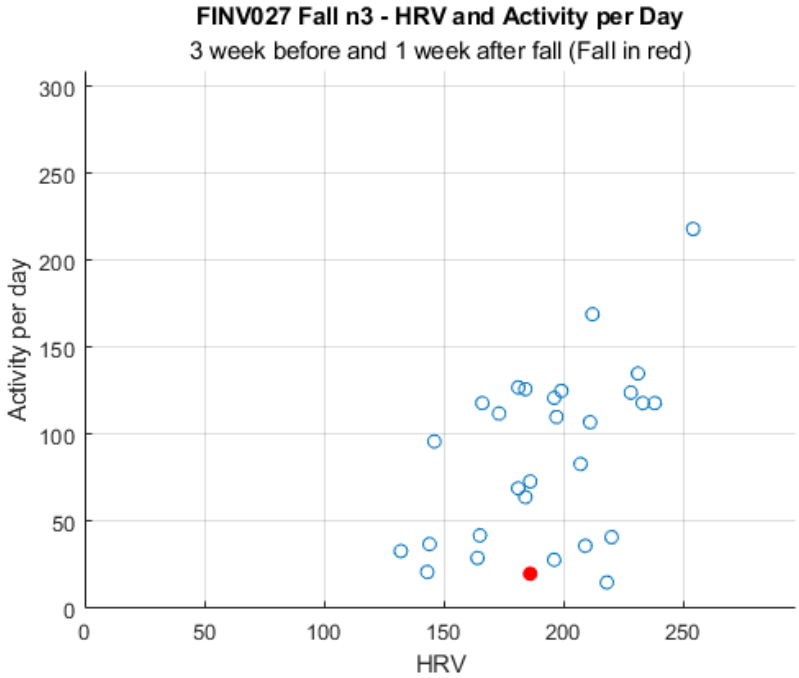

Figure F23. FINV027 Fall 3. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

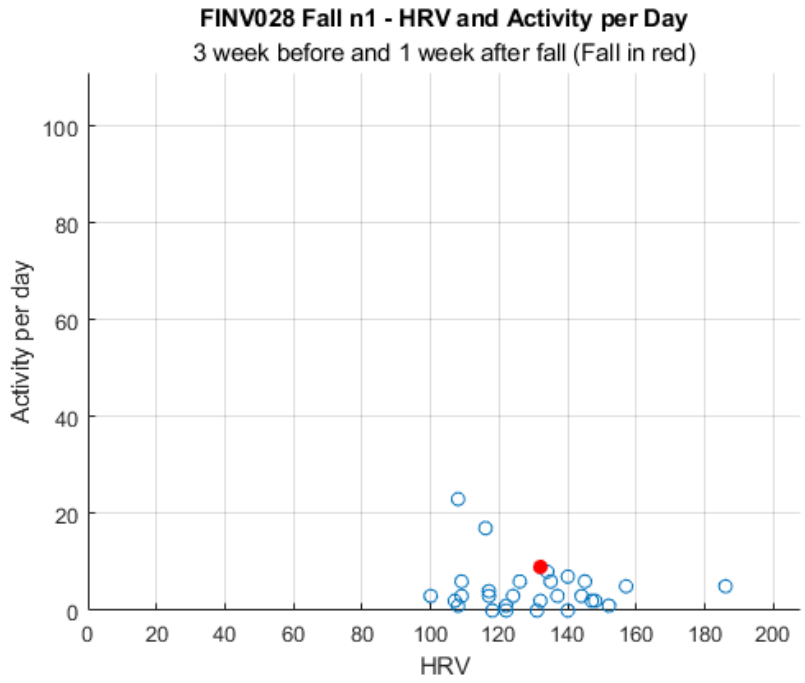

Figure F24. FINV028 Fall 1. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

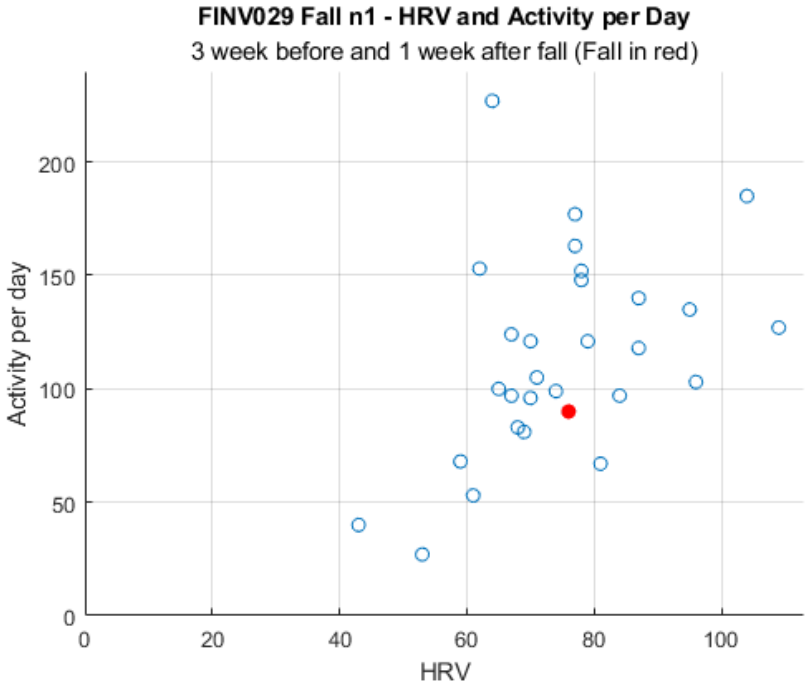

Figure F25. FINV029 Fall 1. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)

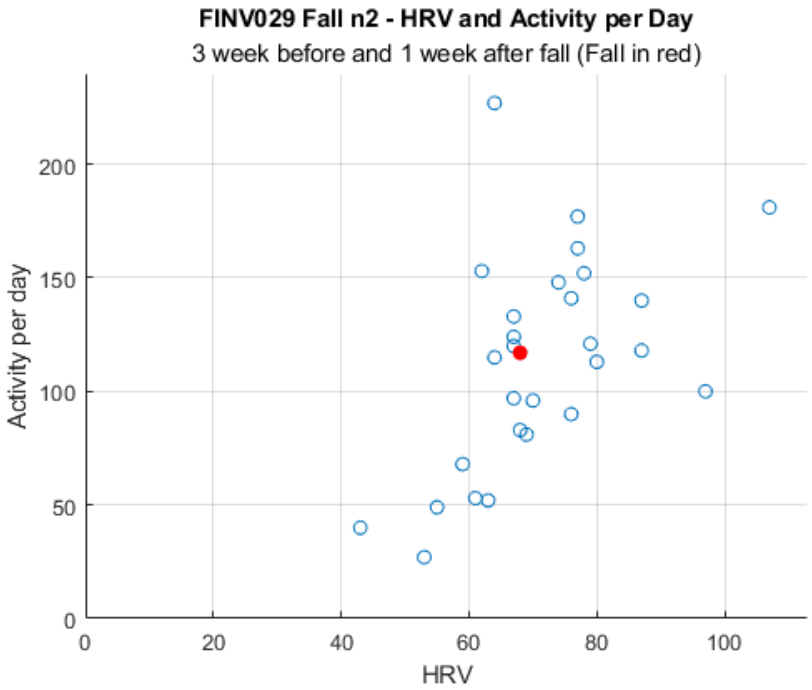

Figure F26. FINV029 Fall 2. Scatterplots of HRV and Activity (3 weeks before and 1 week after a fall)