

**Advancing the measurement and use of daily life heart rate using wearable technology:
applications to Parkinson's disease**

by

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This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

STATEMENT OF CONTRIBUTIONS

F. Elizabeth Godkin was responsible for study conceptualization, data curation and data analysis, statistical analysis, and writing for all studies within this thesis. In addition, she was responsible for assisting with study execution and data collection of this multi-site dataset and has published a paper as lead author (Godkin et al. 2022. *J Neurol.* 269(5):2673-2686) (not included in this thesis) that addresses feasibility of this novel approach.

This thesis consists of a general introduction (Chapter 1), two studies written as manuscripts for publication (Chapters 2 and 3), one study written as a thesis chapter (Chapter 4), and a general discussion (Chapter 5). At the time of thesis preparation, Chapter 2 was published in a peer-reviewed journal and Chapter 3 was under review at a peer-reviewed journal. F. Elizabeth Godkin was the sole author of Chapters 1, 4, and 5, which were written under the supervision of Dr. Bill McIlroy and were not written for publication.

For all chapters featuring a published or submitted manuscript and with multiple authors (i.e., Chapters 2 and 3), the contributions of the candidate and all co-authors are outlined below using the Consortia Advancing Standards in Research Administration Information (CASRAI) CRediT taxonomy (<https://credit.niso.org/>).

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ABSTRACT

Measures of heart rate (HR), including those conducted during resting conditions and in response to physical activity, have been shown to relate to risk of adverse health outcomes and can provide insight into the function of the autonomic nervous system (ANS). However, HR measures have conventionally been conducted at a single point in time and in controlled settings, such as during clinical or laboratory visits. Alternatively, when HR has been measured in uncontrolled, free-living settings, there has been a lack of standardization in the methods used and most have not provided sufficient behavioral context to support the interpretation of HR in daily life. Use of wearable technology, and specifically, a multi-sensor and -device approach, presents a unique opportunity to measure HR continuously in the context of daily life behaviors, and advance understanding of ANS function and context-dependent HR responses. This may be particularly relevant to individuals living with Parkinson's disease (PD), who can experience ANS dysfunction that may manifest with altered diurnal HR profiles and who can have diverse movement characteristics that may affect the HR response to physical activity.

The overarching goals of this thesis work were to 1) advance the development of standard approaches to assess HR from continuously collected data over multiple days and behavioral contexts, and 2) apply these approaches to advance understanding of ANS function and characterization of daily life physical activity profiles among individuals with PD. All studies were based on a collection protocol that instrumented participants with a portable, chest-worn electrocardiography device and two limb-worn inertial measurement units (wrist and ankle) that continuously collected data across a week-long period in daily life. In the first study, HR was measured across accumulated periods of sedentary behavior and sleep within a cohort of adults without PD ("control"), and the high levels of within-participant variability in HR that were observed within a given resting condition led to recommendations being put forth for standardizing the measurement of HR outcomes during resting conditions in daily life. In the second study, standards suggested in Study 1 were applied and extended upon in a cohort of adults with and without PD, and revealed no differences between cohorts in resting condition-specific HR outcomes (e.g.,

minimum HR during sleep) or in measures of nocturnal HR dipping in daily life. However, a significant association was observed between nocturnal HR dipping and a clinical measure of ANS dysfunction in PD. In the third study, resting HR was used as a reference when quantifying the relative intensity of the HR response to daily life walking across the same cohort of adults with and without PD. While no between-cohort differences were observed in the average relative intensity of daily life walking, there was considerable variability in the between- and within-participant HR response to continuous, longer walking bouts (≥ 30 seconds), which were not consistently associated with walking cadence or bout duration.

This dissertation provides recommendations for, and illustrates the importance of, adopting standardized approaches to measure resting and activity-dependent HR in daily life. Findings from the studies in this thesis suggest that context-based ambulatory HR monitoring has the *potential* to improve characterization of daily life behaviors and provide insight into clinically relevant outcomes in individuals with and without PD. Continued research in larger, more heterogeneous populations, which includes robust clinical profiling and continues to attend to the importance of high data quality, is necessary to determine generalizability and advance understanding of within- and between-participant drivers of variability in context-dependent HR measures. This type of future work is required before context-dependent HR monitoring can be integrated and evaluated as a tool to support self-management or clinical health care decision making.

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DEDICATION

This thesis is dedicated to my family for the countless ways that you have supported me over the past 4 (+28) years. To know you is to love you.

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LIST OF ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
ADL	Activities of daily living
ANS	Autonomic nervous system
BP	Blood pressure
CI	Chronotropic incompetence
CO	Cardiac output
CV	Cardiovascular
ECG	Electrocardiography
HANDDS-ONT	Health in Aging, Neurodegenerative Diseases and Dementias in Ontario
HR	Heart rate
HRR	Heart rate reserve
HRV	Heart rate variability
IMU	Inertial measurement unit
LEDD	Levodopa Equivalent Daily Dose
MDS-UPDRS	Movement Disorder Society – Unified Parkinson’s Disease Rating Scale
MoCA	Montreal Cognitive Assessment
NDD	Neurodegenerative disease
NMS	Non-motor symptoms
NTS	Nucleus of the solitary tract
OH	Orthostatic hypotension
PA	Physical activity
PD	Parkinson’s disease
PSNS	Parasympathetic nervous system
PPG	Photoplethysmography
REM	Rapid eye movement sleep
RHR	Resting heart rate
SCOPA-AUT	Scales for Outcomes in Parkinson’s Disease – Autonomic Dysfunction
SNR	Signal-to-noise ratio
SNS	Sympathetic nervous system
SV	Stroke volume

CHAPTER 1:

GENERAL INTRODUCTION

1.1 Overview

Measurement of cardiovascular function, and specifically heart rate (HR) when at rest and in response to activity, represents an important index of health and may predict risk of morbidity and mortality (Cole et al., 2000; Zhang et al., 2016). HR has been commonly measured in clinical settings via “snapshot” assessments, which may be susceptible to clinic-induced constraints or confounders (Eikeseth et al., 2020; Mancia et al., 1983), or via intermittent testing or monitoring approaches that do not permit collection over extended periods of time (Holter, 1961; Sana et al., 2020; Verdecchia et al., 1998). The emergence and advancement of wearable technology provide new opportunities to continuously sample HR in daily life (Alugubelli et al., 2022; Bayoumy et al., 2021; Soon et al., 2020), across longer time periods and during free-living behaviors, which may permit quantification of changes in HR within an individual over time and/or within a given context. The opportunity to deploy and evaluate the use of context-dependent HR in daily life, versus relying on point-in-time assessments or those that lack context, is likely to be particularly important among individuals who may be experiencing dysfunction of the autonomic nervous system (ANS), such as those with Parkinson’s disease (PD) (Chaudhuri, 2001; Gonçalves et al., 2022).

HR is primarily regulated by the activity of the ANS, which contains a parasympathetic and sympathetic limb that act to decrease and increase HR, respectively. Under conditions or states that involve specific activity of the ANS, measurement of context-dependent HR may provide insight into ANS function. For example, resting heart rate (RHR) may be thought of as a static index of ANS tone (Lahiri et al., 2008), and is a necessary measurement to serve as a baseline for characterizing the magnitude of HR responses to various stimuli, such as physical activity (PA). Additionally, the circadian changes in the activity of the parasympathetic (PSNS) and sympathetic nervous system (SNS) may be reflected by a lower HR during sleep than during waking hours (Cajochen et al., 1994; Johansen et al., 2013; Mancia, 1993; Verrier & Tan, 2009), and the increase in HR in response to PA reflects activation and withdrawal of the SNS and PSNS, respectively (Coote, 2010). Quantifying the magnitude of the

ANS-mediated HR response to PA can also be used as an approach to measure the relative intensity of a given activity (Brown et al., 2025; Garber et al., 2011).

Measurement of context-dependent HR outcomes in individuals living with Parkinson's disease (PD) have the potential to yield important insight. Specifically, HR measurement across the day-night cycle may represent a candidate approach for assessing ANS dysfunction (Videnovic & Golombek, 2017; Zis et al., 2015), a non-motor symptom (NMS) that is common in PD and negatively impacts quality of life but is poorly characterized (Sharabi et al., 2021). For example, diurnal ANS dysfunction in PD may compromise the PSNS and SNS response during sleep, and be detectable via blunted nocturnal HR dipping (termed HR “non-dipping”) (Pilleri et al., 2014; Schmidt et al., 2009). In addition to measuring ANS dysfunction, it may also be of value to leverage HR in individuals with PD as a tool to assess the intensity of PA, given the diversity of the individual symptom profile that may alter the cardiovascular demand of, and HR response to, physical activity (Kanegusuku et al., 2022; Katzel et al., 2011; Panassollo, Lord, et al., 2024). Notably, participating in daily life PA has been shown to have functional and symptom-relief benefits in PD (Schenkman et al., 2018; van der Kolk et al., 2019), but requires accurate measurement of PA intensity to appropriately quantify the dose-response relationship.

While wearable technology provides some unique opportunities, it is essential to consider and confront the context under which these HR measurements are made, including the setting and the measurement approach used. Specifically, use of multiple sensors worn on specific body locations (O'Brien et al., 2022; Rietz et al., 2024), including use of limb-worn movement sensors alongside a chest-worn HR monitor (Godkin et al., 2022), may improve the fidelity of free-living behavioral classification. This may enable real world HR measurements to be interpreted in the context of free-living wakeful rest (sedentary behavior), sleep, and PA (Beyer et al., 2024). Detection of free-living behaviors as they are repeated in daily life may also enable exploration into the consistency of an individual's HR response across behavioral bouts and/or days. Despite the potential utility of measuring context-dependent HR outcomes, multi-sensor and-device approaches have been scarcely deployed in free-living settings across

populations, which has resulted in a lack of standards for conducting free-living HR measures in daily life. This extends to people living with PD, for whom most investigations into measuring HR have lacked standardization and/or not been done in real-world, ecologically valid settings.

In light of the potential opportunity afforded by wearable technology, this thesis work is endeavoring to 1) advance the development of standard approaches to assess HR from continuously collected data over multiple days and behavioral contexts, and 2) apply these approaches to advance understanding of ANS function and characterization of daily life physical activity profiles among individuals with Parkinson's disease. This introductory chapter will include an overview of (i) ANS-mediated HR changes during sleep versus wake, different body positions, stress, and physical activity, as well as the potential value and limitations of heart rate variability (HRV) measures, (ii) the relevance of HR measurement in individuals with Parkinson's disease, (iii) some of the individual factors that might impact HR, (iv) the use of ambulatory HR measurement, including a comparison between differing HR monitoring technology and the potential value of a multi-sensor and -device approach to context-dependent HR measurement, and (v) the three studies in this thesis, including study-specific objectives.

1.2 Heart rate as an index of health outcomes and ANS function

Heart rate (HR) is fundamental to health and epidemiological evidence suggests that resting HR (RHR) is a strong, independent risk factor for the development of cardiovascular morbidity and all-cause mortality (Dyer et al., 1980; Jensen, 2019; Jensen et al., 2012; Kannel et al., 1987; Palatini, 2007; Zhang et al., 2016). HR is the number of times the heart beats per minute and contributes to the maintenance of cardiac output (CO) alongside stroke volume (SV), resulting in systemic delivery of blood and oxygen (Jensen, 2019). HR is set by the sinoatrial node and reflects the interplay of multiple processes and pathways that act on the heart to maintain homeostasis (Alugubelli et al., 2022; Valentini & Parati, 2009), including intrinsic and extrinsic mechanisms (Verrier & Tan, 2009). Extrinsic regulation of the sinoatrial node is necessary to appropriately increase or decrease the HR in response to changing conditions or demands on the body. One of the primary extrinsic regulators of HR is the autonomic nervous system

(ANS), which includes two limbs: the parasympathetic (PSNS) and sympathetic nervous systems (SNS) (Gordan et al., 2015; Jensen, 2019; Lahiri et al., 2008; Vogel et al., 2004). The PSNS has a rapid effect on HR, with release of acetylcholine from the postganglionic neuron activating the muscarinic receptor and resulting in a slowing of HR. Conversely, the SNS has a slower and more prolonged effect on HR, with release of norepinephrine from the postganglionic neuron activating the adrenergic receptor and resulting in an increase in HR (Gordan et al., 2015). Autonomic outflows to the heart, including the relative activity of parasympathetic and sympathetic nerves, are determined by the cardiovascular (CV) control center in the medulla of the brainstem, which integrates sensory information from peripheral receptors (e.g., mechanoreceptors that sense blood pressure (BP) change) and from the cerebral cortex and limbic system (Dampney et al., 2002; Salman, 2016). Given the influence of the ANS system on HR, changes in ANS activity across the circadian cycle (sleep versus wake), or due to postural change, stress, PA, or pathological conditions may be reflected in measures of HR (Raven et al., 2006; Vogel et al., 2004; Wieling et al., 2007). Complex oscillations in HR are also characteristic of a healthy system and can be quantified using metrics such as HR variability (HRV), which has been shown to reflect ANS activity (Shaffer & Ginsberg, 2017). Although other factors may impact the regulation of HR, such as hormones released from the endocrine system (Gordan et al., 2015; Ulrich-Lai & Herman, 2009), focus of the present work is largely on the ANS-mediated regulation of HR.

1.3 ANS-mediated regulation of heart rate

1.3.1 Circadian changes in heart rate

Changes in HR across a 24-hr period have been shown to have a circadian variation, with higher HRs typically occurring during the day (wakeful periods) versus the night (sleep) (Johansen et al., 2013; Mancina, 1993; Speed et al., 2023; Verrier & Tan, 2009). Specifically, during the slow wave stages of sleep, which account for most of the sleeping time, PSNS activity predominates and there is a reduction in SNS activity, which results in bradycardia (lowering of HR) and hypotension (Mancina, 1993). Rapid eye movement (REM) sleep represents a smaller proportion of overall sleeping time and occurs as a periodic

interruption to non-REM sleep. REM sleep periods are characterized by increases in HR and BP, compared to non-REM periods, due to transient increases in SNS activity to levels above waking values (and decreases in PSNS activity) (Cajochen et al., 1994; Johansen et al., 2013; Mancina, 1993; Verrier & Tan, 2009). Upon waking, a progressive rise in HR in the early morning has been observed, likely driven by an increase in SNS activity and decrease in PSNS activity (Huikuri et al., 1990). However, more variation in the HR profile during daytime hours has also been noted (Valentini & Parati, 2009), likely due to the impact of numerous factors on wakeful HR, such as body position (posture), stress, and PA (Carlson et al., 2014; Matsuura et al., 2019; Vogel et al., 2004). A reduction of these influences during sleep may make RHR measurements during sleep more reliable (Matsuura et al., 2019; Venkat et al., 2022). Previous work to assess RHR has lacked standardization and/or transparency across both clinical (Aladin et al., 2014; Rennie et al., 2003) and real-world settings (Quer et al., 2020; Schumann et al., 2025), including differences in whether RHR is measured during sleep versus wakeful states, as well as in durations and conditions of measurement (Johansen et al., 2013; Logan et al., 2000; Matsuura et al., 2019). As such, increased attention on measurement of RHR during sleep, in comparison to HR measures during wakeful rest, are warranted because 1) this may allow for the impact of external influences on wakeful RHR to be elucidated and 2) previous work suggests that abnormal nighttime HR profiles (e.g., HR “non-dipping”) are associated with increased risk of all-cause mortality and CV morbidity (Ben-Dov et al., 2007; Johansen et al., 2013; Kannel et al., 1987; Verdecchia et al., 1998).

1.3.2 Change in heart rate with body position

When transitioning from lying down to more upright postures, there is a need for hemodynamic parameters to respond in a way that permits maintenance of sufficient cerebral blood flow in the context of the negative effect of gravity (Smith et al., 1994). With active standing from a lying down position, for example, there is an immediate increase in HR as a result of inhibition of the PSNS, while SV remains stable (Wieling et al., 2007). This parasympathetic inhibition is believed to be due to 1) central command, which involves neural responses from higher brain centres that stimulate regions in the brainstem

involved in CV control and 2) activation of muscle mechanoreceptors within working muscles that send afferent feedback to the ANS (Critchley et al., 2000; Wieling et al., 2007). As a result of an increase in HR and maintenance of SV, there is an increase in cardiac output and thus an increase in the flow of blood into the circulation. At the same time, a decrease in systemic vascular resistance is responsible for a transient fall in BP, which subsequently provokes the arterial baroreflex (Wieling et al., 2007). The arterial baroreflex is a negative feedback control system that buffers moment-to-moment changes in BP by increasing or decreasing HR and vascular tone (Dampney et al., 2002; Raven et al., 2006; Salman, 2015, 2016) (see Figure 1.1).

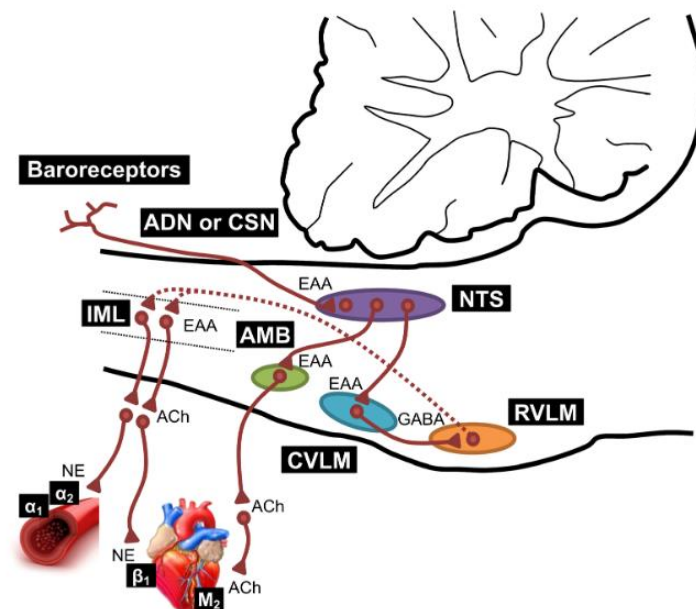


Figure 1. 1. The arterial baroreflex pathway in the lower brainstem and spinal cord (from Salman, 2016; adapted from Dampney et al. 2002). ADN, aortic depressor nerve; CSN, carotid sinus nerve; NTS, nucleus of the solitary tract; CVLM, caudal ventrolateral medulla; RVLM, rostral ventrolateral medulla; AMB, nucleus ambiguus; IML, intermediolateral cell column in the spinal cord; EAA, an excitatory amino acid; GABA, γ -aminobutyric acid; ACh, acetylcholine; and NE, norepinephrine.

Specifically, changes in BP are detected by stretch receptors in the carotid sinus and aortic arch and conveyed via baroreceptor afferent fibres to the nucleus of the solitary tract (NTS), which has two main response pathways (Raven et al., 2006). In one of the pathways, excitatory projections from the NTS synapse at the nucleus ambiguus (AMB) and dorsal motor nucleus of the vagus (DMNV), which then activate parasympathetic fibres to decrease HR (Salman, 2016). In the other pathway, excitatory

projections from the NTS synapse on the caudal ventral lateral medulla (CVLM), which sends inhibitory projections to the rostral ventral lateral medulla (RVLM) (Salman, 2016). The resultant decrease in signaling from the RVLM leads to a lack of sympathetically mediated increase in HR and peripheral vascular tone (Dampney et al., 2002). When standing induces a fall in BP, decreased afferent baroreceptor firing results in PSNS withdrawal and increased SNS outflow, which further increases HR and causes vasoconstriction of peripheral vasculature (Wieling et al., 2007). An increase in the cardiac output (inflow) and increased total peripheral resistance (i.e., reduction in outflow) then leads to an increase in BP by about 20 seconds after standing, which activates the arterial baroreflex and causes a decrease in HR. After this immediate dynamic response phase to a postural transition from lying down to standing, the hemodynamic response to maintain sufficient cerebral blood flow while standing involves an increase in HR of ~ 15-30% from lying down (Valentini & Parati, 2009), as well as an increase in total peripheral resistance, and a decrease in both SV and cardiac output (Smith et al., 1994). Given the impact of body position on HR, and the involvement of the ANS in adjusting HR in response to postural changes, it may be of value to control for or denote the specific posture of an individual when measuring HR.

1.3.3 Acute stress-induced changes in heart rate

The “fight or flight” response, which involves increases in sympathetic nervous system activity, HR and BP, is a well-accepted phenomenon (Cannon, 1915) that can occur in response to emotional stress, fear, or threatening stimuli (Salman, 2016; Ulrich-Lai & Herman, 2009). This stress response involves both an endocrine component, driven by activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, and an ANS component (Dampney et al., 2002; Salman, 2016; Ulrich-Lai & Herman, 2009). The ANS response occurs rapidly, whereas the activation of the HPA axis contributes to a more protracted stress response via peak cortisol release after several minutes (Ulrich-Lai & Herman, 2009). The ANS response to stress has been shown to include activation of the amygdala and projection of excitatory outputs to the dorsomedial hypothalamus (DMH) (Salman, 2016). Once activated, the DMH is then suggested to activate some of the CV control centers in the medulla, which trigger sympathetic nervous

system outflow to the peripheral vasculature to produce vasoconstriction, as well as to the sinoatrial node of the heart to increase HR (Dampney et al., 2002; Salman, 2016; Ulrich-Lai & Herman, 2009).

Sympathetic nerves also act on the adrenal medulla and cause a release of epinephrine, which acts to increase vasoconstriction and HR (Salman, 2016; Ulrich-Lai & Herman, 2009). In terms of the HPA axis, activation of the paraventricular nucleus of the hypothalamus (PVN) initiates a cascade of hormones being released across multiple structures, which ends with an increase in circulating cortisol that can potentiate sympathetic effects (Ulrich-Lai & Herman, 2009). Given the increase in HR that is characteristic of the stress response, it is possible that measured excursions in HR during resting conditions, in the absence of movement, may provide insight into an individual's ANS reactivity and/or propensity to experience stress.

1.3.4 Heart rate response to physical activity

With physical activity (PA), there is an increased demand for oxygen from working muscles and accordingly, a need to increase cardiac output ($HR \times SV$) and BP to ensure adequate blood flow and oxygen delivery to active muscle. To facilitate the necessary increases in BP and HR to increase blood flow to meet the metabolic demands of active muscle, the arterial baroreflex is “re-set” in proportion to the intensity of the activity, to operate around a higher “baseline” BP during dynamic exercise (Potts et al., 1993; Raven et al., 2006, 2019). Mechanisms believed to be responsible for the resetting of the arterial baroreflex with PA primarily include central command and modulation by the exercise pressor reflex (Coote, 2010; Michelini et al., 2015; Raven et al., 2006, 2019). Specifically, the NTS integrates inputs from baroreceptor afferent fibres, higher brain centres (central command) and from metaboreceptors and mechanoreceptors in working muscle (exercise pressor reflex) to control PSNS and SNS outflows in a way that permits increased HR and BP during PA. In terms of the time course of the HR response to dynamic activity (see Figure 1.2), the increase in HR at the onset of activity initially involves parasympathetic withdrawal, and then sustained increases in HR are primarily reliant on sympathetic activation (Coote, 2010).

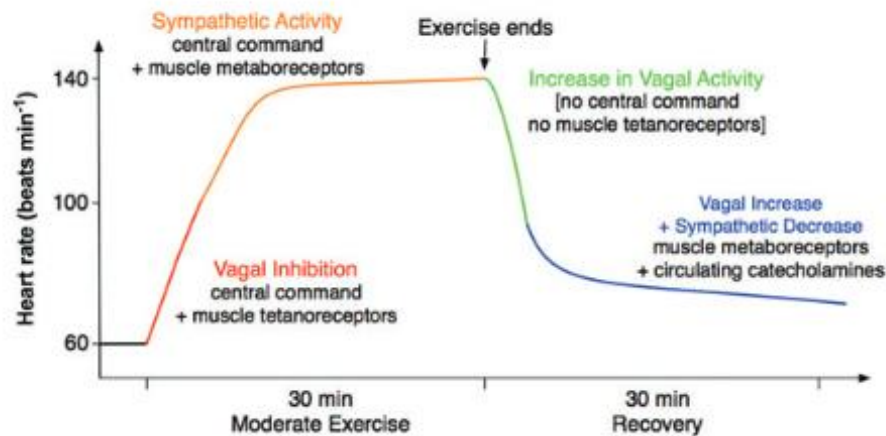


Figure 1. 2. The heart rate response during a period of moderate dynamic exercise and in the post-exercise recovery period, including the timing and contribution of parasympathetic (vagal) and sympathetic nervous system activity (from Coote, 2010).

At the end of a bout of PA, the rapid decrease in HR initially occurs due to PSNS reactivation, which is driven by a decrease in central command and lack of afferent feedback from muscle mechanoreceptors (Lahiri et al., 2008; Sokas et al., 2023). The subsequent slower decay in HR results from a combination of PSNS reactivation and SNS withdrawal, which may be mediated, in part, by reduced input from muscle metaboreceptors (Coote, 2010; Lahiri et al., 2008). The intensity and duration of exercise have an influence on the time course of changes (Kim et al., 2021; Sokas et al., 2019), with the return of HR to baseline taking longer with increases in intensity and duration (Coote, 2010). HR recovery has been shown to have prognostic significance, with blunted HR recovery related to increased risk of mortality, even after submaximal exercise (Cole et al., 2000; Lahiri et al., 2008).

In addition to the more transient changes in HR that occur at the beginning and end of a bout of PA, sustained activity at a constant work rate of a submaximal intensity (and below the first metabolic (or lactate) threshold) will elicit a plateau in HR (“steady state”), with the timing to reach steady state HR impacted by factors such as intensity, training and/or health status (Poole & Jones, 2012). Quantifying the magnitude of the ANS-mediated HR response to PA has been used as an approach to measure and prescribe activity intensity, given the linear relationship observed between HR and oxygen consumption

(VO₂) during aerobic PA (Garber et al., 2011; MacKay-Lyons et al., 2020; Wilmore & Haskell, 1971). Specifically, one common approach for assessing relative intensity involves expressing the HR response to an activity stimulus in proportion to an individual's HR reserve (%HRR) (Karvonen et al., 1957), which involves calculating the difference between an individual's maximal and resting HR (Brown et al., 2025; Garber et al., 2011). Adopting approaches that allow for measurement *relative* to an individual's maximal (and resting) capacity may be preferred over approaches used to quantify the activity intensity based on absolute values (e.g., metabolic equivalent tasks (METS)), whereby simply measuring or prescribing based on an absolute work rate (or amount of movement) does not account for individual physiological capacity and may evoke different physiological responses (Bishop et al., 2025; Brown et al., 2025). Despite the potential advantages of using %HRR over absolute intensity methods, recommendations suggest that the *best* method involves directly measuring metabolic thresholds during a graded exercise test with concurrent collection of respiratory gases and/or blood lactate. A workload can then be prescribed relative to metabolic thresholds, to induce a more homogeneous training stimulus (i.e., similar physiological demands) across individuals of varying capacities (Bishop et al., 2025; Carvalho & Mezzani, 2011; Mann et al., 2013). These metabolic threshold-based methods require laboratory and/or clinical access, resources, and expertise, which may not be available or feasible in certain study or real-world contexts. Recent work by Terada et al., (2024) reinforced the challenges associated with identifying an optimal method for prescribing and monitoring PA intensity, particularly in applied settings that are utilizing self-monitoring of intensity and in populations that live with conditions (e.g., cardiovascular disease) that can affect HR responses to PA. As such, selecting an appropriate method for measuring activity intensity must attempt to balance the desire for accurate monitoring and/or prescription of PA, alongside what is practically feasible and accessible in the current context, and consider cohort-specific characteristics (e.g., sample size, clinical profile, etc.). Continued development, application, and evaluation of approaches to measure PA intensity in real-world settings will enable further exploration into the effect(s) of a specific dose (i.e., frequency, intensity, time, type, volume) or pattern of PA accumulation on health outcomes.

1.3.5 Heart rate variability as an index of ANS activity

One method for quantifying the dynamic modulation of HR by the parasympathetic and sympathetic nervous system is via the measurement of heart rate variability (HRV) (Shaffer & Ginsberg, 2017). Even during “steady state” conditions, HR is not constant and rather, there is variation in the time between successive heartbeats due to fluctuations in autonomic inputs to the heart (Lahiri et al., 2008; Shaffer & Ginsberg, 2017). As was demonstrated by Akselrod et al., (1981), these fluctuations in beat-to-beat HR are the result of the dynamic response of physiological control systems to maintain CV homeostasis. Importantly, this oscillation in the inter-beat interval is only observable when continuous beat-to-beat measurements of HR are conducted and not possible to quantify when HR data is output as an average over time (Shaffer et al., 2014). HRV has been used as a screening or risk stratification tool for diseases that impact ANS function and low HRV has been shown to have prognostic significance for predicting negative health outcomes (e.g., CVD, diabetes, mortality, etc.) (Shaffer & Ginsberg, 2017; Siepmann et al., 2022; Tsuji et al., 1996). Additionally, HRV has been shown to increase in response to exercise training (Ditor et al., 2005), suggesting that measurement of HRV may be a useful tool for evaluating ANS function and responsivity to interventions.

The measurement of HRV is impacted by methodological and participant factors, such as the duration of recording, method used to quantify HRV (e.g., time or frequency domain methods), body position, recency of movement, health status, and the absence of artifacts in the signal (Shaffer & Ginsberg, 2017). In an effort to create standards for HRV measurement that considered and/or controlled for some of these factors, recommendations put forth by an International Task Force included that measurement durations for HRV are either 5 minutes (short) or 24-hrs (long), and that both time and frequency domain methods are used (Task Force of the European Society of Cardiology and North American Society of Pacing Electrophysiology, 1996), given that both duration and method may provide insight into complementary but different physiological information (Lahiri et al., 2008). For example, a common time domain measure, the standard deviation of NN intervals (SDNN), where “N-N intervals”

refers to R-R intervals that have been screened to remove abnormal beats, has been shown to predict risk of cardiac morbidity and mortality when measured across a 24-hr period (Shaffer & Ginsberg, 2017). Emphasis was also placed on using frequency domain methods to measure HRV during short-term recordings because certain frequency ranges have been associated with specific activity of the PSNS and/or SNS (Akselrod et al., 1981; Kaplan, 1994). For example, the high frequency (HF) component of the HRV signal measured during short-term stationary recordings has been shown to reflect the rapid response of the PSNS (Akselrod et al., 1981; Shaffer & Ginsberg, 2017). While recommendations put forth by the Task Force include long term (i.e., 24-hr) HRV measurements, longer duration recordings of this nature may pose practical and interpretative challenges, including the processing required to remove abnormal beats (i.e., isolate N-N intervals) from high data volumes (Ruangsuphaphichat et al., 2023) and the potential for HRV measures to be conducted under changing conditions that may result in differing activations of the ANS (e.g., stress or PA-induced activation of the sympathetic nervous system) (Heimrich et al., 2021). These challenges may have contributed to the common use of short-term, stationary measurements of HRV to assess ANS activity across various research and clinical contexts (Pinna et al., 2007; Uhlig et al., 2020).

To deploy short-term resting HRV measurement as an index of ANS activity, there is a need to first understand the consistency or fluctuation of the HRV measurement over time. Previous work has largely assessed the within- (intra) and between- (inter) day reliability or variability of short-term HRV measurements in controlled clinical settings (Akselrod et al., 1981; Cipryan & Litschmannova, 2013; Fennell et al., 2024; Kowalewski & Urban, 2004; Nunan et al., 2009; Pinna et al., 2007; Uhlig et al., 2020; Young & Leicht, 2011; Žunkovič et al., 2023). For example, Fennell et al., (2024) showed that short-term HRV measurements during supine rest in clinic were reproducible when measured under the same conditions 2-5 days later in younger and older adults, but the level of inter-day variability differed depending on the HRV metric used. Although valuable to support clinical practice or in-lab research studies, determination of the consistency of short-term resting HRV measures in controlled environments

cannot be applied to HRV measurement outside of the clinic. Despite the high potential for variation in methodological and participant factors known to impact HRV that can occur across real-world settings, limited work has assessed the reproducibility of short-term HRV measures using ambulatory HR monitoring in free-living settings (Besson et al., 2025; Kristiansen et al., 2009; Rietz et al., 2024). Future work to comprehensively assess the consistency of, and potentially propose standards for, short-term HRV measures in free-living may be required before these measures can be used for identifying between-cohort differences in ANS function or the responsivity of the ANS to an intervention.

1.4 Relevance of heart rate measurement to Parkinson's disease

1.4.1 Introduction to Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease (NDD) and affects more than 11 million people worldwide (Dorsey et al., 2018; Luo et al., 2025). PD is primarily diagnosed based on medical history and physical examination in clinic to assess for the presence of cardinal motor symptoms (Armstrong & Okun, 2020). Specifically, according to UK PD Society Brain Bank Criteria, bradykinesia (slowness of movement) and either rest tremor, rigidity, or postural instability must be present to receive a diagnosis of PD (Gibb & Lees, 1988). The pathological hallmarks of PD include loss of dopaminergic neurons in the nigrostriatal pathway of the basal ganglia and the presence of Lewy body pathology in the remaining neurons (Kalia & Lang, 2015). In the absence of neuroprotective therapies that alter disease progression, the primary treatment for PD involves targeting the motor symptoms of the disease with dopaminergic-centric therapy, such as levodopa, to minimize the impact of symptoms on the performance of activities of daily living (ADL) and quality of life (Armstrong & Okun, 2020). Exercise and PA have also been proposed as non-pharmacological approaches to symptom management and as tools to improve aerobic capacity and support physical functioning in PD (Cheng & Su, 2020; Panassollo, Mawston, et al., 2024). Although traditionally thought of as a dopaminergic/basal ganglia-centric disease manifesting with cardinal motor symptoms, increasing evidence supports the view that PD is a complex, heterogeneous disorder that impacts other nervous system structures and

neurotransmitter systems and results in the occurrence of diverse non-motor symptoms (Chaudhuri et al., 2005, 2006; Kalia & Lang, 2015; Poewe, 2009; Sethi, 2008; Titova et al., 2017).

Non-motor symptoms (NMS) include neuropsychiatric/cognitive symptoms (e.g., depression, anxiety, psychosis), sleep disorders, gastrointestinal symptoms, sensory symptoms and autonomic dysfunction (Chaudhuri et al., 2006; Sethi, 2008). NMS can develop within the prodromal period several years prior to formal diagnoses (e.g., constipation, REM sleep behavior disorder (Kalia & Lang, 2015)). NMS can also contribute to increased disability and institutionalization as disease progresses (Hely et al., 2005), and may fluctuate in varied ways in response to levodopa (Aquino & Fox, 2015). Although the basal ganglia and dopaminergic system may contribute to the manifestation of some NMS of PD, dysfunction of other neurotransmitter systems and degeneration of other nervous system structures are likely to play a critical role in driving the complex and multifactorial pathogenesis of NMS (Ehgoetz Martens & Lewis, 2017; Titova et al., 2017). Despite this heterogeneity and the negative impact that NMS have on quality of life for those living with PD (Chaudhuri et al., 2005; Merola et al., 2018), NMS have been traditionally less well-reported and investigated compared to motor symptoms of PD.

1.4.2 Measurement of cardiovascular ANS dysfunction in Parkinson's disease

ANS dysfunction is a common NMS of PD, and may manifest with impacts on several body systems, such as those that govern thermoregulation, the gastrointestinal tract, the urogenital system, and the cardiovascular system (Chaudhuri, 2001; Gonçalves et al., 2022). Cardiovascular (CV) dysautonomia is reported to occur in up to 50% of people with PD (Fanciulli et al., 2020; Gonçalves et al., 2022; Hiorth et al., 2019; Merola et al., 2018) and may be the result of degeneration and impairments both centrally and peripherally (Sethi, 2008; Titova et al., 2017). Specifically, Lewy body pathology may exist centrally in the CV control center of the brainstem, including structures such as the rostral ventral lateral medulla (RVLM) and dorsal motor nucleus of the vagus (DMNV), and peripheral degeneration may result in postganglionic parasympathetic and sympathetic denervation (Goldstein, 2003; Gonçalves et al., 2022; Titova et al., 2017). Impacts to these structures may impair neural pathways involved in regulation of

autonomic outflows to the heart and vasculature, including the arterial baroreflex and the capacity of the PSNS and SNS to respond to perturbations in homeostasis, resulting in dysregulation of BP and HR (Fanciulli et al., 2020; Goldstein, 2003; Hiorth et al., 2019). As such, development of objective and quantifiable measures that provide insight into cardiovascular ANS degeneration and/or dysfunction is a goal of current PD research (Sharabi et al., 2021).

One of the most recognized symptoms of CV dysautonomia in PD is orthostatic hypotension (OH) (Goldstein, 2003; Gonçalves et al., 2022), which presents as a sustained drop in BP with a positional change from supine to standing and can increase susceptibility to falling or other adverse outcomes (Zis et al., 2015). It was previously thought that OH in PD occurred due to BP-altering effects of dopaminergic medication (Goldstein, 2003); however, work done in initially drug naïve people with PD has shown that OH can occur early in PD (in the absence of medication) and may worsen with disease progression, with a 10-fold increased risk of “clinically significant” OH in PD versus controls after 7 years of follow up (Hiorth et al., 2019). Measurement of CV dysautonomia via examination of BP responses to postural challenges traditionally occurs in controlled clinical settings (Sharabi et al., 2021), requiring performance of provocations and access to clinical resources, which may not be as accessible as a screening or diagnostic tool in the broader PD population (Sabino-Carvalho et al., 2020; Salman, 2015).

As an alternative to BP monitoring, there is the potential for HR measurement to provide insight into ANS function in PD during certain behaviors or states (e.g., sleep versus wake, PA) or as a function of the variability in the HR signal. For example, chronotropic incompetence (CI), or the inability to raise HR in proportion to increased workload demands (Panassollo, Lord, et al., 2024), is a feature of CV dysautonomia that has an estimated prevalence of 40-50% in people with PD (Griffith et al., 2023; Kanegusuku et al., 2022). This feature of CV dysautonomia threatens the maintenance of adequate blood flow to working muscle and makes engagement in safe PA more of a challenge (Sabino-Carvalho et al., 2018), which may be problematic given the prescription of exercise as a management strategy in PD. Additionally, some individuals with PD, who experience concomitant OH, have been shown to experience

altered diurnal ANS function (Videnovic & Golombek, 2017; Zis et al., 2015), as reflected by reduced nocturnal BP and HR dipping (i.e., “non-dipping”) (Pilleri et al., 2014; Schmidt et al., 2009). Despite that one of the potential advantages of HR monitoring is that it can be conducted in real-world settings, previous investigations into nocturnal measures of CV dysautonomia in PD have frequently been confined to clinical or hospital settings (Kallio et al., 2004; Pilleri et al., 2014; Pursiainen et al., 2002; Schmidt et al., 2009; Stübner et al., 2013). Clinical protocols may permit deployment of robust HR measures (e.g., 12-lead ECG) (e.g., Kallio et al., 2004), but may lack ecological validity if unable to recapitulate sleep-wake behavior as it occurs in daily life. To overcome some of these potential limitations and continue to determine if HR outcomes should be added to the toolkit for measuring cardiovascular ANS dysfunction in PD, there is opportunity to utilize ambulatory HR monitoring to characterize nocturnal HR dipping in daily life, and to explore if/how nocturnal HR dipping relates to clinical measures of ANS dysfunction.

1.4.3 Using heart rate to quantify the intensity of aerobic activity in Parkinson’s disease

Regular aerobic exercise of sufficient intensity to challenge the cardiovascular system is recommended to minimize morbidity and maximize positive health outcomes across populations (Garber et al., 2011; MacKay-Lyons et al., 2020; Pedersen & Saltin, 2006; Piercy et al., 2018; Ross et al., 2020; von Rosen et al., 2020). Specific to individuals with PD, aerobic exercise and physical activity have been proposed as an approach to manage or alleviate symptoms, improve aerobic capacity, and support physical functioning (Cheng & Su, 2020; Gamborg et al., 2022; Johansson et al., 2022; Panassollo, Mawston, et al., 2024; Schenkman et al., 2018; van der Kolk et al., 2019). Identifying non-pharmacological strategies is important in PD because despite the ubiquitous use of levodopa to manage the symptoms of PD, people with PD still can experience medication-unresponsive symptoms (e.g., gait/postural instability) (Hely et al., 2005; Sethi, 2008), levodopa-induced complications (e.g., dyskinesias), and a diminished responsiveness to medication over time (Aquino & Fox, 2015).

As mentioned, studies in PD have shown that regular aerobic exercise may attenuate motor symptoms (Panassollo, Mawston, et al., 2024; Schenkman et al., 2018; van der Kolk et al., 2019) and is associated with improved quality of life and physical function (Oguh et al., 2014). For example, a 6-month training study randomized individuals with PD (n=125) to complete 30-45 minutes of moderate-vigorous intensity aerobic exercise or stretching on 3 days/week (van der Kolk et al., 2019). Following this intervention, “OFF” state motor symptoms, as measured by the Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS), were attenuated in the aerobic exercise group to an extent similar to what has been observed with pharmacological treatments (van der Kolk et al., 2019). In alignment with this work, current recommendations specific to PA in PD include suggestions for participating in moderate-vigorous intensity aerobic exercise in 20–60-minute bouts on 3-5 days per week (Kim, Lai, et al., 2019; Panassollo, Mawston, et al., 2024). Beyond only structured aerobic exercise, participating in routine daily life PA has been shown to have positive impacts in people with PD (Tsukita et al., 2022; Xu et al., 2010), including a specific focus on engaging in daily walking behavior as a way to slow the progression of PD-related disability (Zajac et al., 2021).

Despite these purported benefits of engaging in structured and unstructured PA, people with PD have been shown to be less active and engage in PA at a lower intensity compared to age-matched healthy controls (Lord et al., 2013; Pradhan & Kelly, 2019; Speelman et al., 2012; van Nimwegen et al., 2011). However, the limited studies that have assessed PA behavior in daily life in PD have deployed various methods to measure PA volume and intensity, including self-report and wearable accelerometer-based measures that provide absolute intensity estimates (Wallén et al., 2015). It may not be prudent to rely on absolute methods for intensity estimation in PD, given a lack of cohort-specific thresholds (e.g., Jeng et al., 2020) and the heterogeneity observed in individuals with PD, in terms of diverse symptoms and movement characteristics, which may result in a certain (or absolute) quantity of movement being associated with diverse CV demands (Brown et al., 2025; Schrack et al., 2018). For example, people with PD may have altered movement characteristics (e.g., gait patterns) that involve higher energy demands

and a higher HR response (Katzel et al., 2011; Wallén et al., 2015), or may experience a blunted HR response to a given amount of movement as a result of chronotropic incompetence (CI) (Kanegusuku et al., 2022; Panassollo, Lord, et al., 2024; Sabino-Carvalho et al., 2018). As such, there is opportunity to confront the use of HR as a potential method to assess the relative intensity of PA in PD, to further characterize the daily life PA profile of people with PD and understand the dose-response relationship between aerobic PA and health outcomes. Accurate measurement of PA intensity as it occurs in daily life may also be important to guide therapeutic and individual decisions regarding engagement in adequate levels of PA (Prajapati et al., 2013).

1.5 Individual factors impacting heart rate

HR is influenced by many individual factors, such as age, sex, fitness level, certain comorbidities or conditions, and corresponding medication usage (Gordon & Duncan, 1991; Hill et al., 2015; Jensen, 2019; Matsuura et al., 2019; Valentini & Parati, 2009; Vogel et al., 2004). Of specific relevance to the present work is aging. In terms of the effect of aging on the CV system, aging is associated with a decreased responsivity of autonomic cardiovascular reflexes, reduced sensitivity of adrenergic receptors, and a drop in the intrinsic HR (Kostis et al., 1982). When evaluating how aging impacts conventionally measured HR outcomes, differing effects have been observed depending on the outcome being measured, including: consistent decreases in maximal HR with increasing age (Kostis et al., 1982; Ogawa et al., 1992), evidence of a delayed HR recovery after exercise (Norris et al., 1953), and inconsistent findings related to RHR, with evidence suggesting a potential decrease (Jaquet et al., 1998; Quer et al., 2020), increase (Kannel et al., 1987), or relative stability (Jensen, 2019) with age. Certainly, age-related changes in HR responses are also impacted by other factors such as fitness level and sex. For example, females have consistently been shown to have higher RHR values compared to males (Jaquet et al., 1998; Jensen, 2019; Kannel et al., 1987; Quer et al., 2020; Valentini & Parati, 2009). Additionally, regular PA and higher fitness levels are associated with lower RHRs, lower HRs during submaximal exercise, unchanged maximal HRs, and faster HR recovery (Coote, 2010; Darr et al., 1988; Jensen, 2019; Jensen et al., 2013;

Kostis et al., 1982; Rennie et al., 2003). While several comorbidities have been shown to impact RHR and/or the HR response to PA (Jensen, 2019), most relevant to the present work are cardiovascular (e.g., hypertension, heart failure) (Palatini, 2009), endocrine (e.g., diabetes) (Duque et al., 2021), respiratory (e.g., COPD) (Jensen et al., 2013), psychological (Kemp et al., 2014), and sleep conditions (e.g., obstructive sleep apnea, restless leg syndrome) (Bradley & Floras, 2009). It may also be prudent to consider certain medications that are commonly used in the treatment of cardiovascular diseases and their impacts on the cardiovascular system, such as beta blockers (Gordon & Duncan, 1991). Beta blockers bind to beta-adrenergic receptors on the heart (and vascular smooth muscle) and have inhibitory effects, resulting in a reduction in RHR, HR during submaximal exercise, and maximal exercising HR (Reybrouck et al., 1977; Wilmore et al., 1985). When assessing HR, it may be important to try to control for and/or consider how some of these individual factors could contribute to inter-individual differences in measured HR outcomes. Other factors that are known to alter HR and that could affect both inter- and intra-individual variability in HR measures, such as consumption of food, alcohol, caffeine, and nicotine (smoking), are commonly controlled for within clinic- or laboratory-based approaches (Compher et al., 2006); however, it may not be feasible to control or account for these factors when measuring HR in real-world conditions.

1.6 Ambulatory heart rate measurement using wearable technology

An important consideration for measuring HR is the setting with which the measurement occurs, and the tool or technique used to record HR. Conventionally, when HR is assessed in controlled clinical settings, techniques may include palpation or use of multi-lead electrocardiography (ECG), which is considered the gold standard for measurement of HR (Alugubelli et al., 2022; Dahiya et al., 2024). These in-clinic assessments may be susceptible to clinic-induced constraints and confounders (e.g., white coat syndrome), and only provide a “snapshot” that reveals the HR response (or state) of the individual at that specific moment in time (Eikeseth et al., 2020; Mancina et al., 1983). For example, if an individual is experiencing stress during an in-clinic visit, it is possible that elevations in HR may occur due to

activation of the “fight or flight” response, as previously described, which could compromise the HR measurement or lead to inaccurate conclusions. Beyond the clinic, Holter monitor ECG systems have been used extensively within clinical cardiology as a diagnostic tool and as the gold standard for ambulatory assessment of heart function over the past 50 years (Bent et al., 2020; Bouzid et al., 2022; Holter, 1961; Lindsey et al., 2025). Holter monitoring provides both HR and heart rhythm information; however, the multi-lead set up may be cumbersome to the wearer and preclude extended wear (Hinde et al., 2021; Sana et al., 2020). Another clinically deployed approach is ambulatory BP monitoring (ABPM), which can intermittently assess HR across the day and night (e.g., every 20-30 minutes) and derive circadian HR outputs that have prognostic significance (Ben-Dov et al., 2007; Verdecchia et al., 1998), but may interfere with behavior (e.g., interrupt sleep) and lack the temporal resolution needed to characterize time-varying changes in HR in response to a given stimulus. The emergence and proliferation of wearable technologies, including lower profile portable ECG devices and optical sensor systems (i.e., photoplethysmography (PPG)), have added to the landscape of options for ambulatory HR monitoring (Bayoumy et al., 2021; Soon et al., 2020). Specifically, there exists an opportunity to leverage wearable HR monitoring technology as a tool to further examine how HR changes in free-living environments, in the context of behaviors, and to explore the stability of HR across extended periods of time. However, it is necessary to first consider the strengths and limitations of wearable HR monitoring technology, including PPG and portable ECG, to identify the most suitable candidate for free-living HR measurement and highlight areas that are in need of further attention.

1.6.1 Wearables for ambulatory heart rate measurement: PPG versus ECG

Photoplethysmography (PPG) sensing technology is ubiquitously used to measure HR within commercial smartwatches and fitness trackers and has the potential for widespread applications within clinical physiological measurement (Allen, 2007; Bent et al., 2020; Henriksen et al., 2018; Moscato, Lo Giudice, et al., 2022; Natarajan et al., 2020; Quer et al., 2020). PPG uses light emitting diodes (LEDs) and a photodetector to measure changes in microvascular blood volume caused by fluctuations in the

cardiac cycle (Alugubelli et al., 2022; Majumder et al., 2017). Specifically, the intensity of light that is detected changes as a function of arterial blood volume, and results in a PPG signal and corresponding waveform, including a systolic peak that can be used to estimate HR (Majumder et al., 2017; Moscato, Lo Giudice, et al., 2022). Advantages of PPG sensing technology include that it is highly portable, unobtrusive, compact, inexpensive, and presents the capacity to potentially derive other information relevant to cardiovascular health from the PPG waveform (e.g., indirect estimation of arterial stiffness, BP) (Allen, 2007; Moscato, Lo Giudice, et al., 2022; Moscato, Palmerini, et al., 2022). Deployment of PPG technology in controlled settings has revealed that while device performance may be deemed “acceptable” (or “adequate”) during resting conditions, HR measurement error increases during physical activities across many PPG devices (e.g., Düking et al., 2020; Georgiou et al., 2018; Hajj-Boutros et al., 2023; Pradhan et al., 2019; Rozanski et al., 2018; Shcherbina et al., 2017; Wallen et al., 2016; Wang et al., 2017), which may limit the clinical utility and reliability of PPG-based HR measures during daily life activities (Bent et al., 2020; Fine et al., 2021). In alignment with this suggestion, past work has also revealed that estimates of certain HRV outcomes derived from PPG (i.e., pulse rate variability (PRV)) differ considerably from ECG-derived HRV measures under free-living conditions in healthy adults (Lam et al., 2020; Schäfer & Vagedes, 2013) and people with vascular disease (Hoog Antink et al., 2021) or PD (Janssen Daalen et al., 2024). These discrepancies could be due to the susceptibility of PPG to several sources of inaccuracy, including being affected by individual demographic variables (e.g., skin tone, health status), physiological factors (e.g., temperature, respiration), and external perturbations or movement (e.g., motion artifact, change in contact pressure between sensor and skin, changes in ambient light, etc.) (Allen, 2007; Fine et al., 2021; Moscato, Palmerini, et al., 2022; Sana et al., 2020; Tamura et al., 2014). Comprehensive identification of the sources of noise that can affect PPG signal quality and feature extraction are important to understand the suitability of PPG for certain real-world use cases and to design systems in the future that may attempt to control for or mitigate the impact of certain sources of variation. Given the integration of PPG technology into various commercial devices that use proprietary algorithms, there is also often a lack of access to raw sensor data and a lack of transparency about the data

processing steps and settings or conditions of free-living HR measurement during PA and rest (Dial et al., 2025; Fuller et al., 2020; Natarajan et al., 2020; Rietz et al., 2024; Speed et al., 2023). For example, in a study assessing intra- and inter-individual variability in the RHR of 92 000 people who wore a commercial wrist-based PPG device (i.e., FitBit) for at least 35 weeks over a 2-year period, no methodological details were provided about how individual daily “resting HR” values were derived (Quer et al., 2020). An inability to understand the methodological approach used to derive specific HR outcomes makes it challenging to evaluate if the method is robust to some of the known sources of inaccuracy of PPG technology or suitable for application to populations who may have complex health conditions.

Electrocardiography (ECG) involves direct recording of the electrical activity of the heart via electrodes and as mentioned previously, is considered the gold standard for measurement of HR (Alugubelli et al., 2022; Bayoumy et al., 2021; Bent et al., 2020). With each heartbeat, a characteristic change in voltage throughout the cardiac cycle results in the production of certain waveforms on an ECG trace, including the QRS complex, which corresponds to ventricular depolarization and the onset of ventricular contraction. Identification of the QRS complex is fundamental to R-peak detection algorithms that generate an R-R interval series to be used for calculation of beat-to-beat HR (Alugubelli et al., 2022; Kristof et al., 2024). The characteristic waveforms and timing within the ECG signal during normal sinus rhythm also allow for the identification of abnormal beats (e.g., ectopic beats) (Shaffer et al., 2014). Although the multi-lead nature of Holter monitors enables robust measurement of heart rhythm abnormalities, the use of portable and lower profile single-lead ECG technology in consumer and research grade devices permits free-living measurement of beat-to-beat data that can be used to assess HR outcomes (Alugubelli et al., 2022; Bouzid et al., 2022; Kristof et al., 2024; Sana et al., 2020). For example, an ECG chest strap (Polar H10) was worn for a 24-hr period in daily life and provided access to raw ECG data that was subscribed to a peak detection algorithm to assess how beat-to-beat HR data relates to movements during sleep (Sicbaldi et al., 2024). As demonstrated by this example, access to raw ECG data may be advantageous because it allows for the application of customized analytics for a given

use case; however, a wearable chest strap may not be comfortable for continuous, extended wear periods and may result in poor compliance (e.g., Mansfield et al., 2016). As an alternative to a chest strap, single-lead ECG devices that attach to the chest via an electrode patch (e.g., Zio Patch) have been deployed in protocols that involve monitoring HR across up to 14 days of continuous sensor wear (Bouzid et al., 2022; Sana et al., 2020), and have produced high levels of ECG data suitable for HR analysis during daily life conditions (Goergen et al., 2023; Solomon et al., 2016; Turakhia et al., 2013). Given that these devices usually involve electrodes attached to the skin with adhesives, skin irritation may occur with longer term wear (Hoog Antink et al., 2021). However, continuous wear of a single-lead ECG chest patch across a week-long period, within a protocol that involved additional limb-worn sensors, was shown to be well tolerated by a group of older adults, including people living with NDD (Godkin et al., 2022). Ambulatory ECG is also susceptible to noise in the signal, from motion, for example (Majumder et al., 2017; Rahman et al., 2022), and as such, it is necessary to apply signal quality algorithms to reject sections of poor signal quality, prior to application of peak detection algorithms (Bouzid et al., 2022; Sana et al., 2020). If not, and ECG signal that has been corrupted by noise is included in subsequent analyses, this may result in inaccurate peak detection and HR estimates, that could have negative implications if aberrant HR outputs are acted upon via self- or clinical-based management strategies. In summary, use of a single-lead ECG device in free-living collection protocols, which provides access to raw sensor data, permits application of signal quality screening and an assessment of the proportion of ECG data that is of sufficient quality for HR calculation. Continued integration of ECG-based HR monitoring of this nature into wearable approaches may also afford the temporal resolution required to assess real-world HR outcomes that can provide insight into ANS function or into the activity-dependent HR response.

1.6.2 A multi-sensor and -device approach for context-dependent heart rate measures

As presented earlier, ANS-mediated changes in HR may occur due to circadian variation, changes in body position, stress, and physical activity. When monitoring HR in uncontrolled, free-living settings, it is important to try to identify some of these different states (e.g., sleep versus wake) or movement

behaviors (e.g., rest versus PA) to provide *context* for interpreting real-world HR. Use of wearable inertial measurement units (IMUs) has made it possible to measure different resting conditions and physical activities in daily life. Approaches that deploy only a single wearable device, such as a wrist-worn accelerometer, have been commonly used to measure free-living behaviors, including measuring PA and sedentary behavior at the population level within large-scale epidemiological studies (e.g., Chastin et al., 2021; Doherty et al., 2017; Ramakrishnan et al., 2021; Stamatakis et al., 2022; Strain et al., 2020; White et al., 2016). Single wrist accelerometer-based approaches have been shown to be well-tolerated (high compliance) and convenient (Bayoumy et al., 2021; Botros et al., 2019; Fisher, Hammerla, Rochester, et al., 2016; Henson et al., 2013; Mahadevan et al., 2020), and represent an objective method that may overcome some limitations of self-report measures (e.g., recall bias) (Chastin et al., 2021; Ryan et al., 2018; Sattler et al., 2020). It is also possible that behavioral outputs derived from single-device approaches can serve as context for interpreting concurrently collected HR, via an onboard PPG sensor in a wristwatch, for example (Henriksen et al., 2018; Schrack et al., 2018; Speed et al., 2023; Williams et al., 2023). However, single IMU-based approaches may not be capable of capturing multiple domains of health (Espay et al., 2016; Godkin et al., 2022) and certain wear locations may be susceptible to error in detecting free-living PA (Chastin et al., 2021; Leinonen et al., 2016), particularly across older adults or people living with complex health conditions that involve considerable within and between-participant variability in movement characteristics (Kim, Hassett, et al., 2019; Treacy et al., 2017; Weber et al., 2023). For example, previous work has illustrated the misclassification of free-living walking as sedentary behavior, across older adults and people living with NDD, when relying only on wrist accelerometer-based estimates of activity intensity (Weber et al., 2023) (see Figure 1.3). Variability was observed between participants in the proportion of walking misclassified; however, up to 56% of walking time was classified as sedentary behavior based on the wrist within a given participant, even when constrained to continuous, long walking periods likely to reflect a moderate intensity (Weber et al., 2023).

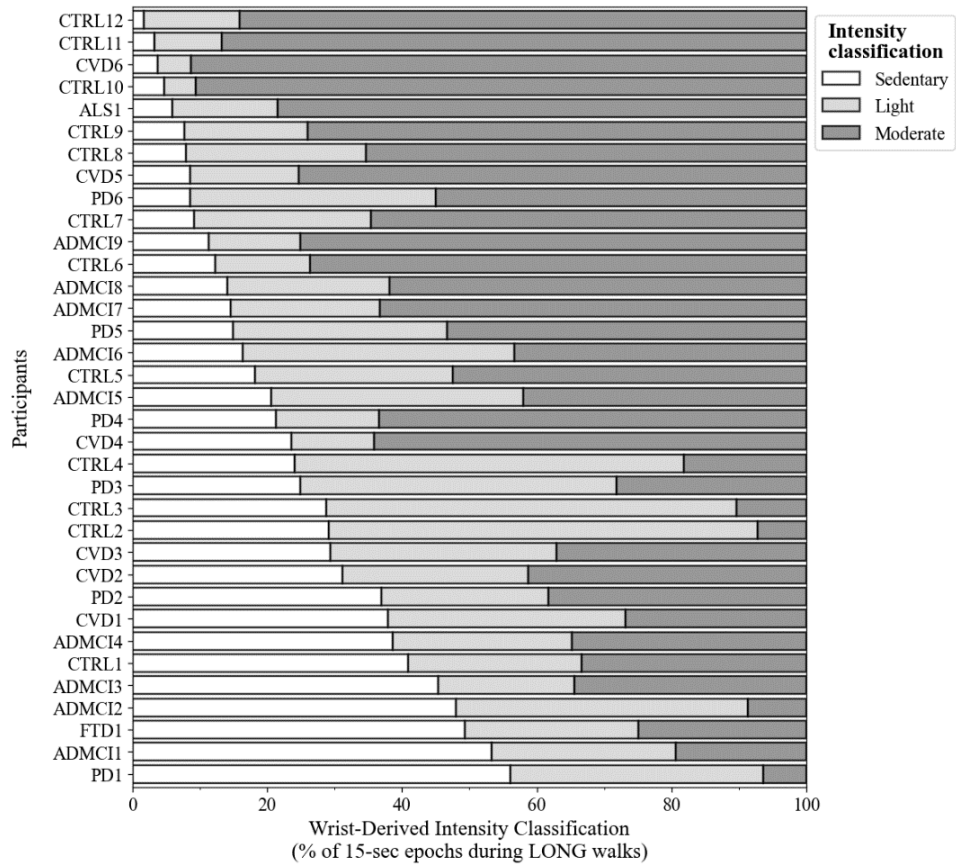


Figure 1. 3. Wrist accelerometer-derived intensity classification during walking across individual participants (from Weber et al., 2023). Proportion of free-living walking classified as sedentary (white), light intensity (light grey), and moderate-to-vigorous intensity (dark grey) based on wrist accelerometry. Each row is a single participant, either an older adult or person living with a neurodegenerative disease.

Instead, an approach that deploys multiple sensor types and devices worn on specific body locations, including a HR monitoring device, may reduce uncertainty and improve the fidelity of free-living behavioral classification for context-dependent HR measures (Beyer et al., 2024; Rietz et al., 2024; Storm et al., 2016). Use of an ankle and wrist-worn IMU, alongside a chest-worn portable ECG device, may enable beat-to-beat HR responses to be measured across active and resting states. Specifically, ankle-worn devices can detect walking and other activities such as cycling (Fortune et al., 2015; Rhudy & Mahoney, 2018), and provide more accurate results than other wear locations (e.g., wrist, hip) at slower gait speeds, which are often exhibited by older adults and people living with mobility impairments (Treacy et al., 2017; Weber et al., 2023). Use of a wrist-worn accelerometer is a conventional approach

for assessing sleep in free-living settings (de Zambotti et al., 2024), based on a good level of agreement between device- and polysomnography-derived sleep measures (Full et al., 2018; Janssen Daalen et al., 2024; van Hees et al., 2015). Although optimal measurement of sedentary behavior includes posture classification (Tremblay et al., 2017), which may be commonly achieved in free-living settings via a thigh-worn accelerometer (Copeland et al., 2025; O'Brien et al., 2022; Sasai, 2017), use of IMU data from synchronized wrist and ankle devices has the potential to enhance wrist threshold-derived intensity estimates of sedentary behavior (Frayssé et al., 2021; Powell et al., 2017) via removal of concurrent ankle-detected stepping (Weber et al., 2023). Measuring a profile of daily behaviors, including ankle-derived walking periods, wrist-derived sleep periods, and multi-device-derived estimates of sedentary behavior, may permit characterization of the HR response to free-living behaviors across prolonged, continuous wear protocols. Furthermore, continuous sampling of HR across days and behaviors enables exploration into the consistency of an individual's HR response to repeating stimuli. For example, it may be possible to profile the within-person variation in HR during resting behaviors or in response to PA, when several resting periods or bouts of PA are accumulated within or across days. Profiling the consistency of the HR response across repetitive bouts of a specific behavior in daily life may have implications for recommending specific collection durations or parameters to capture representative HR responses. Despite the demonstrated adherence to and tolerability of a multi-sensor and -device approach in people with NDD, including PD, when worn for up to two weeks in daily life (Adams et al., 2017; Boroojerdi et al., 2019; Godkin et al., 2022; Heijmans et al., 2019), there is still a paucity of work that has utilized an approach of this nature to measure and explore changes in HR during device-detected behaviors *in free-living* (e.g., Asher et al., 2025). Given the increased application of free-living HR monitoring in clinical and research settings, it may be prudent to explore context-dependent changes in HR, and the consistency of HR responses within a given context, as a first step towards standardizing the measurement of free-living HR outcomes.

1.7 Study-specific objectives and hypotheses

The overarching goals of this thesis are to 1) advance the development of standard approaches to assess HR from continuously collected data over multiple days and behavioral contexts, and 2) apply these approaches to advance understanding of ANS function and characterization of daily life physical activity profiles among individuals with Parkinson's disease. This will be achieved within three linked studies. Common to all of the studies are: (i) a need to capture continuous, multi-day, multi-sensor and multi-device data to allow for an examination of HR in real-world settings under different behaviors and states, and (ii) to attend to, with great care, the analysis of these large raw data sets to ensure necessary data quality and sensor integration for context.

Study 1. Measuring resting heart rate during daily life using wearable technology: examining the impact of behavioral context and methodological criteria

Resting HR (RHR) is an important measurement to serve as a reference for characterizing and quantifying the magnitude of a change in HR, such as the HR response to physical activity. RHR has also been commonly measured in clinical and research settings as a risk stratification tool. However, there is considerable variability in the criteria and approach used when measuring RHR, and an opportunity to remove some of the barriers associated with in-clinic assessments by using wearable technology to evaluate HR during resting conditions in daily life. Thus, the overall goal of **Study 1 (Chapter 2)** was to guide specific recommendations for a standardized RHR measurement approach from multi-sensor data collected during daily life in a cohort of adults without PD ("control"), with focus on both the "how," which refers to the statistical criterion and window length used to define RHR, and the "when," in terms of the resting condition (i.e., sleep vs. sedentary) and duration (i.e., day vs. week). Specific objectives included (i) characterizing the impact of statistical criterion and measurement window length on RHR estimates, (ii) determining if type of resting condition, specifically sedentary behavior versus sleep, impacted overall RHR estimates and the consistency of daily RHR estimates, and (iii) characterizing the distribution of HR values during sedentary behavior and sleep in order to profile how the distribution of HR varies between free-living resting conditions. It was hypothesized that overall RHR estimates,

between-day variability in RHR, and median and range in HR values would be greater during sedentary behavior compared to sleep.

Study 2. Wearable ECG-derived measures of nocturnal heart rate dipping: Exploring an approach for assessing autonomic dysfunction in Parkinson's disease in daily life

Non-motor symptoms have a negative impact on the quality of life of individuals living with Parkinson's disease (PD), and yet, they have been traditionally understudied and inadequately managed. Cardiovascular ANS dysfunction occurs in PD and may alter diurnal cardiovascular regulation. Although most studies measuring HR as a potential window into ANS dysfunction in PD have done so in controlled environments, ambulatory HR monitoring could potentially be used as an accessible tool to measure HR responses in daily life. Specifically, the application of recommendations from Study 1 on measurement of daily life resting HR, in the context of sedentary behavior and sleep, permits investigation into novel indices of nocturnal HR dipping in daily life. **Study 2 (Chapter 3)** aimed to compare measures of daily life nocturnal HR dipping between adults without ("control") and with PD, and test if nocturnal HR dipping was related to clinical measurement of ANS dysfunction in PD. It was hypothesized that there would be blunted nocturnal HR dipping in PD compared to controls, and that less nocturnal HR dipping would be associated with greater ANS symptoms.

Study 3. Use of a context-based wearable technology approach to characterize the ambulatory HR response to daily life walking in people with and without PD

Engagement in aerobic PA is recommended for people with PD given the potential symptomatic and functional benefits. And yet, there is a need to ensure accurate quantification of the PA intensity to appropriately quantify the dose-response relationship. HR monitoring of the activity-dependent cardiovascular demand may serve as an index of the relative intensity of the activity, which may be particularly important in PD, whereby absolute intensity approaches may be less suitable because PD symptoms and movement characteristics may result in a certain amount of movement being associated with diverse cardiovascular responses. Despite the potential value, a lack of work has been done using context-based ambulatory HR monitoring to assess the HR responses to daily life PA in people with PD.

Thus, the overarching goal of **Study 3 (Chapter 4)** was to utilize a multi-device and -sensor approach to characterize and compare activity-dependent changes in HR during daily life walking, as an index of relative intensity, between a cohort of adults with and without PD. Specific objectives included (i) determining the volume of analyzable HR data derived from single-lead ECG during daily life behaviors, including walking, (ii) quantifying and comparing between control and PD participants the mean and within-participant variability of the HR response to longer, continuous, daily life walking bouts, and (iii) determining if the HR response to daily life walking was related to walking characteristics, including cadence and bout duration. It was hypothesized that cadence and bout duration would be positively associated with the HR response to walking for both control and PD participants.

This work will advance the measurement and use of HR from data collected continuously during daily life, with a current focus on the application to adults with and without Parkinson's disease. The long term goal of this work is to set the stage for broader future use of HR data extracted from everyday life to inform self-management and/or clinical health care decision making across populations.

CHAPTER 2 (STUDY 1)

Measuring resting heart rate during daily life using wearable technology: Examining the impact of behavioral context and methodological criteria

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TITLE: Measuring resting heart rate during daily life using wearable technology: examining the impact of behavioral context and methodological criteria

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OVERVIEW

Objective: Advances in the collection of high-quality, continuous electrocardiography (ECG) data via wearable technology have the potential to transform heart rate (HR) measurement in daily life. This study aimed to characterize the impact of methodological criteria and behavioral context on estimates of resting heart rate (RHR) to guide recommendations for a standardized approach to measure daily life RHR.

Methods: Ten adults (9 female, 61 ± 12 years) wore a chest-mounted ECG device and wrist and ankle movement sensors continuously for 7-10 days. Following signal quality screening and beat-to-beat calculations, HR was analyzed using rolling averages of 15-, 30-, and 60-sec windows within periods of device-detected sedentary behavior and sleep. ECG data during sedentary and sleep were compared for differences in: 1) RHR, 2) between-day consistency of daily RHR, and 3) HR median and range.

Results: During sedentary and sleep, respectively, there was no difference in RHR (56 ± 7 bpm vs. 54 ± 7 bpm, $p=0.055$) or in between-day consistency of RHR (coefficient of variation: $6 \pm 3\%$ vs. $5 \pm 3\%$, $p=0.12$; maximum between-day range of RHR=14 bpm). However, the median HR (71 ± 6 bpm vs. 62 ± 7 bpm, $p=0.001$) and HR range (35 ± 6 bpm vs. 23 ± 7 bpm, $p<0.01$) were significantly greater during sedentary versus sleep.

Conclusions: Behavioral context and method of analysis impact ECG-based HR measures at rest. This study recommends a novel wearable-based method for measuring daily life RHR that maximizes use of available data and confronts variability that exists with extended monitoring. Use of a standard method for measuring daily life RHR may advance the use of HR to inform clinical and/or personal health decisions.

KEYWORDS: Heart Rate, Wearable Technology, Daily Life Measurement, Electrocardiography (ECG), Cardiovascular Index, Sleep, Sedentary Behavior, Activity Intensity

INTRODUCTION

Measures of cardiovascular function, including heart rate (HR), are critically important for evaluating sleep, stress, and heart health across a range of populations, as well as to guide physical activity prescription and monitoring.¹⁻³ With the exception of the use of Holter systems for those with cardiac health concerns, monitoring of HR for the purposes of clinical decision-making is often restricted to supervised in-clinic measurements, including brief manual palpation or use of an automated blood pressure (BP) cuff to derive an average of multiple readings over short intervals (e.g., 30 seconds).⁴ However, advances in accessible wearable technology (“wearables”), which can provide high quality HR and movement data for extended periods of time, has the emerging potential to transform the ability to use HR to inform clinical and/or personal health decisions. While continuous HR monitoring over multiple days or weeks presents a unique opportunity to understand heart function, the large volume of data introduces complexities with respect to the method of analysis and how to interpret data spanning days or weeks.

As an important starting point, acquiring HR data over many days permits a reconsideration of the method of determining resting heart rate. Resting heart rate (RHR) is associated with risk of poor cardiovascular-related outcomes and all-cause mortality across populations, independent of conventional cardiovascular risk factors.^{1,5-8} Resting heart rate has been thought to reflect an individual’s resting metabolic rate⁹ and is a necessary measurement to serve as a baseline for characterizing the magnitude of HR responses to various stimuli, such as physical activity. Despite well accepted guidelines for the measurement of other cardiovascular indices such as resting BP,¹⁰ there is a lack of standardization and considerable variability among the criteria and approach used to measure RHR.^{1,3,11,12} Notably, many studies provide inadequate specificity about controlling or accounting for factors that are likely to influence HR, such as preceding (or on-going) behavioral state, co-existing medical conditions, participant posture, window length of recording, and tool or analysis approach used.^{3,13-15} In addition to a lack of transparency about the specific approach to measurement,¹⁶ point-in-time, clinically-derived RHR

“snapshots” may not be ecologically valid, as they are subject to clinic-induced constraints or confounders (e.g., lack of time, white coat effect), and are characterized by low reproducibility.¹⁷ The lack of a global standard and limitations associated with in-clinic RHR measurements makes it difficult to compare across studies, populations, or time points, and is problematic given the ongoing use of RHR as a tool for health risk stratification^{18,19} and/or reference point for prescribing activity intensity across research and clinical settings.^{20–22}

Leveraging wearables to conduct continuous HR monitoring and profile HR in the context of free-living resting conditions (i.e., sleep and sedentary behavior)²³ is important for many reasons, including the opportunity to assess the circadian rhythmicity of HR. HR has been reported to drop during slow wave stages of sleep compared to awake values,^{6,24} and HR non-dipping (i.e., the absence of a reduction in HR during sleep) has been associated with increased risk of all-cause mortality.²⁵ Heart rate measurements during sleep may also be less susceptible to the influence of external factors, such as movement or stress, compared to wakeful resting measures.²⁶ Providing behavioral context for interpreting HR has been possible through concurrent use of inertial measurement units (IMUs). For example, data from a limb-worn IMU have been used to differentiate sleep from wakeful states,²⁷ thus enabling further insight into HR change across day-night cycles. In addition to changes in HR during sleep, HR increases with increasing activity intensity² and remains elevated during recovery as a function of the activity intensity and duration.²⁸ Inertial measurement units worn on the wrist, hip, or thigh have commonly been used to stratify awake periods into activity intensity categories,^{29–33} including identification of sedentary behavior, which could be used as a window for assessing RHR. For example, one study assessed RHR in a free-living setting and identified sedentary periods based on wrist sensor-derived activity estimates that were < 1.5 metabolic equivalent tasks (METs).¹² Importantly, the ability to use wearables to appropriately capture behavioral context and movement characteristics, such as activity intensity, is dependent on numerous factors including number of sensors and wear location. Reliance on single wrist-sensor approaches may be inadequate for isolating sedentary behavior given evidence to

suggest that wrist-derived estimates of activity intensity frequently misclassify periods of free-living walking as sedentary behavior in older adults and clinical cohorts.³⁴ The changes in HR during sleep and physical activity highlight the importance of specifying and standardizing whether RHR is measured during sleep or waking states, and if measured when awake, the value of limiting its measurement to robustly defined periods of sedentary behavior.

Studies that have used wearables to examine RHR in daily life have largely adopted single-device approaches using Holter-based electrocardiography (ECG) monitoring or photoplethysmography (PPG) technology.^{35–37} Although ECG is considered the gold standard for HR monitoring, traditional Holter monitors use multiple leads in a setup that may be burdensome to the wearer.^{38,39} Conversely, most PPG sensors that continuously measure pulsatile blood flow as a proxy measure of HR are embedded in wrist-worn sensors,^{40,41} which are accessible and low profile but suffer from compromised accuracy relative to outcomes derived from ECG during periods of physical activity due to a susceptibility to motion artifacts.^{35,42–44} Additionally, most previous work to assess daily life RHR has relied on commercial devices containing proprietary algorithms that lack transparent analyses and/or provided inadequate detail about how and when estimates of RHR were derived (e.g.,⁴⁵), resulting in the adoption of varied criteria and methodologies. For example, Logan et al., (2000) determined a free-living RHR estimate by calculating the mean HR from the lowest 60-sec HR interval and all 60-sec HR values within three beats per minute (bpm), based only on daytime measurement (i.e., no nighttime recordings), without restricting analyses to sedentary periods. In contrast, Johansen et al., (2013) and Matsuura et al., (2019) both anchored their RHR estimates to “assumed” sleeping periods based on overnight windows, but differed in the duration with which HR was averaged (i.e., 15 minutes vs. 10 hours) and did not provide any information about the sampling frequency. Including details about the conditions and criteria used to calculate daily life RHR, such as the measurement window length, if measures are restricted to a specific resting condition, and the frequency of HR sampling, enables understanding about whether the RHR

estimate is likely to reflect a minimum HR value or a summary value of average HR during an inactive state.

A multi-sensor approach using devices that provide access to raw sensor data may 1) overcome some of the data quality limitations of other wearable technologies, 2) decrease the likelihood of misclassifying resting behaviors (e.g., sedentary behavior), and 3) enable the development of novel, standardized, and transparent methods for profiling how HR varies during daily resting conditions and estimating minimum HR during rest. Specifically, wearing multiple limb-worn IMUs alongside a chest-worn ECG device permits robust, continuous, daily life HR data over extended wear periods to be connected to reliable movement data that can provide essential behavioral context for interpreting HR.⁴⁶ This wear paradigm has also been shown to be feasible and well-tolerated in a cohort of older adults and persons living with complex health conditions over the course of a week-long, continuous wear period.⁴⁷ However, there has been little work using this approach to examine free-living RHR. Thus, the overall goal of this study is to guide specific recommendations for a standardized RHR measurement approach from multi-sensor data collected during daily life, with focus on both the “how”, which refers to the statistical criterion and window length used to define RHR and the “when”, in terms of the resting condition (i.e., sleep vs. sedentary) and duration (i.e., day vs. week). Firstly, this study aimed to characterize the impact of statistical criterion and measurement window length on RHR estimates. Secondly, this study aimed to determine if type of resting condition, specifically sedentary behavior versus sleep, impacted overall RHR estimates and the consistency of daily RHR estimates. It was hypothesized that overall RHR estimates would be greater during sedentary compared to sleep and that the between-day consistency of daily RHR values would be lower during sedentary compared to sleep. Thirdly, this study aimed to characterize the distribution of HR values during sedentary and sleep in order to profile how the distribution of HR varies between free-living resting conditions. It was hypothesized that the range in HR and median HR values would be larger during sedentary versus sleep. By identifying some of the factors that impact RHR estimates and profiling how HR varies during resting conditions in

daily life, this study may help to expand conventional thinking and guide specific recommendations for measuring daily life RHR in future studies using wearables. The work will also highlight the importance of ensuring daily life HR is referenced to a given behavioral context.

METHODS

Participants

Participants were enrolled in the Health in Aging, Neurodegenerative Diseases and Dementias in Ontario (HANDDDS-ONT) study, which was a fully remote, prospective, observational study conducted as part of the Ontario Neurodegenerative Disease Research Initiative (ONDRI) from August 2021 to April 2023.⁴⁸ Individuals were included in the present study if they were part of the HANDDDS-ONT control cohort, who also did not self-report any cardiovascular, endocrine, or metabolic disease. These additional inclusion criteria were applied to restrict initial HR analyses to a carefully selected convenience sample of relatively “healthy” adults, who were free from comorbidities and/or diseases that are known to impact the cardiovascular and/or autonomic nervous system. Additionally, estimates of RHR for each participant were generated from an average of approximately 500 000 data epochs, providing a robust and highly stable basis for calculating individual-level metrics. The HANDDDS-ONT study was approved by Clinical Trials Ontario (Project ID: 3589) with Sunnybrook Research Institute in Toronto, Ontario as the Board of Record (REB approval: 2021-1517), and, due to the fully remote nature of the study, all participants provided verbal informed consent prior to study initiation. The REB-approved protocol for obtaining consent involved a virtual visit in which the research coordinator reviewed the informed consent document with the potential participant prior to obtaining consent, which was documented as a verbal attestation.

Procedures

Participants received a kit in the mail that contained three wearable devices, instruction cards, and paper logs. Participants then attended a virtual baseline visit with a research coordinator, where they were

oriented to the study package and assisted with wearable device instrumentation, before completing a detailed health history. All devices were data logging and required minimal interaction (i.e., no charging or manual participant data entry required). Participants were instructed to wear devices on the chest, and on the dominant (or least impaired) wrist and ankle (Figure 2.1), for up to 10 days continuously, except for bathing or swimming. Participants were encouraged to go about their usual activities while wearing the devices. A research coordinator conducted a virtual check-in visit on the third or fourth day of sensor wear, and then a discharge visit at the end of the collection period to assist with sensor removal and return of the study package. Once the study team received back the study kit in the mail, data was offloaded from the devices, before being processed and analyzed.



Figure 2. 1. Participant set up with devices. Schematic representation of wearable device type and location on body segments, including Bittium Faros 360 device on chest and Axivity 6 devices on wrist and ankle.

Data Collection

Demographic and Clinical Measures

During the virtual baseline visit, participants self-reported demographic information and health history, including current and past medical conditions and medications. All demographic and clinical information was collected and stored using REDCap^{49,50} electronic case report forms and hosted on Brain-CODE.⁵¹

Wearables Data Collection

Limb-worn IMUs were Axivity 6 devices (AX6, Axivity Ltd) and contained a tri-axial accelerometer and gyroscope, as well as a temperature and light sensor. Accelerometer and gyroscope data were collected at a sampling frequency of 50 Hz. AX6 devices were worn on the wrist using a rubber watch strap and just proximal to either the medial or lateral malleolus, as selected by the participant, using a customized medical-grade wrap (Fabrifoam, PA). The chest device was a Bittium Faros 360 ECG unit (Bittium, Finland), which also contained a tri-axial accelerometer, and has been used as a reference standard for HR in free-living conditions.^{35,52} Bittium Faros devices were affixed to the chest using a 2-lead OmegaSnap electrode adhesive, which was waterproof and did not require removal for bathing or swimming. ECG data were sampled at a frequency of 250 Hz, while the accelerometer sampled at a frequency of 25 Hz. All devices provided access to raw unprocessed data and underwent a simultaneous manual synchronization procedure at the start, during the check-in visit, and at the end of the collection period. This involved placing the devices in their shipping container and flipping the container periodically for approximately ten seconds. The task produced a standard waveform across all devices, which could be used to temporally align signals during data processing. Once collection finished and devices were returned to the study team, sensor data was offloaded to a secure network drive and processed using a customized analytics pipeline (⁴⁶; <https://github.com/nimbal/nimbalwear>) and additional custom analytics implemented in Python (Version 3.12), as described below.

Data Processing and Analysis

IMU data

Once offloaded, IMU data was converted to a standardized European Data Format (EDF), before resampled to a constant sample rate and temporally synchronized across devices, including the concurrently collected accelerometer sensor on the chest-worn ECG device. During stationary periods, accelerometer calibration was evaluated using gravity as a constant, known acceleration value, and

corrected as necessary.⁵³ The customized analytics pipeline⁴⁶ was then run to remove periods of device non-wear⁵⁴ and to detect the following behaviors: stepping from the ankle,^{55,56} sleep from the wrist,^{27,57} and activity intensity estimates from the wrist using age-based cut-points that differentiate between sedentary, light, and moderate-vigorous intensity.^{58,59} Specifically, cut-points were applied to participant data as follows: those < 60 years⁵⁹ and those ≥ 60 years⁵⁸. To classify sedentary behavior, periods of time when intensity was coded as sedentary by the wrist were isolated and then any periods with overlapping ankle-derived stepping were removed.

ECG data

Raw ECG data underwent signal quality screening to restrict analyses to data with a high signal-to-noise ratio that permitted beat-to-beat HR analysis.⁶⁰ R-peaks were detected from the ECG data using the NeuroKit peak detection algorithm (NeuroKit2) and beat-to-beat HR was calculated.⁶¹ The continuous beat-to-beat HR data was resampled using a 1 Hz interpolation, and a low pass filter (0.1 Hz) was applied. The interpolated heartbeat data was used and was also averaged using rolling averages of 15-, 30-, and 60-second window lengths.

HR Analyses for Objective 1: Establishing statistical criterion and window length for measuring RHR

Full calendar days were included if the chest device was worn for at least 20 hours and if the wrist device was worn for at least 10 hours during waking hours, consistent with studies of physical activity.^{34,62} A minimum of seven usable days (could be non-consecutive) were required for a participants' data to be included in the analysis. To determine a statistical criterion for defining free-living RHR, independent of behavioral context, interpolated beat-to-beat HR values during included days across the entire collection were plotted in a histogram for each participant. The statistical criterion derived from the distributions to identify an RHR estimate initially included minimum, 1st, 5th, and 10th percentile HR values. A threshold was set at 30 bpm based on physiologically possible HR values,^{63,64} and the per-participant minimum and 1st percentile HR values were compared to this threshold to identify the proportion of HR values that were

≤ 30 bpm (i.e., non-physiological values). This approach was taken to exclude statistical criteria that resulted in unrealistic HR values. Next, 1st, 5th, and 10th percentile HR values were compared. The statistical criterion that identified the lowest possible physiologically probable HR values across participants was carried forward into subsequent analyses when defining RHR. To determine the impact of conventional measurement window lengths on RHR estimates, rolling average HR values of 15, 30, and 60 seconds were calculated during included days across the entire collection, and RHR was calculated for each window length based on the statistical criterion identified above.

HR Analyses for Objective 2: Examining differences in RHR between resting conditions

To examine the impact of resting condition on RHR, RHR was calculated for both sedentary and sleep periods. First, only sedentary periods of a minimum five-minute duration were included to identify windows where participants were likely to be at rest and based on work to suggest HR stabilization post-activity after a minimum of four minutes duration.¹² Next, all sedentary periods (≥ 5 mins) and sleep periods with usable HR data during included days were identified. The criteria established in Objective 1 were then applied to identify an “overall sedentary RHR” and “overall sleep RHR” estimate per participant. Next, sedentary periods were grouped based on each day of collection, from midnight to midnight. Sleep periods were grouped based on examining days from noon to noon, and noon-to-noon segments were included if the wrist device was worn for at least 11 hours during the corresponding overnight period from 8:00pm to 8:00am. This allowed for estimation of a “daily sedentary RHR” and a “daily sleep RHR” per day for each participant, by pooling all of the HR values across sedentary periods within a day and across sleep periods within a day, before applying the criteria for RHR established in Objective 1 to these pooled HR values. Once estimates of daily sedentary RHR and daily sleep RHR were calculated for each participant, within-participant variability in daily RHR estimates was assessed via calculation of a between-day standard deviation, range, and coefficient of variation (CV) for each participant, as well as the lowest daily RHR (minimum) and highest daily RHR (maximum) estimate.

HR Analyses for Objective 3: Characterizing the distribution of HR values during resting conditions

To characterize the distribution and profile the variation in HR during resting conditions, HR range values (defined as 99th minus 1st percentile values) and median HR values were calculated from the same distributions of data generated in Objective 2 (as described above), where HR data was pooled across the collection per participant during 1) all included sedentary periods and 2) all sleep periods. These outcomes are referred to as “overall sedentary HR range,” “overall sedentary median,” “overall sleep HR range,” and “overall sleep median”.

Statistical Analyses

Demographic and clinical data were summarized using descriptive statistics. Shapiro-Wilk tests were run to test for normality of each dataset included in the statistical analyses.

In terms of objective 1, to confront the impact of window length on RHR estimates, a one-way repeated measures ANOVA was conducted to assess the difference between RHR estimates derived from 15, 30, and 60-sec rolling average HR window lengths. If significant, pairwise comparisons (linear contrasts) were conducted with Bonferroni-corrected p values based on number of planned comparisons.

Additionally, absolute (bpm) differences in RHR estimates derived from each of the rolling average HR window lengths were assessed to assess clinical meaningfulness of any differences. In terms of objective 2, a one-way paired samples t-test was used to test for differences between per-participant overall sedentary RHR and overall sleep RHR values. To determine if differences in between-day consistency existed depending on resting condition, a one-way paired samples t-test was used to compare the within-participant coefficient of variation (CV) of daily sedentary RHR and daily sleep RHR. Descriptive statistics were run on between-day standard deviation, range, mean, minimum and maximum of daily RHR values for each participant. Intraclass correlation coefficients (ICC) with 95% confidence intervals were also calculated (ICC (2, 1), absolute agreement)⁶⁵ to assess the day-to-day variation in the RHR estimate for sedentary behavior and sleep. In terms of objective 3, two one-way paired samples t-tests were used to test for differences between 1) overall sedentary and overall sleep HR range values and 2) overall sedentary and overall sleep median HR values.

All statistical analyses were conducted in Pingouin (Python, Version 3.12)⁶⁶ and statistical significance was set at $\alpha < 0.05$. Data are presented as mean $\pm$ SD (range) unless otherwise noted.

RESULTS

Participant Characteristics

A total of 10 adults met the study-specific inclusion criteria. The mean age was 61 ± 12 years and 90% of participants were female. Two participants self-reported taking prescribed medication for anxiety and depression (one on selective serotonin reuptake inhibitor (SSRI) daily and another on daily SSRI and bupropion and benzodiazepine as needed), whereas the remaining eight participants reported taking no medication. Table 2.1 summarizes demographic and behavioral characteristics of the participants. In terms of compliance, daily wear times averaged 98.7 ± 0.47 % (97.9 – 99.4) for the chest device, 98.2 ± 0.96 % (97.0 – 99.3) for the wrist device, and 99.2 ± 0.27 % (98.8 – 99.6) for the ankle device (Table 2.1). The amount of time wearing the devices did not differ across days for any of the devices (all p values > 0.05). Usable HR data, defined as HR data that passed the signal quality screening (i.e., adequate signal-to-noise to reliably extract HR), was available during 87.9 ± 9.8 % of the time spent wearing the chest device. Of this time, 90.1 ± 9.8 % of the time spent sedentary and 97.4 ± 1.8 % of the time spent sleeping contained usable HR data.

Table 2. 1. Participant Characteristics

		Overall (n = 10)
Demographics		
Age (years)		61.4 ± 11.7
Sex (n, % Female)		9 (90%)
Ethnicity (n, %) ^a		8 (80%) European
Device Wear		
Chest (% wear/day)		98.7 ± 0.47
Wrist (% wear/day)		98.2 ± 0.96
Ankle (% wear/day)		99.2 ± 0.27

Behavioral Characteristics	
Sedentary time (hours/day)	11.2 $\pm$ 0.9
Sleep (hours/night)	6.3 $\pm$ 0.9
Walking (steps/day)	12850 $\pm$ 3700

Data are presented as grand mean $\pm$ standard deviation unless otherwise noted.

^a Remaining 20% of participants responded as “Don’t know”

Objective 1 – Establishing criteria and window length for measuring RHR

The frequency distributions of interpolated beat-to-beat HR values measured across the entire collection period, independent of behavioral context, are displayed for each participant in Figure 2.2. Minimum HR values were ≤ 30 bpm for 40% of participants ($n = 4$), whereas 1st percentile HR values were > 30 bpm for all participants (Figure 2.2). Across participants, the 1st, 5th, and 10th percentile HR values were 52 ± 6 (43-63), 56 ± 6 (46-66), and 58 ± 6 (47-68) bpm, respectively (Figure 2.2). The difference between 1st and 5th percentile values and 1st and 10th percentile values were 3 ± 1 (2-5) bpm and 5 ± 1 (3-8) bpm, respectively. Given the desire to select a physiologically possible value that is not overly conservative, the 1st percentile value was adopted as the criterion for estimating the RHR for all subsequent analyses.

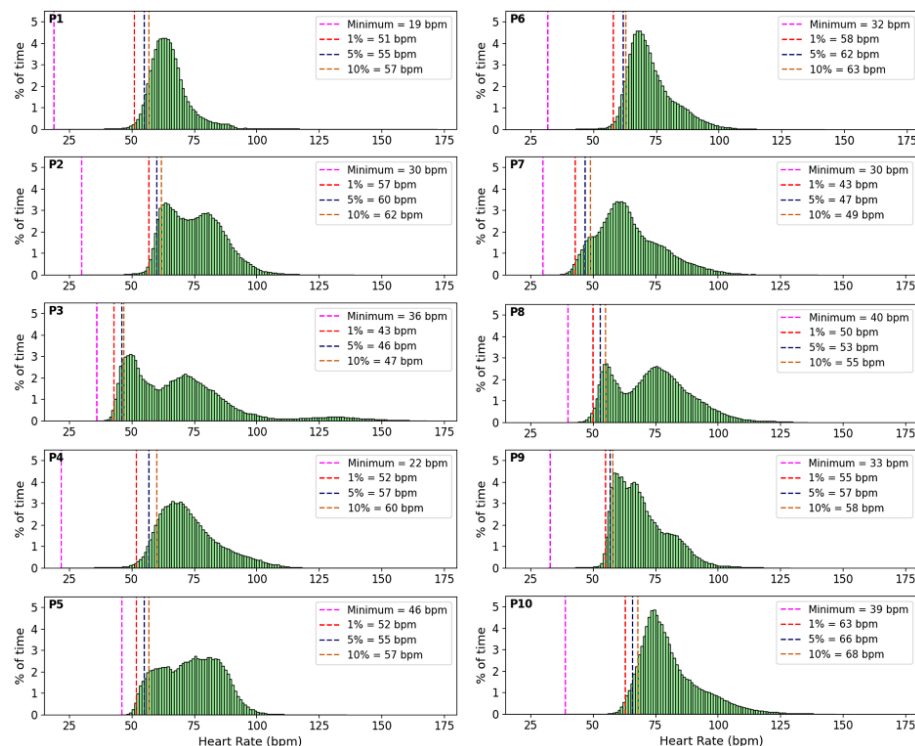


Figure 2. 2. Distribution of beat-to-beat HR values across the entire collection period for each participant ($n = 10$). Each plot is annotated with four lines that represent the minimum (purple), 1st (red), 5th (blue), and 10th (orange) percentile HR values for each participant. Given that 40% of participants had minimum HR values ≤ 30 bpm, 1st percentile HR values were adopted as the criterion for estimating RHR in subsequent analyses.

The frequency distributions of 15-,30-, and 60-sec rolling average HR values measured across the entire collection period are displayed for two sample participants in Figure 2.3. The one-way repeated measures ANOVA that was conducted to assess the difference between RHR estimates (i.e., 1st percentile values) derived from 15, 30, and 60-sec rolling average HR window lengths was statistically significant ($F(2, 18) = 6.8$, $\eta^2 = 0.92$, $p = 0.007$, $n^2 = 0.002$). Contrast tests revealed that the RHR estimate derived from the distribution of 60-sec rolling average HR values (54.2 ± 6.3 bpm, mean $\pm$ SD) was significantly higher than the RHR estimates derived from the 15- and 30-sec rolling average HR window length distributions (53.5 ± 6.3 bpm and 53.7 ± 6.4 bpm, respectively, $p < 0.05$ after Bonferroni correction applied). However, the lack of clinically meaningful difference when comparing the absolute RHR values derived from 15, 30, and 60-sec window lengths (i.e., < 1 bpm difference) suggests that choosing any of the rolling average HR window lengths is likely to result in comparable RHR estimates. Given that a 30-sec measurement duration is feasible and commonly used when measuring RHR clinically, all subsequent analyses adopted a 30-sec rolling average window length for assessing RHR and characterizing the HR distribution.

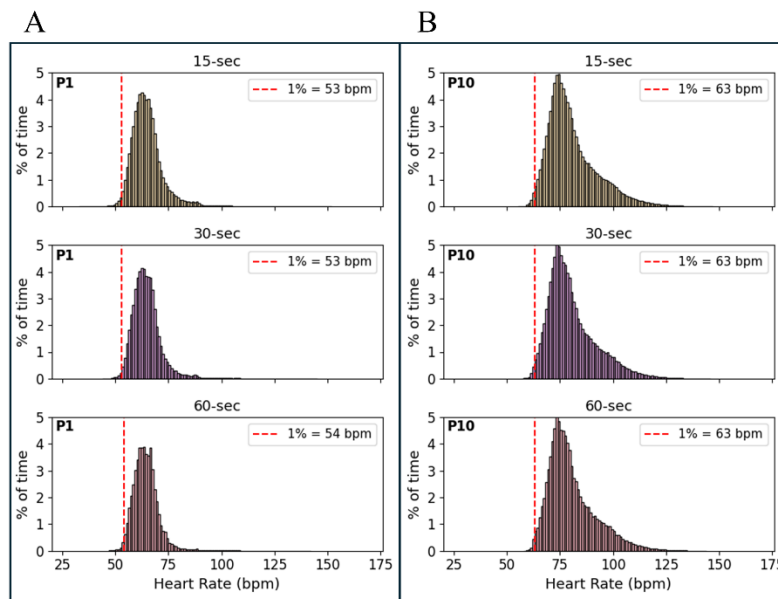


Figure 2. 3. Comparison of RHR estimates derived from 15-, 30-, and 60-sec rolling average HR window lengths across the entire collection for two sample participants. Each column (A, B) represents an individual participant, each row represents a window length (15-, 30-, and 60-sec), and the red dotted line on each plot denotes the RHR estimate.

Objective 2 – Examining differences in RHR estimates based on resting condition

The distribution of 30-sec rolling HR values within all included sedentary periods and sleep periods across the full collection are displayed for a representative participant in Figure 2.4A. When assessed across participants, the RHR estimate during sedentary (overall sedentary RHR) was not significantly different than the RHR estimate during sleep (overall sleep RHR) (56 ± 7 bpm vs. 54 ± 7 bpm, respectively) ($t = 1.78$, $df = 9$, $p = 0.055$, $d = 0.36$) (Figure 2.4B).

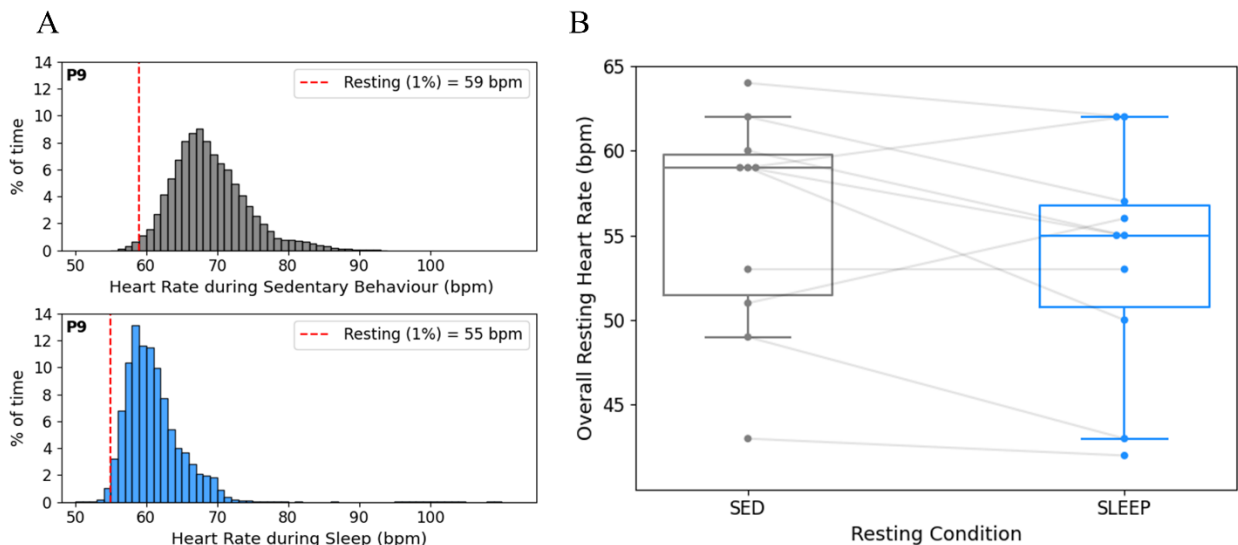


Figure 2. 4. Comparison of RHR estimates between sedentary behavior and sleep when HR data is pooled across the collection period per resting condition. Panel A displays the distribution of 30-sec rolling HR values during sedentary (top, gray) and sleep (bottom, blue) periods across the collection, with a red line denoting overall sedentary RHR (top) and overall sleep RHR (bottom) for a representative participant. Panel B is a box and whisker plot showing the distribution of individual RHR estimates for sleep and sedentary conditions. The horizontal line within the box corresponds to the median value. RHR during sleep was not significantly different than during sedentary ($p = 0.055$). Connector lines are used in panel B to denote individual participants across resting conditions ($n = 10$).

The distribution of 30-sec rolling HR values during all sedentary periods and all sleep periods within each day of collection are displayed, and daily sedentary RHR and daily sleep RHR are denoted, for two sample participants in Figure 2.5.

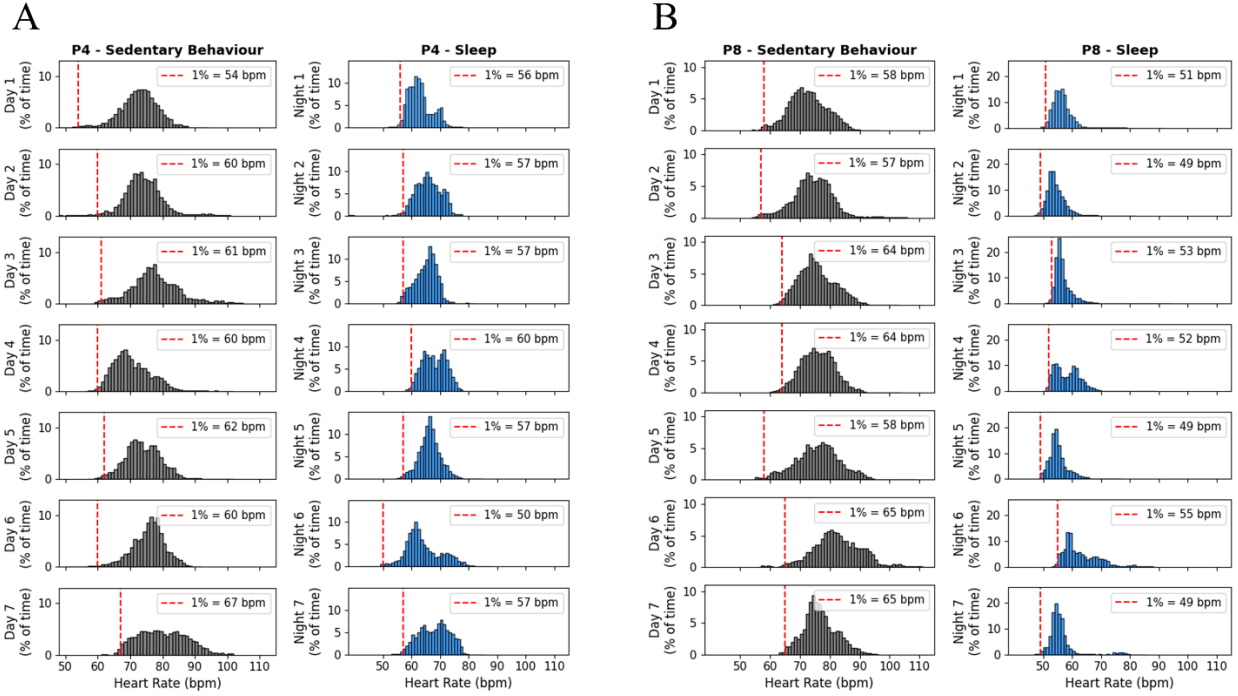


Figure 2. 5. Comparison of daily RHR estimates during sedentary behavior and sleep for two sample participants. Panel A shows data from one participant and panel B shows data from a different participant. Within each panel, the left column displays the distribution of 30-sec rolling HR values during all sedentary behavior per day (gray) and the right column displays the distribution of 30-sec rolling HR values during all sleep per day (blue). The red dotted lines denote daily RHR estimates for sedentary (daily sedentary RHR) and sleep (daily sleep RHR).

In terms of consistency of daily RHR estimates, there was no significant difference in the between-day CV of daily RHR when comparing sedentary and sleep ($6 \pm 3\%$ vs. $5 \pm 3\%$, respectively) ($t = 1.28$, $df = 8$, $p = 0.12$, $d = 0.24$). However, across participants, the between-day range of daily RHR spanned from 4-14 bpm for sedentary and from 3-14 bpm for sleep (Table 2.2). The ICC was 0.75 (95% CI: 0.53-0.92) for sedentary behavior and 0.82 (95% CI: 0.63-0.95) for sleep (both $p < 0.01$). Table 2.2 includes additional descriptive statistics that summarize the between-day consistency in daily RHR per participant during sedentary and sleep.

Table 2. 2. Between-day variability of daily RHR estimates during sedentary behavior and sleep.

Participant	Sedentary Daily RHR (bpm)					Sleep Daily RHR (bpm)				
	Average	SD	Min (Lowest)	Max (Highest)	Between- day range	Average	SD	Min (Lowest)	Max (Highest)	Between- day range
1	52.1	1.6	50	54	4	57.1	2.0	54	60	6
2	65.3	3.8	60	70	10	57.0	3.2	50	59	9
3	52.9	4.3	48	60	12	45.3	2.2	43	49	6
4	60.6	3.8	54	67	13	56.9	3.5	50	61	11
5	54.0	2.4	51	58	7	53.1	1.2	52	55	3
7	48.4	5.6	42	56	14	45.4	5.0	40	54	14
8	61.6	3.7	57	65	8	51.1	2.3	49	55	6
9	59.9	2.0	57	63	6	55.6	1.8	53	59	6
10	66.0	2.6	63	71	8	65.7	3.7	60	72	12
Average	58	3	54	63	9	54	3	50	58	8
SD	6	1	7	6	3	6	1	6	6	4

RHR Resting Heart Rate; BPM beats per minute; SD Standard deviation.

Note: A single participant (#6) was removed from analysis of between-day variability of RHR estimates because only 4 nights of sleep met criteria for inclusion in day-to-day sleep analysis.

Objective 3 – Characterizing the distribution of HR during resting conditions

For each participant, median and HR range values (1st to 99th percentile) derived from 30-sec rolling HR data pooled across the entire collection per resting condition are shown in Figure 2.6.

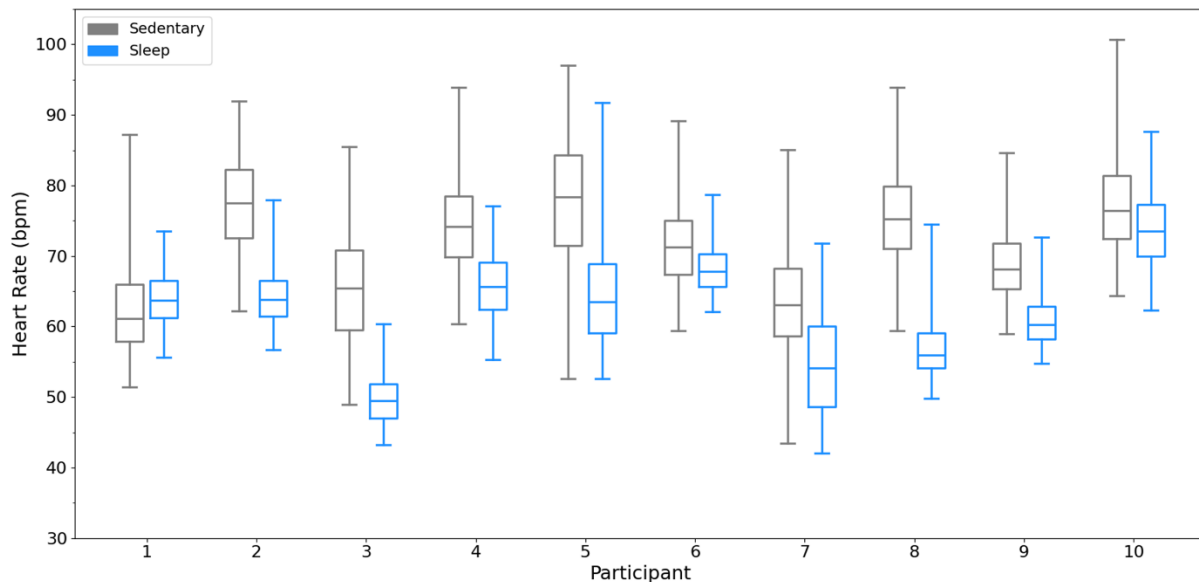


Figure 2. 6. Overall HR median and range values per participant during sedentary (grey) and sleep (blue) when HR data is pooled across the collection period per resting condition. Box and whisker plots include whiskers that correspond to the 1st and 99th percentile (with the difference reflecting the HR range), and a horizontal line within the box that corresponds to the median.

The median HR value during sedentary (overall sedentary median HR) was significantly greater than the median HR value during sleep (overall sleep median HR) (71 ± 6 bpm vs. 62 ± 7 bpm, respectively) ($t = 4.24$, $df = 9$, $p = 0.001$, $d = 1.37$) (Figure 2.7A). The range in HR values during sedentary (overall sedentary HR range) were significantly greater compared to the range in HR values during sleep (overall sleep HR range) (35 ± 6 bpm vs. 23 ± 7 bpm, respectively) ($t = 8.54$, $df = 9$, $p < 0.001$, $d = 1.88$) (Figure 2.7B).

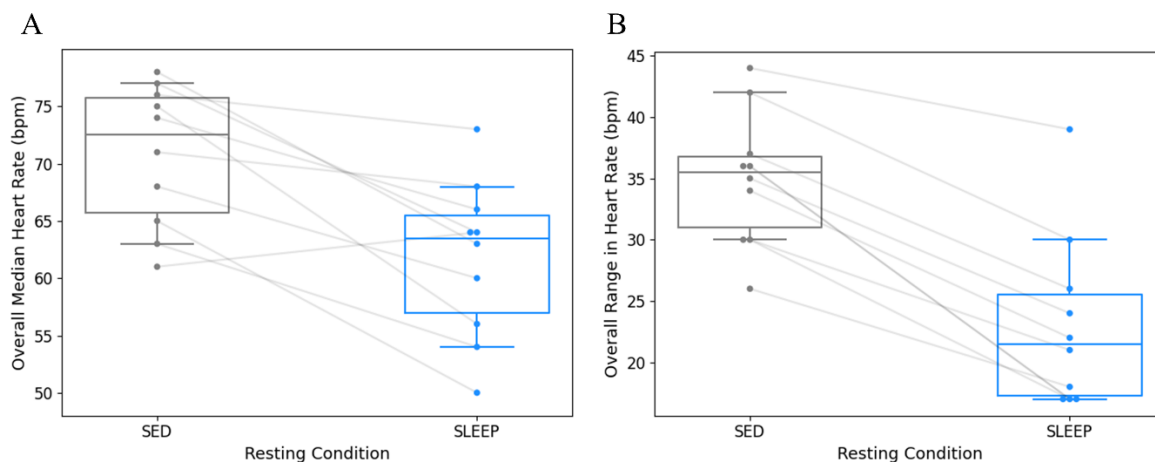


Figure 2. 7. Comparison of HR median (A) and range values (B) between sedentary behavior (gray) and sleep (blue) when HR data is pooled across the collection period per resting condition. Each panel is a box and whisker plot, and the horizontal line within the box corresponds to the median value. Panel A shows that overall sedentary median HR was significantly greater than overall sleep median HR ($p = 0.001$). Panel B shows that overall sedentary HR range was significantly greater than overall sleep HR range ($p < 0.001$). Connector lines are used to denote individual participants ($n = 10$).

DISCUSSION

This study demonstrates a novel approach to measurement of daily life resting HR (RHR) using wearable technology. The approach relies on all available data, rather than a single moment in time, to provide what arguably is a more robust indicator of RHR. Importantly, this approach is dependent on the ability to reference to specific behavioral contexts. Defining RHR based on a 1st percentile statistical criterion and consistent averaging window length (e.g., 30-sec) enabled standardized comparisons to be made across resting conditions (sleep vs. sedentary) and days. Although estimates of RHR based on pooling several days of HR data did not reveal differences between sedentary and sleep, a larger range in

HR values during sedentary compared to sleep supports the use of sensor wear protocols that include both day and nighttime periods, to be able to distinguish between resting conditions. Additionally, when RHR estimates were derived per day, the between-day variability was as large as 14 bpm for both sedentary and sleep, suggesting that measuring RHR based on HR data from a single 24-hour period may be insufficient and could misrepresent an individual's RHR. Instead, adopting an approach to measure RHR from continuous free-living HR data that involves segmenting a multi-day collection period into days, and identifying the day with the lowest RHR estimate, may permit more accurate RHR assessment and enable quantification of HR change from a standardized reference point during extended HR monitoring.

Assessing beat-to-beat HR, which is often not possible when deploying devices with proprietary analytics, revealed that potentially non-physiological HR values occurred across participants when the minimum HR value was used. When defining RHR by applying the 1st percentile statistical criterion to 30-sec rolling windows of HR data that were pooled across the collection for each resting condition, there was no significant difference in the resultant RHR estimates, in contrast to the hypothesis that RHR estimates during sedentary would be higher than during sleep. Similarly, in contrast with the hypothesis, there was no difference in day-to-day variability (i.e., CV) in daily RHR estimates between sedentary and sleep. It is possible that the apparent lack of difference in overall RHR and between-day variability are related to limitations in how sleep is commonly determined in free-living settings (i.e., wrist actigraphy-based methods). Though the algorithm adopted in this study has been shown to produce sleep estimates that have good agreement with polysomnography derived parameters,²⁷ the wrist-based approach is susceptible to classifying periods of wakeful rest with a lack of body movement as sleep. In such instances, it is possible that higher HR values would be measured during those misclassified "sleep" windows than what is physiologically occurring during actual sleep. Alternatively, this lack of difference in overall RHR estimates and between-day variability in daily RHR between sedentary and sleep may be related to adoption of the 1st percentile statistical criterion, which does not provide a direct measure of lowest possible HR. While measuring the minimum HR is potentially of interest, simply choosing the

lowest 30-sec window is not practical given the potential for some erroneous “low” HR values as a function of noise in the free-living ECG signal. One important next step involves comparing these data-driven, daily life RHR estimates during sleep and sedentary behavior to a well-controlled clinical measurement of resting HR to determine the magnitude and direction of potential differences. Additionally, application of this daily life RHR criterion in a larger cohort of individuals, including those who live with complex health conditions, is ongoing to address the limited diversity of the current study sample and to test if differences in RHR exist between resting conditions across various cohorts.

Beyond assessment of group means, focusing on individual participant between-day variability in daily RHR estimates demonstrated that the absolute difference in RHR between days was as high as 14 bpm for both sedentary and sleep, even in this control cohort. Between-day differences of this magnitude may have impacts on the use of RHR as a risk stratification tool and implications when using RHR to prescribe or classify exercise intensity. For example, epidemiological evidence suggests that an increase in RHR of 10 bpm is meaningful in terms of risk of cardiovascular and all-cause mortality.^{18,19} Therefore, a participant with a high degree of between-day variability could have their “risk” level misclassified if only a single day of continuous HR monitoring is used to estimate RHR. Additionally, in the context of calculating HR reserve as a tool to prescribe exercise intensity, differences in a daily estimate of RHR could change the target HR for an activity in a way that may require an individual to exercise at an intensity that may not be appropriate for their physical capacity or exercise goals. An important next step involves understanding the characteristics of the sedentary and sleep periods that contain the daily resting HR estimates (e.g., bouts of a certain length) and when within these periods the resting HR is measured (e.g., middle or end of a bout). Nonetheless, within-person variability in RHR between days, irrespective of resting condition, suggests that a single 24-hr measurement period may be insufficient for determining free-living RHR. Rather, a multi-day collection is warranted to assess RHR per day and identify the day with the lowest RHR estimate as a more suitable reference point for quantifying HR change and/or assessing links to health outcomes.

A wear paradigm that involves multiple sensors and body locations can improve free-living behavioral classification, which includes improved assessment of the intensity of daily life physical activities by referencing workload-related HR increases to a reliable measurement of resting HR. Within the present study, the inclusion of multiple limb-worn IMUs allowed for periods of ankle-derived walking to be detected and removed from analysis, thus more accurately isolating periods of sedentary behavior compared to wrist only-derived estimates of activity, which have been shown to be prone to misclassification.³⁴ However, the finding that the within-participant range in HR values was larger during sedentary (mean range of 35 bpm) compared to sleep (mean range of 23 bpm) aligned with the hypothesis that certain variables known to impact HR may be more influential during the waking versus sleeping state. Notably, current classification of sedentary behavior does not distinguish sitting versus lying down, which is important because HR is impacted by body posture, with a reduction in HR from an upright to lying down position.^{13,67} Additionally, other factors that impact HR, such as emotional stress, elevated blood pressure, consumption of substances like caffeine, or use of medications (in two participants), could affect HR,¹⁵ and could have contributed to the increased range in HR values during sedentary compared to sleep. This larger range in HR values during sedentary suggests that if someone is measuring RHR at a single time point, without the capacity to pool the HR values within a given resting condition and anchor the RHR measurement to the low end of the distribution, the resultant “RHR” estimate is more likely to be inflated during sedentary compared to sleep. As such, if using technology that does not permit customized data analyses, focusing on HR data during sleep may be the preferred strategy to avoid inflating the RHR estimate. Ongoing work to integrate posture detection during sedentary behavior will enable a comparison to be made between HR range during sedentary lying postures versus HR range during sleep to re-assess the magnitude of HR differences that can be attributed to resting condition and better elucidate the impacts of external influences on HR during wakeful rest.

One notable observation from the present study is that collecting a high volume of HR data across several days provides a unique opportunity to profile the distribution of HR during resting conditions

within and between participants. In addition to the focus on 1st percentile values as a statistical criterion for estimating RHR, it is possible to determine differences in HR distributions between resting conditions, days, and participants. Rather than using the term “resting heart rate” to encompass a broad range of potential measurement approaches and possible states, it may be prudent for more specific nomenclature to be adopted that considers both the context and where the measurement falls within the HR distribution. Given the noise that accompanies the collection of biometric signals, including ECG, in truly uncontrolled, free-living settings, it may not be feasible to omit all low, erroneous HR values as a function of poor signal quality or imperfect R peak detection, and therefore, may not be possible to identify the HR value that corresponds to an individual’s lowest possible HR at rest. However, if the 1st percentile criterion adopted in this study could be considered as an approach for measurement of context-specific “minimum” values and referred to as a “minimum sedentary HR” and “minimum sleep HR”, this may permit a daily life HR estimate to be made that is near to the biologically lowest HR and serve as a consistent reference for quantifying HR change. Additionally, the median HR value within a given resting domain could be re-defined as the “typical sleep HR” or “typical sedentary HR”, with the latter potentially being reflective of what is measured in a clinical setting. Beyond nomenclature, the capacity to profile the distribution of HR during resting conditions from continuous HR monitoring may challenge conventional thinking about what is clinically meaningful in terms of risk reduction and prognostic information and allow for further study into whether certain RHR distribution profiles have health implications. For example, future work could look to investigate if poorer health outcomes and increased risk are associated with the free-living “minimum”, “typical”, or range in HR values, or alternatively, associated with a distribution-based/composite HR measure during resting conditions. Additionally, continuous HR monitoring within a multi-sensor setup could be integrated into the pre-post evaluation structure of an intervention such as an exercise training program, to better elucidate if and/or how the distribution of HR values during rest changes, and if there are novel indicators of improved health outcomes.

CONCLUSION

This study highlights the shortcomings of conventional RHR monitoring approaches (i.e., single estimates that lack standardization) and details the development of a novel method for calculating RHR and characterizing the distribution of HR values during resting conditions based on free-living, continuous HR monitoring. The proposed method for measuring RHR is relevant to those using wearable device set ups that include a reliable HR monitoring device that provides access to raw or beat-to-beat data, in combination with the identification of resting behavioral conditions. The potential value of distinguishing between resting conditions and stratifying a multi-day collection into individual days is demonstrated via differences in HR range values between sedentary behavior and sleep, and differences in daily RHR estimates within a person across days. Use of a multi-sensor and device approach and consistent method for measuring daily life RHR may enable improved health risk stratification and quantification of the magnitude of HR change from a known reference point. Further investigation is warranted to 1) apply this approach to characterizing daily life RHR in a larger cohort, including those living with complex health conditions, 2) improve free-living resting behavioral classification via integration of postural information, and 3) confront the nomenclature used for defining RHR and describing the HR profile during daily life resting conditions. This may permit identification of novel resting HR indices that link to health outcomes or change as a function of health status or intervention.

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AUTHOR CONTRIBUTIONS

FEG, KVO, KBB, KW, BFC and WEM contributed to study conception and design, gaining ethics approval, and assisted with participant recruitment. FEG, KVO, and WEM performed and supported data collection. FEG, KVO, KW and WEM developed the data analytics plan, with input from AT and KEM. Data management, curation, and analysis were performed by FEG, with support from KVO, KBB, KW, BFC and WEM. The first draft of the manuscript was written by FEG. All authors critically reviewed and edited the manuscript and have read and approved of the final version.

STATEMENTS AND DECLARATIONS

Ethical Approval: The HANDDS-ONT study was approved by Clinical Trials Ontario (Project ID: 3589) with Sunnybrook Research Institute in Toronto, Ontario as the Board of Record (REB approval: 2021-1517).

Consent to participate: All participants provided verbal informed consent remotely prior to study initiation, and this information was documented by the research coordinator.

Consent for publication: The authors affirm that human research participants provided informed consent for publication of their data.

Declaration of conflicting interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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partially by the Ontario government. The opinions, results, and conclusions are those of the authors and no endorsement by the Ontario Brain Institute is intended or should be inferred. FEG is supported by a Canadian Institutes of Health Research (CIHR) Doctoral Research Award (Funding Reference Number: 181435).

Guarantor: WEM.

Data availability: ONDRI data—including but not limited to the data in this article—will be accessible through the Ontario Brain Institute (<https://braininstitute.ca/>) to qualified researchers. Please see the Ontario Brain Institute website for information on when the data will be released and how to access the data: <https://braininstitute.ca/>.

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CHAPTER 3 (STUDY 2)

Wearable ECG-derived measures of nocturnal heart rate dipping: Exploring an approach for assessing autonomic dysfunction in Parkinson's disease in daily life

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TITLE: Wearable ECG-derived measures of nocturnal heart rate dipping: Exploring an approach for assessing autonomic dysfunction in Parkinson's disease in daily life

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KEYWORDS: Cardiovascular dysautonomia, Wearable technology, Heart rate, Parkinson's disease, Daily life measurement, Sedentary behavior, Sleep

OVERVIEW

Introduction: Autonomic nervous system (ANS) dysfunction is common in Parkinson's disease (PD) and may alter diurnal cardiovascular regulation. The use of wearable devices to continuously measure heart rate (HR), in the context of sedentary behavior and sleep, permits investigation into nocturnal HR dipping in daily life as an index of ANS dysfunction. This study aimed to compare measures of nocturnal HR dipping in daily life between PD and controls, and test if nocturnal HR dipping was related to clinical measurement of ANS dysfunction in PD.

Methods: PD (n=13, mean age(range):66(58-75) years) and control (n=13, 64(51-76) years) participants wore 3 devices continuously for up to 10 days to determine electrocardiography-based beat-to-beat HR during sedentary behavior and sleep. Sedentary behavior and sleep HR outcomes were used to derive measures of nocturnal HR dipping, which were tested for associations with a clinical measure of ANS dysfunction (SCOPA-AUT).

Results: Nocturnal HR dipping was observed but there were no group differences in the median HR difference (9 ± 6 vs 9 ± 6 bpm ($p=0.52$)) or percentage overlap in HR distributions ($46\pm24\%$ vs $46\pm17\%$ ($p=0.49$)), between sedentary behavior and sleep, for control and PD participants, respectively. Significant associations were found between the SCOPA-AUT and nocturnal dipping measured by median HR difference ($r=-0.79$, $p=0.02$) and percentage overlap ($r=0.91$, $p=0.002$).

Conclusion: Continuously collected, beat-to-beat HR during daily life resting conditions may provide insight into ANS dysfunction in PD. Larger studies are necessary to confirm the utility for clinical decision-making and investigate responsivity of nocturnal HR dipping measures to ANS-targeted interventions.

INTRODUCTION

Parkinson's disease (PD) is often characterized by cardinal motor symptoms such as bradykinesia, tremor, rigidity, and postural instability. However, several non-motor symptoms, including autonomic nervous system (ANS) dysfunction, also occur and negatively impact quality of life [1,2]. Cardiovascular (CV) ANS dysfunction (or dysautonomia) is reported to occur in up to 50% of people with PD [2,3], and may be the result of impairments to the parasympathetic and sympathetic nervous systems, resulting in dysregulation of blood pressure (BP) and heart rate (HR) [4,5].

One of the most recognized symptoms of CV dysautonomia in PD is orthostatic hypotension (OH) [4,6], which increases susceptibility to falling or other adverse outcomes [6,7]. However, diagnosing OH traditionally occurs in controlled settings where orthostatic symptoms are provoked, requiring time, expertise, and use of clinical resources. Furthermore, patient reports of daily life orthostatic symptoms (e.g., light-headedness or dizziness with standing) have been shown to dissociate from the clinical measurement of OH in PD [8], which may be due to orthostatic changes occurring beyond the time frame of the clinical measurement or because of interactions with other daily-life stimuli [7]. Thus, there is a need to explore other measures that may reveal underlying CV dysautonomia and align with the manifestation of orthostatic symptoms in daily life as a complement to conventional clinical assessment.

In addition to orthostatic-related changes in ANS activity, circadian patterns of ANS activity, including a tonic decrease in sympathetic and increase in parasympathetic nervous system activity during sleep [9], results in a characteristic decline in BP and HR during sleep compared to wakeful states (i.e., BP/HR “dipping”) [5,7,10]. Some individuals with PD who experience OH have also been shown to experience alterations to their diurnal autonomic CV regulation [6,11], as reflected by diminished nocturnal heart rate variability [9,12,13] and reduced nocturnal BP and HR dipping (i.e., “non-dipping”) [5,10]. These investigations have also largely been conducted within clinical or hospital settings [7,9,13], using approaches that may be cumbersome to the user and disruptive to sleep, including ambulatory blood pressure monitoring (ABPM) [5,7,10]. Some work has also explored circadian HR patterns in PD using

clinic-based electrocardiography (ECG) recordings (e.g., 12-lead ECG, Holter devices) [9,14], but opportunity exists to leverage less cumbersome ambulatory HR monitoring systems.

The advances in wearable technology for ambulatory HR monitoring enable unobtrusive measurement of HR across extended periods in daily life. Adopting an accessible, ambulatory approach may enable a larger proportion of people with PD to be screened, and permit insight to be gained into the impact of daily life factors (e.g., time of day, activity level, etc.) on HR. An important first step for a wearables-based approach to daily life HR monitoring is addressing the measurement of resting HR outcomes. However, monitoring to assess resting HR outcomes during daily life in PD is relatively scarce and has been characterized by methodological heterogeneity across studies, including measurement of varied outcomes across varying time scales, and with limited context in the form of “daytime” or “nighttime” measurements [9,10,12,14]. The application of a standardized method for measuring daily life resting HR outcomes based on including large volumes of ECG-derived HR data in the context of inertial sensor-defined periods of rest provides an opportunity to profile the characteristics of HR during sedentary behavior and sleep [15,16]. Such an approach also provides insight into the daily life circadian HR profile with context and therefore details nocturnal HR dipping by allowing comparison of daily sleep and wakeful rest HR [10]. Subsequently, understanding if and/or how nocturnal HR dipping relates to reported ANS symptoms in PD is necessary to assess the potential relevance of this approach to measure CV dysautonomia. As such, the first objective of this study was to characterize minimum, median, and range in HR during sedentary behavior and sleep among individuals with PD and community-dwelling older adults without a diagnosis of neurodegeneration (“controls”). The second objective was to test differences between individuals with PD and controls in nocturnal HR dipping (difference in HR between sedentary and sleep states), measured as median HRs and as the degree of overlap between HR distributions for each state. It was hypothesized that there would be blunted nocturnal HR dipping in PD compared to controls, as reflected by a smaller median difference and a greater overlap of HR distributions between sedentary and sleep. The third objective was to test whether indices of nocturnal HR dipping in daily life related to clinical measurement of ANS function in PD. It was hypothesized that less

nocturnal HR dipping would be associated with greater ANS symptoms. The identification of novel wearable HR-based measures of ANS function has the potential to improve characterization of ANS dysfunction in PD, as well as the responsiveness of ANS activity to interventions (e.g., medication), which may facilitate improvements in treatment and management.

METHODS

Study Design

This study includes data from a subset of participants enrolled in the Health in Aging, Neurodegenerative Diseases and Dementias in Ontario (HANDDS-ONT) study, a prospective observational study conducted as part of the Ontario Neurodegenerative Disease Research Initiative (ONDRI) from August 2021 to April 2023 [17]. The HANDDS-ONT study included adults (≥ 18 years of age) who self-reported meeting clinical criteria for possible or probable cerebrovascular disease, Alzheimer's disease or amnesic mild cognitive impairment, frontotemporal dementia, PD, or amyotrophic lateral sclerosis, as well as adults who lived independently in the community with no neurodegenerative or cerebrovascular disease ("control" cohort). The HANDDS-ONT study was designed as a master observational trial that permitted additional "sub-studies" to be conducted. A brief overview of the HANDDS-ONT methods are included here. A more fulsome description is provided in Godkin et al. (2025) [15] and Van Ooteghem et al. (2023) [17].

Participants

Individuals were included in the present study if they were part of the HANDDS-ONT control or PD cohort and had sensor data available for processing (total of 109 control and 62 PD participants). For Objective 1 and 2 analyses, additional criteria were applied to exclude participants on HR-altering medication (i.e., beta blockers) or with comorbidities known to impact HR [12,14], including: a) any cardiovascular conditions, b) diabetes, hypo- and hyper-thyroidism, or chronic obstructive pulmonary disease, c) any psychiatric/psychological conditions, and d) obstructive sleep apnea, restless leg

syndrome, or narcolepsy. Thirteen PD participants were eligible after applying these additional criteria. Of the 26 controls that also met the criteria, 13 were selected based on their age (between ~ 55 and 75 years) to approximate the age range of the PD cohort. For Objective 3 analyses, eight PD participants were included who were enrolled in a HANDDS-ONT sub-study of PD that involved completion of the Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction (SCOPA-AUT) questionnaire [18].

Ethics Statement

The HANDDS-ONT study and the PD sub-study were approved by Clinical Trials Ontario (Project ID: 3589 and 3684, respectively) with Sunnybrook Research Institute in Toronto, Ontario as the Board of Record (REB approval: 2021-1517), and all participants provided verbal (HANDDS-ONT) or written (PD sub-study) informed consent prior to study initiation.

Procedures

Participants attended a baseline visit with a research coordinator, where they were assisted with wearable device instrumentation, before completing a detailed health history. Participants were instructed to wear devices on the chest, and on the dominant (or if impaired, the least affected) wrist and ankle, for up to 10 days continuously, except during bathing or swimming. Participants were encouraged to continue their usual activities while wearing the devices. Once the study team received the returned study kit by mail, data were offloaded from the devices, before being processed and analyzed.

Data Collection

Demographic and Clinical Measures

During the HANDDS-ONT and PD sub-study baseline visits, self-reported health and clinical measurements were collected and stored using REDCap [19] electronic case report forms and hosted on Brain-CODE [20]. Participants recorded demographic information and healthy history, including current and past medical conditions and medications, and completed several clinical questionnaires.

Questionnaires relevant to the current analysis include the Pittsburgh Sleep Quality Index (PSQI) and the Generalized Anxiety Disorder-7 (GAD-7). Only those with PD completed the Schwab and England Activities of Daily Living Scale. Participants in the PD sub-study completed the SCOPA-AUT, with the total score being used as a clinical measure of ANS dysfunction [18]. A trained member of the study team administered the Montreal Cognitive Assessment (MoCA) to all participants.

Wearables Data Collection

Limb-worn IMUs were Axivity 6 devices (AX6, Axivity Ltd), with accelerometer and gyroscope data collected at a sampling frequency of 50 Hz. The chest device was a Bittium Faros 360 ECG and tri-axial accelerometer unit (Bittium, Finland) affixed using a 2-lead electrode adhesive (OmegaSnap), which has been used as a reference standard for HR in free-living conditions [21]. ECG data were sampled at a frequency of 250 Hz, while the chest accelerometer sampled at a frequency of 25 Hz. All devices provided access to raw unprocessed data and underwent a simultaneous manual synchronization procedure to temporally align signals during data processing. Data was processed using a custom analytics pipeline developed by the research team ([22]; <https://github.com/nimbal/nimbalwear>) and additional custom analytics implemented in Python (Version 3.12), as described below.

Data Processing

IMU data

The customized analytics pipeline embeds approaches commonly reported in the literature and was run to remove periods of device non-wear and to detect the following behaviors: stepping from the ankle, sleep from the wrist, and activity intensity estimates from the wrist using threshold-based approaches that differentiate between sedentary, light, and moderate-vigorous intensity [22]. Importantly, periods of sedentary behavior were determined after non-wear, sleep, and concurrent ankle-detected stepping were removed [15,22], reducing the likelihood of misclassification of behavior [23].

ECG data

Raw ECG data underwent automated signal quality screening to restrict analyses to usable data (i.e., a high signal-to-noise ratio that permitted beat-to-beat HR analysis) [24]. R-peaks were detected from the ECG data using the NeuroKit peak detection algorithm (NeuroKit2) and beat-to-beat HR was calculated [25]. The continuous beat-to-beat HR data was resampled using a 1 Hz interpolation, and a low pass filter (0.1 Hz) was applied. The interpolated heartbeat data was then averaged using a rolling average window of 30 seconds, based on previous work by Godkin et al. (2025) [15].

Statistical and Data Analysis

Demographic and clinical data were summarized using descriptive statistics. Shapiro-Wilk tests were run to test for normality of each dataset. Parametric tests were then used because all datasets were normally distributed.

Objective 1: Characterizing HR during sedentary behavior and sleep in daily life

Previously identified criteria for assessing daily life minimum, median, and range in HR per participant during sedentary behavior and sleep were applied [15]. Briefly, all sedentary periods (≥ 5 mins) with usable HR data were identified within full calendar days (midnight-midnight, ≥ 20 hours chest wear and ≥ 10 hours wrist daytime wear), and all sleep periods with usable HR data were identified within full nights (noon-noon, ≥ 11 hours wrist wear between 8PM-8AM). All 30-sec HR values across all included sedentary and sleeping periods were pooled separately, per resting condition. The first percentile (as an estimate of “minimum” HR), median, and range (99th – 1st percentile) in HR were calculated per participant for each resting condition, and two-tailed independent samples t-tests were used to compare PD and control participants for all outcomes.

Objective 2: Examining group differences in potential indices of nocturnal HR dipping in daily life

The nocturnal decline in HR was calculated for control and PD participants using the following formula: $((\text{mean HR sedentary} - \text{mean HR sleep}) / \text{mean HR sedentary}) \times 100$ [5]. Two indices of nocturnal HR dipping were determined: 1) median HR difference between states and 2) percentage overlap of HR

distributions for sedentary and sleep. First, the median HRs during sedentary behavior and sleep were used to calculate a difference estimate per participant (i.e., sedentary median HR – sleep median HR). This approach was modelled off the ABPM-based methods of measuring BP dipping, whereby a single summary value of daytime and nighttime BP recordings are compared to profile circadian changes [5,10]. Second, the percentage overlap was calculated by first conducting a two-sample Kolmogorov-Smirnov test for goodness of fit [26] to compare the sedentary and sleep HR distributions per participant, and then subtracting the test statistic (D) from 1. To test if there was blunted (less) HR dipping in PD compared to control participants, two one-tailed independent samples t-tests were run on 1) the difference between sedentary and sleep median HR values and 2) the percentage overlap in sedentary and sleep HR distributions.

Objective 3: Exploring the relationship between HR dipping in daily life and clinical measurement of ANS function in PD

To explore whether potential indices of nocturnal HR dipping relate to clinical measurement of ANS function, correlations (Pearson) were run between the SCOPA-AUT total score and 1) the difference between sedentary and sleep median HR values and 2) the percent overlap in sedentary and sleep HR distributions.

All statistical analyses were conducted in Pingouin (Python, Version 3.12) and statistical significance was set at $\alpha < 0.05$. Data are presented as mean $\pm$ SD (range) unless otherwise noted.

RESULTS

Participant and Data Volume Characteristics

Table 3.1 summarizes demographic, behavioral, and data volume outcomes for all included participants. Daily wear times averaged 97-99% for the chest, wrist, and ankle devices across all participants demonstrating high compliance to the study protocol. Usable HR data was available during an average of 81-91% of time spent sedentary and 88-98% of time spent sleeping across cohorts.

Table 3. 1. Demographic, Behavioral, and Data Volume Characteristics

	OBJECTIVES 1 and 2		OBJECTIVE 3
	Control (n=13)	PD (n=13)	PD (n=8) ^a
DEMOGRAPHICS			
Age (years)	64 (51-76)	66 (58-75)	68 (59-77)
Sex (n, % female)	8 (62%)	6 (46%)	4 (50%)
Ethnicity (n, %)			
White (European descent)	11 (85%)	10 (77%)	7 (87.5%)
Multiple/Other ^b	2 (15%)	2 (15%)	1 (12.5%)
Prefer not to answer	0	1 (8%)	0 (0%)
Education (n, %)			
Completed post-secondary	11 (85%)	11 (85%)	7 (87.5%)
Some post-secondary	2 (15%)	2 (15%)	0 (0%)
Did not complete high school	0 (0%)	0 (0%)	1 (12.5%)
MoCA (/30)	26 (23-30)	26 (20-29)	25 (22-29)
PSQI (/21)	4 (1-11)	6 (1-15)	7.4 (3-15)
GAD-7 (/21)	2.6 (0-7)	1.2 (0-6)	4.6 (0-14)
Schwab & England (% independence)			
ON state		92 (80-100)	77 (60-100)
OFF state		89 (50-100)	56 (40-80)
Disease Duration (years)		12 (8-18)	7 (0-18)
LEDD (mg/24-hr)		551 (150-1663)	1353 (874-2014)
MDS-UPDRS			
Part IA ^c			2 (1-3)
Part IB			11 (7-18)
Part II			18 (12-24)
Part III			25 (13-37)
Part IV			9 (5-12)
Total ^c			62 (42-80)
Hoehn & Yahr			2.6 (2-3)
SCOPA-AUT (/69)			17 (10-31)
BEHAVIORAL SUMMARY			
Activity			
Mean Sedentary (hours/day)	11 (8-13)	12 (10-14)	13 (8-14)
Mean Light (mins/day)	72 (29-131)	74 (31-170)	68 (28-170) ^d
Mean MVPA (mins/day)	85 (33-190)	50 (13-174)	43 (19-85) ^d
Walking			
Mean Total Steps (steps/day)	11 780 (4644-18032)	10 317 (4993-21618)	8 969 (1979-20068)
Sleep			
Mean Duration (hours/day)	6.4 (5.7-7.8)	6.2 (4.1-7.7)	5.7 (4.3-7.1)
Mean Efficiency (%)	84 (65-92)	78 (60-94)	79 (65-90)
DATA VOLUME CHARACTERISTICS			
Daily Wear Times (%/24-hr)			
Mean Chest Device	98 (97-100)	98 (94-100)	98 (94-99)
Mean Wrist Device	97 (92-100)	98 (95-99)	98 (94-100)
Mean Ankle Device	99 (95-100)	99 (95-100)	99 (95-100)
Usable HR Data (total %)			
Overall	88 (65-98)	78 (53-97)	84 (61-99)
Sedentary	91 (66-99)	81 (51-98)	83 (62-99)
Sleep	98 (93-99)	88 (39-99)	96 (82-99)
Total HR Volumes ^e			
Sedentary Behavior (hours)	54 (29-80)	49 (25-74)	52 (25-81)
Sleep (hours)	46 (23-61)	38 (20-60)	43 (24-62)

Data presented as mean (range) unless otherwise noted. *MoCA* Montreal Cognitive Assessment, *PSQI* Pittsburgh Sleep Quality Index, *GAD-7* Generalized Anxiety Disorder-7, *LEDD* Levodopa Equivalent Daily Dose, *SCOPA-AUT* Scales for Outcomes in Parkinson's disease-Autonomic Dysfunction, *MVPA* Moderate-to-vigorous physical activity

^a Two of the participants in the PD cohort for Objective 3 met the criteria for inclusion in the PD cohort for Objective 1/2 analyses

^b Multiple ethnicities or other ethnicities, including South African, Canadian, Caribbean

^c Missing 4 participants who did not complete Part IA of the MDS-UPDRS

^d Upon review of the data, three participants were removed from the light and MVPA analysis due to evidence of involuntary movement (e.g., tremor) that could have impacted physical activity classification

^e Total number of hours of HR data included per participant during sedentary behavior and sleep

Objective 1 – Characterizing HR during sedentary behavior and sleep in daily life

The minimum, median, and range in HR during sedentary behavior and sleep are shown in Figure 3.1A

for a sample participant. There were no statistically significant differences between control and PD

participants in the minimum, median, or range in HR during sedentary behavior or sleep (all $p \geq 0.07$)

(Fig 3.1B). However, the comparisons between control and PD in sedentary median HR ($t = -1.85$, df

$=24$, $p = 0.08$, $d = 0.73$) and in sleep median HR ($t = -1.91$, $df = 24$, $p = 0.07$, $d = 0.75$) had medium-large

effect sizes, with higher HR values in PD versus control participants.

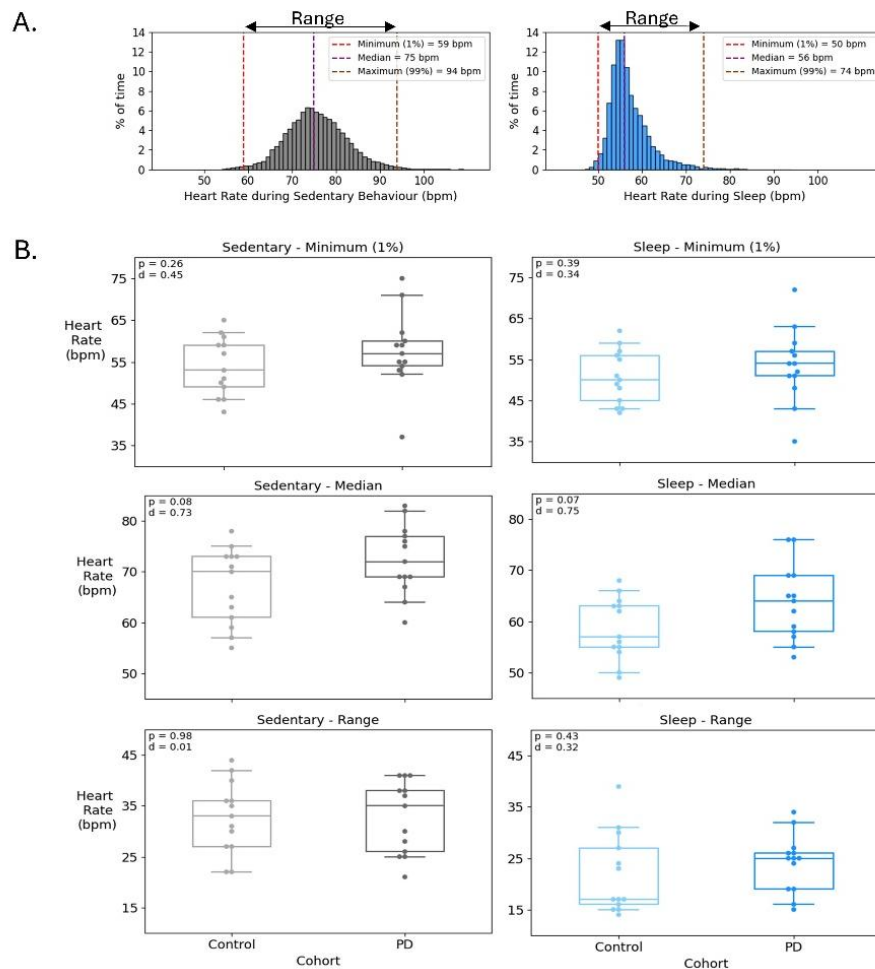


Figure 3. 1. Characterizing HR during sedentary behavior and sleep in control and PD participants. Panel A shows HR distributions during sedentary behavior (grey) and sleep (blue) for a sample control participant, with minimum, median, and range in HR denoted. Panel B is a series of box and whisker plots demonstrating that minimum, median and range in HR during sedentary behavior (left) or sleep (right) were not different between control and PD participants (all $p \geq 0.07$).

Objective 2 – Examining group differences in potential indices of nocturnal HR dipping in daily life

The nocturnal HR decline was $12 \pm 8\%$ (-3 to +25%) in control and $11 \pm 8\%$ (-6 to +25%) in PD participants. Potential measures of nocturnal HR dipping are visualized in Figure 3.2A for two sample participants. There was no statistical difference between control and PD participants in 1) difference between sedentary and sleep median HRs (9 ± 6 bpm vs. 9 ± 6 bpm, respectively) ($t = -0.06$, $df = 24$, $p = 0.52$, $d = 0.02$) or 2) percentage overlap in sedentary and sleep HR distributions ($46 \pm 24\%$ vs. $46 \pm 17\%$, respectively) ($t = -0.02$, $df = 24$, $p = 0.49$, $d = 0.01$) (Fig 3.2B). There was considerable between-participant variability, with the difference between sedentary and sleep median HR values ranging from -3 to +19 bpm in control and -5 to +19 bpm in PD participants, and the percentage overlap ranging from 12-91% in control and 21-70% in PD participants (Fig 3.2B). Unique overlap patterns between sedentary and sleep HR distributions occurred across participants (Fig 3.2C).

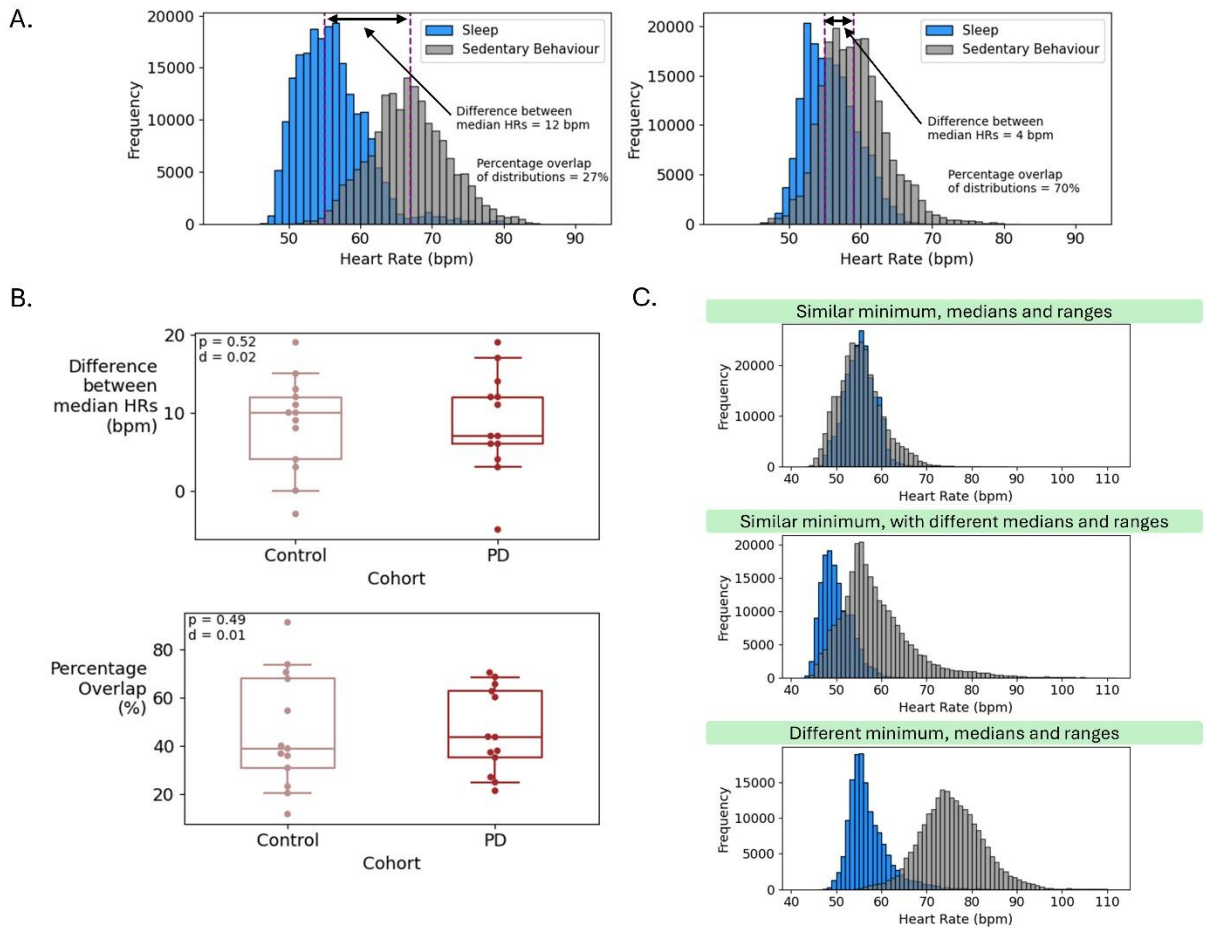


Figure 3. 2. Comparison of measures of nocturnal HR dipping between control and PD participants. Panel A illustrates the difference between sedentary and sleep median HRs and the percentage overlap between sleep and sedentary HR distributions for two sample participants. Panel B shows that the two measures of nocturnal HR dipping were not different between control and PD participants ($p = 0.05$ for both). Panel C profiles the unique patterns of overlap between sleep and sedentary HR distributions across three sample participants.

Objective 3 – Exploring the relationship between HR dipping in daily life and clinical measurement of ANS function in PD

A significant negative association was detected between the sedentary-sleep difference in median HR values and the SCOPA-AUT total score ($r(6) = -0.79$, $p = 0.02$) (Fig 3.3A). A significant positive association was detected between the percentage overlap in sedentary behavior and sleep HR distributions and the SCOPA-AUT total score ($r(6) = 0.91$, $p = 0.002$) (Fig 3.3B).

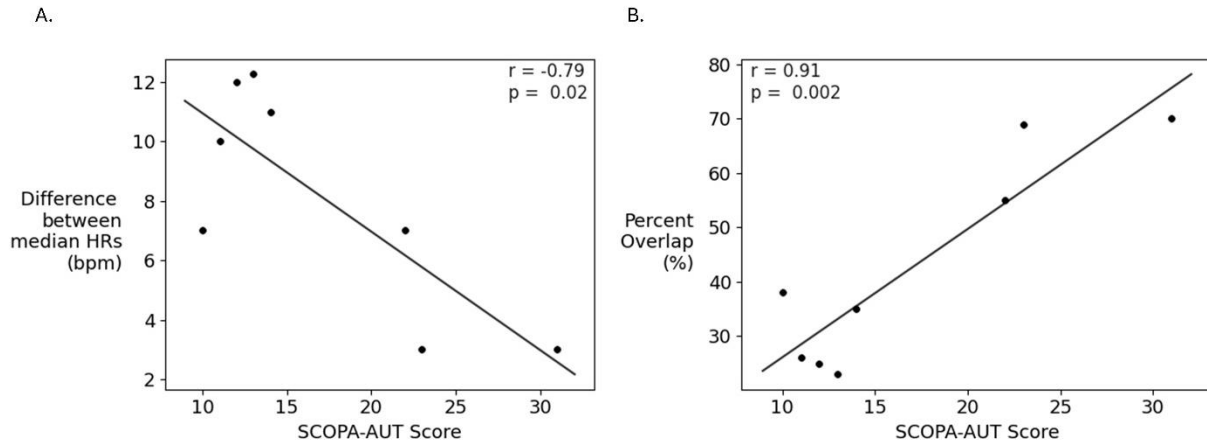


Figure 3. 3. Assessing the relationship between nocturnal HR dipping in daily life and clinical measurement of ANS dysfunction in PD participants. There was a significant association detected between the SCOPA-AUT total score and the A) difference between median HR values ($p = 0.02$) and B) percentage overlap between sleep and sedentary HR distributions ($p = 0.002$).

DISCUSSION

This study investigated a novel approach to understanding nocturnal HR dipping using continuous, ambulatory HR monitoring in daily life. This work represents a potentially important step in advancing the use of continuously collected ECG, interpreted in the context of resting conditions, to reveal health outcomes relevant to PD. Large volumes of continuously collected, context-specific HR revealed that a range of within-person HR occurs in daily life sedentary and sleep states, emphasizing the need to adopt a standardized approach to resting HR measurement in free-living conditions. In terms of HR dipping, the measured nocturnal decline in HR of $\sim 11\%$ in the PD cohort is comparable to a previous ABPM-based measure of $\sim 14\%$ in PD [5]. However, in contrast to the hypothesis that there would be blunted nocturnal HR dipping in PD compared to controls, no difference was observed between PD and control participants. This lack of statistical difference may be linked, in part, to the high between-participant variability across PD and control participants in percentage overlap of sedentary and sleep HR distributions (e.g., a range of 21-70% in PD). Importantly, the study demonstrated that individuals with PD with higher SCOPA-AUT total scores (i.e., those reporting more or greater frequency of autonomic

symptoms) had less nocturnal HR dipping. Previous work has linked BP “non-dipping” to ANS dysfunction in PD [7,10] and profiled differences in the circadian HR pattern between PD and controls but in the absence of linkage to a clinical measure of ANS function [12,13]. To our knowledge, this is the first study that has explored and shown a relationship between a measure of nocturnal HR dipping in daily life and a clinical measure of ANS dysfunction in PD. While findings must be interpreted cautiously, given the small number of participants, this study provides valuable insight into the feasibility and utility of context-based wearable HR monitoring. The discussion that follows addresses the unique value of the proposed approach, factors that might contribute to the lack of difference observed between PD and control cohorts, and opportunities for continuing to advance and apply context-based wearable HR monitoring.

The potential value of incorporating continuous, ambulatory HR monitoring into the clinical toolkit for measuring ANS dysfunction in PD is demonstrated by the relationship detected between nocturnal HR dipping in daily life and the SCOPA-AUT total score. However, establishing a link between ANS dysfunction and HR dipping based on the link to the SCOPA-AUT must consider several factors. To begin, the SCOPA-AUT is a validated scale that has been used to assess ANS function in PD (e.g., [14,27]), but it is a self-report questionnaire that does not provide a threshold for ANS dysfunction or detailed insight into individual symptom severity [28]. Therefore, further work is required to understand if and/or how these nocturnal HR dipping measures relate to other clinical tests of ANS function (e.g., head-up-tilt test for OH) or the severity of patient-reported symptoms of CV dysautonomia that negatively impact quality of life (e.g., lightheadedness, fatigue). It is also necessary to understand if these measures of nocturnal HR dipping are responsive to medications or other interventions targeting the ANS, which may first require assessing the test re-test reliability of HR dipping measures calculated per day to determine the expected within-participant variability. Importantly, the application of continuous, ambulatory HR monitoring in a larger cohort of individuals with PD who have undergone measurement of and have varied levels of ANS function is necessary to test if associations exist across a broader

sample, and thus confirm the utility of measuring daily life HR dipping for objective assessment of ANS dysfunction in PD.

The hypothesis that there would be less nocturnal HR dipping in PD compared to controls was founded in prior literature that measured blunted HR dipping [5,10] or diminished HR-based measures of ANS function during sleep (i.e., heart rate variability) [9,12,13] in individuals with PD. There are multiple possible explanations for the lack of between-group differences observed in measures of nocturnal HR dipping in the present study, including the potential for heterogeneity in study participant characteristics and the limited cohort sizes. Despite the attempt to identify a control cohort that was free of ANS dysfunction, it is possible that some participants across both cohorts were experiencing age-related ANS dysfunction given that ANS activity is reduced with advancing age [29]. It is also possible that PD participants included in the cohort comparison were not experiencing ANS dysfunction, based on a relatively mild disease severity (i.e., mean Schwab & England of 80% in the OFF state) [28]. This potential for heterogeneity in the manifestation of ANS dysfunction within control and PD cohorts may have contributed to the considerable between-participant variability that occurred within each cohort, which has previously been observed when measuring HR outcomes in PD [30]. High levels of inter-individual variation have implications for personalizing treatment protocols, highlighting a need to continue understanding individual participants. The limited cohort sizes (n=13 per group) were the result of the decision to only include PD and control participants that were free of comorbidities and medications known to impact HR, which is a conservative approach that has been adopted when investigating HR as an index of ANS function in PD (e.g., [12,14]), but does limit generalizability of the results. Next steps will involve including cohorts that use HR-altering medications (i.e., beta blockers) and adopting detailed medication monitoring (i.e., dose, timing, frequency) to understand if/how medication impacts circadian HR behavior. Additionally, if clinical measures are included that further characterize ANS dysfunction and symptoms, this may permit a comparison to be made between control participants that are screened to be free of ANS dysfunction and PD participants with confirmed ANS

dysfunction, to determine if cohort differences in HR dipping emerge and to identify potential determinants of between-participant variability.

Unique to this study is that multiple devices were worn on specific body locations to provide behavioral context for interpreting HR data [15,16], which has not otherwise been possible with conventional clinical CV monitoring approaches (e.g., ABPM, Holter). This multi-device approach is critically important to provide context, with the wrist-worn IMU permitting periods of sleep and sedentary behavior to be detected and the ankle IMU improving the classification of sedentary behavior by ensuring that periods of walking were not misclassified based on a lack of wrist movement [23]. Very few previous investigations into HR-based measures of CV dysautonomia in PD have stratified and compared HR outcomes within or between daily life wakeful rest (sedentary behavior) and sleep [9,12]. However, the importance of providing activity/behavioral context to the ECG data cannot be overstated. The application of stringent criteria to define daily life resting behaviors with increased fidelity may also present an opportunity to 1) explore other indices of HR dipping based on resting condition-specific HR distributions that could reveal insight into ANS function, 2) anchor common approaches for quantitatively measuring ANS function, such as heart rate variability or BP and OH measures [6,9,12,14], to well-defined periods of real-world rest, and 3) use these daily life, resting condition-specific HR markers as reference points for characterizing physical activity-dependent changes in HR, including potentially measuring chronotropic incompetence as an indicator of ANS dysfunction in PD. However, there will be a need to continue to work to pare down the number of wearable devices required to provide sufficient behavioral context, which may also support investigations involving extended monitoring (i.e., several weeks) of nocturnal HR profiles within longitudinal collection paradigms. This may permit changes in HR outcomes over time to be tracked in relation to symptom progression or underlying CV dysautonomia manifestation within individual PD participants or those at-risk for or in prodromal stages of PD.

CONCLUSION

The work presented here is an important step toward understanding the potential for unobtrusive and context-based continuous ECG to serve as a clinical monitoring tool in PD. Further application into a larger, well-characterized cohort of individuals with PD and/or symptoms of ANS dysfunction is necessary to confirm the potential utility of the proposed nocturnal HR dipping measures as an objective method for assessing ANS dysfunction. Identifying an accessible, wearable technology-based approach to capture meaningful autonomic changes in daily life has the potential to expand the clinical toolkit for monitoring ANS dysfunction in PD and its responsiveness to interventions.

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CHAPTER 4 (STUDY 3)

Use of a context-based wearable technology approach to characterize the ambulatory HR response to daily life walking in people with and without PD

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease, with a significant increase in incidence and prevalence observed since 1990, and an expected 1.5-fold increase projected by 2035 (Dorsey et al., 2018; Li et al., 2025; Luo et al., 2025). In the absence of neuroprotective therapies, the primary treatment for PD involves minimizing the impact of symptoms via use of dopaminergic-centric medication such as levodopa (Armstrong & Okun, 2020), which may not address medication-unresponsive symptoms (Hely et al., 2005; Sethi, 2008) and may evoke levodopa-induced complications (e.g., dyskinesias) (Aquino & Fox, 2015). As a non-pharmacological alternative, participation in regular aerobic exercise and daily physical activity (PA), including walking specifically, has been shown to have functional and symptom-relief benefits in PD (Cheng & Su, 2020; Gamborg et al., 2022; Johansson et al., 2022; Panassollo, Mawston, et al., 2024; Schenkman et al., 2018; Tsukita et al., 2022; van der Kolk et al., 2019; Xu et al., 2010; Zajac et al., 2021). Guidelines for PA in people with PD include participating in aerobic exercise at a moderate-vigorous intensity on at least 3 days per week (Kim, Lai, et al., 2019; Panassollo, Mawston, et al., 2024). Despite the benefits of an active lifestyle, previous work has shown that people with PD are less active and engage in PA at a lower intensity compared to age-matched healthy controls (Lord et al., 2013; Pradhan & Kelly, 2019; Speelman et al., 2012; van Nimwegen et al., 2011). However, a lack of standardization across studies in the methods used to assess PA makes it difficult to draw robust conclusions about how the overall quantity and intensity of PA may differ in people with PD compared to controls (Wallén et al., 2015). To further characterize the daily life PA profile of people with PD and understand the dose-response relationship between aerobic PA and health outcomes, there is a need to explore a PA measurement approach that 1) considers PA accumulated throughout daily life (including both structured and unstructured physical activity) and 2) confronts the method used to assess the PA intensity.

Given the positive impacts of aerobic PA on PD outcomes and function, and the potential value of specifically targeting daily life walking (Zajac et al., 2021), it is important to be able to reliably measure

the intensity of walking as it occurs in free-living settings, outside of the clinic (Lord et al., 2013). Most studies assessing daily life walking in PD have relied on self-report (Oguh et al., 2014; Tsukita et al., 2022; Zajac et al., 2021) or objective assessment via wearable technology. Specifically, objective measures of walking in PD have largely been derived from wearable accelerometers that use cut points (or thresholds) to determine the absolute intensity of walking, based on differing wear locations (e.g., wrist, thigh) and considering varied outcomes of interest (e.g., total steps, bouts of brisk walking) (Bonde-Jensen et al., 2024; Correno et al., 2022; Lord et al., 2013; Wallén et al., 2015). Despite the potential improvement over self-report, accelerometer-based approaches may be prone to misclassify the activity intensity during walking in PD. This may be particularly relevant in those with PD who have an altered gait pattern that involves higher energy demands (Katzel et al., 2012; Wallén et al., 2015) or altered movement characteristics (e.g., reduced arm swing) (Katzel et al., 2011) that make the use of “one size fits all” movement thresholds, or thresholds developed in non-PD cohorts, less appropriate (Correno et al., 2022; Schrack et al., 2018). The impact of these potential limitations of an accelerometer-only approach is demonstrated in previous work in older adults and those with PD that revealed that up to half of known periods of free-living walking were classified as sedentary behavior in some individuals based on wrist accelerometer-derived estimates of absolute intensity (Weber et al., 2023). Instead of relying on accelerometer-based estimates of walking, including monitoring of the activity-dependent cardiovascular demand via HR may reduce misclassification (Brown et al., 2025) and provide an opportunity to estimate the relative intensity of daily life walking (Garber et al., 2011; MacKay-Lyons et al., 2020).

One common approach for assessing relative intensity involves expressing the HR response to an activity stimulus in proportion to an individual’s heart rate reserve (HRR), which involves calculating the difference between an individual’s maximal and resting heart rate (HR) (Brown et al., 2025; Karvonen et al., 1957; Panassollo, Mawston, et al., 2024). While commercial-grade devices that utilize photoplethysmography (PPG) technology to continuously and unobtrusively measure HR may seem like candidate options for measuring resting HR and monitoring the HR response to daily life walking,

deployment of PPG technology within free-living settings has revealed that it is susceptible to several sources of inaccuracy (e.g., motion artifact, skin tone, etc.) (Bent et al., 2020; Fine et al., 2021; Moscato, Palmerini, et al., 2022; Sana et al., 2020), often lacks transparency about the settings or conditions of free-living HR measurement during PA and rest (Fuller et al., 2020; Quer et al., 2020; Speed et al., 2023), and may lack the capacity to provide the necessary behavioral context when relying on a single wear location (e.g., single wrist watch). Instead, use of chest-worn portable electrocardiography (ECG) represents a potential alternative for ambulatory HR monitoring, given previously measured high levels of single-lead ECG data suitable for HR analysis during daily life conditions (Godkin et al., 2025; Goergen et al., 2023; Solomon et al., 2016; Turakhia et al., 2013). Multi-lead ECG is considered the gold standard for measurement of HR (Alugubelli et al., 2022; Bent et al., 2020; Lindsey et al., 2025); however, single-lead portable ECG devices have lower profiles that are less obtrusive and permit extended collections in real-world settings. Despite these advantages, real-world ambulatory ECG monitoring is still susceptible to factors that may compromise signal quality (e.g., motion artifact) (Rahman et al., 2022), thus warranting further investigation into the quantity of good quality single-lead ECG data that is available during daily life walking periods.

In addition to the choice of HR device, recent studies have highlighted the important advantages of a multi-device and -sensor approach to assess context-dependent HR during daily life behaviors (Godkin et al., 2025; Godkin et al., submitted (Chapter 3)). This approach relies on research-grade devices to extract raw sensor data from multiple sensor types worn across specific body locations, to try to ensure both high quality HR data and accurate classification of walking. Specifically, use of an ankle and wrist-worn inertial measurement unit (IMU) and a chest-worn portable ECG device afford the opportunity for continuous measurement of HR with high temporal fidelity and synchronicity to automatically-detected, IMU-defined physical activities (i.e., walking, non-walking PA) and resting behaviors (i.e., sleep and sedentary behavior) (Beyer et al., 2024; Godkin et al., 2025; Sokas et al., 2023; Weber et al., 2023). An important benefit of an approach that records data from multiple wearable sensors

across several days is the ability to profile the within-person consistency of HR in the context of continuous sampling of daily life behaviors across time. For example, previous work has revealed that there is considerable within-participant variability in HR during daily life resting conditions across a week-long collection period, and therefore, a standard approach to measuring resting HR in daily life requires the use of methodological criteria to anchor the measurement to a “minimum” HR during a specific resting condition (Godkin et al., 2025). Application of this daily life resting HR standard is necessary to be able to reference the amplitude of the HR response and quantify the relative intensity of daily life walking periods. Furthermore, previous work has visualized and explored the distribution profile of HR within and between daily life resting conditions and revealed that the percentage overlap of sleep and sedentary HR distributions may provide insight into relevant health outcomes (e.g., ANS dysfunction) (Godkin et al., submitted (Chapter 3)). This suggests that it may be prudent to also consider the distribution of HR when pooled across daily life walking periods, compared to the HR distributions of other daily life behaviors. Lastly, the ability to fuse HR data with precise walking bout information (e.g., start/end times) may make it possible to 1) stratify walking to assess HR within bouts that are more likely to reflect ADL-type walking (i.e., < 30 seconds) versus medium-long bouts of continuous walking (e.g., ≥ 30 seconds) (Lord et al., 2013), and 2) explore if activity-dependent changes in HR are related to walking characteristics, such as cadence (Tudor-Locke et al., 2021) and duration (Sokas et al., 2023). Understanding the variability in the HR response across free-living walking bouts within an individual, and if there is a predictable stimulus-response relationship (e.g., consistent HR response to a given cadence), has implications for PA prescription and monitoring.

Despite the potential value of combining robust IMU-based measures of daily life behaviors with simultaneous HR measurement across an extended monitoring period (Godkin et al., 2025; Godkin et al., submitted (Chapter 3)), and the previously demonstrated adherence to a multi-sensor and multi-device approach in older adult and NDD populations (Godkin et al., 2022), a lack of work has deployed this approach to measure the relative intensity of daily life walking in adults with and without PD. Thus, the

overarching goal of this study is to utilize a multi-device and -sensor approach to characterize and compare activity-dependent changes in HR during daily life walking, as an index of relative intensity, between individuals living with PD and controls. The specific objectives are as follows:

- 1) To determine the volume of analyzable HR data derived from a single-lead portable ECG system during daily life behaviors, including walking.
- 2) To characterize and compare the HR distribution profile between daily life behaviors sampled continuously over 7 days, including sedentary behavior, physical activity that does not include walking (i.e., “non-walking-related PA”), and walking, in both PD and control participants.
- 3) To quantify and compare between control and PD participants the relative intensity and the within-participant variability of the HR response to medium-long bouts of continuous daily life walking (i.e., ≥ 30 sec) based on assessing a) the mean HR per bout, and b) the peak HR per bout.
- 4) To determine the proportion of medium-long (i.e., ≥ 30 sec) walking bouts that would be classified as moderate intensity based on relative (HR-based) and absolute (cadence-based) intensity thresholds.
- 5) To determine if the HR response to daily life walking (i.e., mean HR response per bout) is related to walking characteristics, including cadence (i.e., mean cadence per bout) and bout duration.
 - a. It is hypothesized that mean cadence per walking bout (and bout duration) will be positively associated with the mean HR per bout for both control and PD participants.

METHODS

Participants

This study includes data from a subset of participants enrolled in the Health in Aging, Neurodegenerative Diseases and Dementias in Ontario (HANDDS-ONT) study, a prospective observational study conducted

as part of the Ontario Neurodegenerative Disease Research Initiative (ONDRI) from August 2021 to April 2023 (Godkin et al., 2025; Van Ooteghem et al., 2023). The HANDDS-ONT study included adults (≥ 18 years of age) who self-reported meeting clinical criteria for possible or probable cerebrovascular disease, Alzheimer’s disease or amnesic mild cognitive impairment, frontotemporal dementia, PD, or amyotrophic lateral sclerosis, as well as adults who lived independently in the community with no neurodegenerative or cerebrovascular disease (“control” cohort). Individuals were considered for inclusion in the present study if they were part of the HANDDS-ONT control or PD cohort and had sensor data available for processing (total of 109 control and 62 PD participants). Additional criteria, as described more fully in Godkin et al., submitted (Chapter 3) and detailed in the participant flow diagram (Figure 4.1), were applied to exclude participants with comorbidities known to impact HR or on HR-altering medication (i.e., beta blockers) that could impact the activity-dependent HR response (Arnao et al., 2020; Mastrocola et al., 1999). The HANDDS-ONT study was approved by Clinical Trials Ontario (Project ID: 3589) with Sunnybrook Research Institute in Toronto, Ontario as the Board of Record (REB approval: 2021-1517), and all participants provided verbal informed consent prior to study initiation.

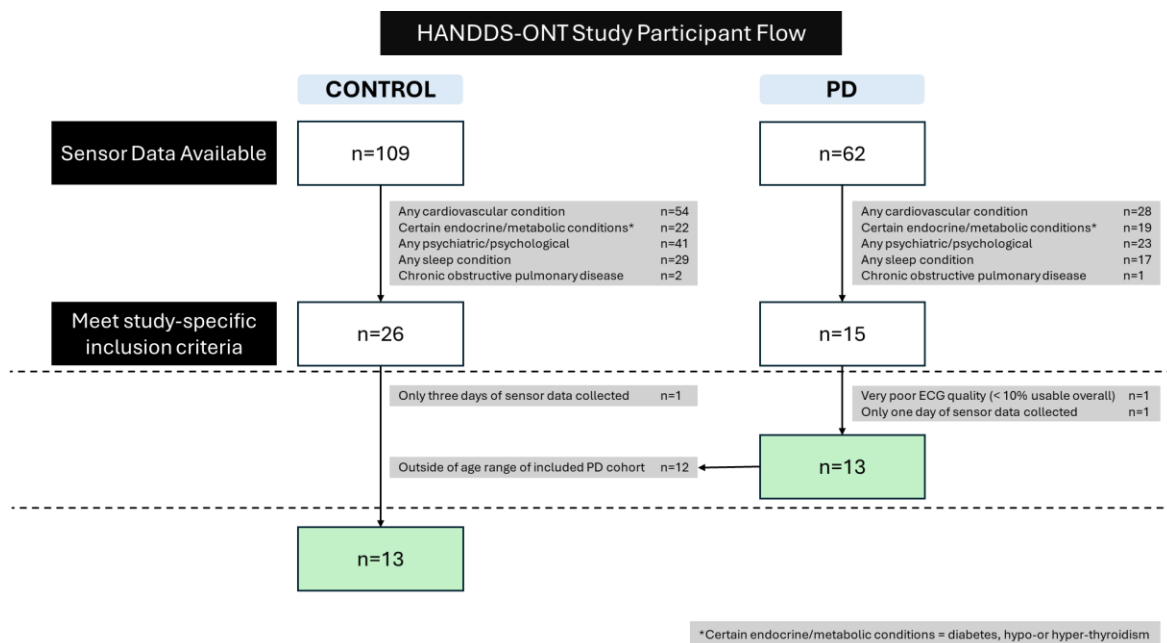


Figure 4. 1. Flow of control and Parkinson’s disease participants in the HANDDS-ONT study. Showing the number of participants excluded from the present work based on the presence of comorbidities known to impact HR. Of the excluded participants, 11 control and 3 PD reported using beta-blockers.

Procedures

Participants attended a baseline visit with a research coordinator, where they were assisted with wearable device instrumentation, before completing a detailed health history. Participants were instructed to wear devices on the chest, and on the dominant (or if impaired, the least affected) wrist and ankle, for up to 10 days continuously, except during bathing or swimming. Participants were encouraged to continue their usual activities while wearing the devices, and were asked to use paper logs to record notable events (e.g., relevant activities, bed/wake times, and device removal). Once the study team received the returned study kit by mail, data were offloaded from the devices, before being processed and analyzed.

Data Collection

Demographic and Clinical Measures

During the baseline visit, self-reported health and clinical measurements were collected and stored using REDCap (Harris et al., 2009, 2019) electronic case report forms and hosted on Brain-CODE (Vaccarino et al., 2018). Participants recorded demographic information and healthy history, including current and past medical conditions and medications, and completed several clinical questionnaires. Only those with PD completed the Schwab and England Activities of Daily Living Scale. A trained member of the study team administered the Montreal Cognitive Assessment (MoCA) to all participants.

Wearables Data Collection

Limb-worn IMUs were Axivity 6 devices (AX6, Axivity Ltd), with accelerometer and gyroscope data collected at a sampling frequency of 50 Hz. AX6 devices were worn on the wrist using a rubber watch strap, and just proximal to either the medial or lateral malleolus, as selected by the participant, using a customized medical-grade wrap (Fabrifoam, PA). The chest device was a Bittium Faros 360 ECG and tri-axial accelerometer unit (Bittium, Finland) affixed using a 2-lead electrode adhesive (OmegaSnap), which has been used as a reference standard for HR in free-living conditions (Bent et al., 2020; Kinnunen et al., 2020). ECG data were sampled at a frequency of 250 Hz, while the chest accelerometer sampled at a

frequency of 25 Hz. All devices provided access to raw unprocessed data and underwent a simultaneous manual synchronization procedure to temporally align signals during data processing (as described in Godkin et al., 2025). Data was processed using a custom analytics pipeline developed by the research team (Beyer et al., 2024; <https://github.com/nimbal/nimbalwear>) and additional custom analytics implemented in Python (Version 3.12), as described below. All pipeline-generated behavioral outputs were reviewed by trained analysts in the context of individual demographic and clinical data, as well as participant-logged sleep and activity (where recorded) (Godkin et al., 2022; Van Ooteghem et al., 2023).

Data Processing

IMU data

Initial processing of the IMU data, including file conversion, resampling, synchronization, and accelerometer calibration, was performed as described in Godkin et al., (2025). The customized analytics pipeline (Beyer et al., 2024) was then run to remove periods of device non-wear (Vert et al., 2022) and to detect the following behaviors: stepping from the ankle (Fraccaro et al., 2014; Greene et al., 2010), sleep from the wrist (van Hees et al., 2015, 2018), and activity intensity estimates from the wrist using threshold-based approaches that differentiate between sedentary, light, and moderate-vigorous intensity (Frayssé et al., 2021; Powell et al., 2017). Periods of sedentary behavior were determined after non-wear, sleep, and concurrent ankle-detected stepping were removed (Godkin et al., 2025), reducing the likelihood of misclassification of behavior (Weber et al., 2023). Periods of PA that occurred separate from walking-related activity (i.e., “non-walking related PA”) were determined by isolating all of the segments classified as light and moderate-vigorous intensity activity by the wrist, and then removing any segments that had concurrent ankle-detected stepping.

Using steps detected by the ankle accelerometer, walking bouts of a minimum duration of 30 seconds were identified (“medium-long” length bouts), and differentiated from bouts less than 30 seconds in duration (“short” length bouts) (Lord et al., 2013). These criteria were selected to try to identify and separate shorter walking bouts that may be likely to reflect engagement in ADL from longer, continuous

bouts of walking (i.e., medium-long length), while considering previous work that has shown that even longer walking bouts (i.e., > 60 or 120 seconds) make up a very small proportion of daily life walking in those with PD (Del Din et al., 2016) and without (Orendurff et al., 2008). Walking bouts required at least 3 steps and a maximum resting period (MRP) of 2 seconds was used, which means that a pause of at least 2 seconds was required to differentiate between two bouts of walking (Barry et al., 2015; Beyer et al., 2024). Once step detection outputs were generated, participant logs were screened for the reporting of cycling, and periods of step detection that overlapped with logged bouts of cycling > 30 minutes were identified to be removed from further analysis. This resulted in the manual removal of periods of detected “steps” for one participant (from the control cohort) who logged several hours of cycling that was misclassified as stepping.

ECG data

As described in Godkin et al., (2025), raw ECG data underwent automated signal quality screening to identify “analyzable” HR data, which refers to ECG data with a high signal-to-noise ratio that permits beat-to-beat HR analysis (Smital et al., 2020). Specifically, only ECG data classified into quality levels 1 (Q1) and 2 (Q2) were included for subsequent analyses, which represent segments that permit full ECG waveform analysis (Q1) and segments that enable R-peak detection (Q2) (Smital et al., 2020). R-peaks were detected from the ECG data using the NeuroKit peak detection algorithm (NeuroKit2) and instantaneous beat-to-beat HR was calculated (Makowski et al., 2021). The continuous beat-to-beat HR data was resampled using a 1 Hz interpolation, and a low pass filter (0.1 Hz) was applied. During sedentary behavior, the interpolated heartbeat data was then averaged using a rolling average window of 30 seconds, based on previous work by Godkin et al., (2025).

Data and Statistical Analysis

Demographic and clinical data were summarized using descriptive statistics. Shapiro-Wilk tests were run to test for normality of each dataset. A corresponding parametric or non-parametric test was then run, as described in more detail below.

Only full calendar days were included if the chest device was worn for at least 20 hours and if the wrist and ankle device were worn for at least 10 hours during waking hours, consistent with studies of physical activity (Bonde-Jensen et al., 2024; Skender et al., 2016; Weber et al., 2023).

Objectives 1 and 2: Determining the volume of analyzable HR data and characterizing the HR distribution profiles of daily life behaviors sampled continuously across the entire collection

All periods of sleep, sedentary behavior (≥ 5 mins), non-walking related PA, and short and medium-long length walking bouts (as defined above) that contained analyzable HR data were identified across full calendar days. All analyzable HR values within a given behavior sampled across the entire collection were then a) totaled to arrive at an estimate of the volume of analyzable HR available per behavioral condition (expressed as hours of analyzable HR data), b) expressed as a percentage of wear time within a given behavioral condition (i.e., percentage of analyzable time) (Objective 1) and c) plotted in a histogram per behavioral condition to visualize the spread and distribution of HR (Objective 2). From these histograms, the minimum (1st percentile), median, maximum (99th percentile) and range in HR per behavioral condition were calculated (Godkin et al., 2025). Descriptive statistics were used to summarize the minimum, maximum and range in HR per behavioral condition. Two-tailed paired samples t-tests were used to test if there were differences between the median HR during medium-long walking and the median HR during a) sedentary behavior, b) non-walking related PA, and c) short length walking, for both PD and control participants. The percentage overlap of HR distributions was also calculated between the HR distribution of medium-long length walking and the HR distribution during a) sedentary behavior, b) non-walking related PA, and c) short length walking bouts using a two-sample Kolmogorov-Smirnov test for goodness of fit (as described in Godkin et al., submitted (Chapter 3)). A Mann-Whitney U test or two-

tailed independent samples t-test was then used (depending on normality) to test for differences between control and PD participants in the percentage overlap of medium-long length walking bouts with a) sedentary behavior, b) non-walking related PA, and c) short length walking bouts.

Objectives 3-5: Characterizing and comparing the relative intensity of the HR response to medium-long length walking bouts and exploring determinants of within-participant variability in the HR response

The proportion of analyzable HR data contained within each medium-long length walking bout was calculated per participant. Next, medium-long length walking bouts that contained nearly complete HR data (i.e., $\geq 90\%$ analyzable HR data) were isolated (and referred to as “included walking bouts”), to move forward with only including bouts suitable for between-bout comparisons and subsequent testing of associations with per bout cadence and durations. For each included walking bout, the mean and peak HR response per bout were calculated, and expressed as both an absolute HR response (bpm) and as a percentage of heart rate reserve (%HRR) to estimate relative intensity. The Karvonen formula (Karvonen et al., 1957) was used to calculate %HRR, which was derived based on the participant’s age-predicted maximum HR (Tanaka et al., 2001) and free-living minimum HR value during sleep (Godkin et al., 2025). An average and estimates of variability, including standard deviation (SD) and coefficient of variation (CV), of the mean and peak HR response across bouts were then calculated per participant. To test for differences between control and PD participants in the average or within-participant variability of the relative intensity of included walking bouts (Objective 3), two-tailed independent samples t-test (for comparing the grand mean of the mean and peak HR response per bout) or Mann-Whitney U tests (for comparing the within-participant SD and CV of the mean and peak HR per bout) were run. A box and whisker plot was also generated, with individual participants on the x axis and relative intensity per bout on the y axis, to better visualize the within-participant variability of the mean HR response to included walking bouts across participants.

To determine what proportion of included walking bouts would be classified as moderate intensity (Objective 4) in alignment with PA guidelines, the magnitude of the mean HR response per bout (when measured as %HRR) was compared to the 40 %HRR moderate intensity threshold (Garber et al., 2011;

Prajapati et al., 2013). All included bouts across all participants were first considered to identify the total number of bouts that exceeded 40 %HRR (overall proportion) and to calculate an average %HRR across all included bouts. Then per participant, the number of bouts that exceeded 40 %HRR were tallied and expressed as a proportion of that participant's total included bouts, prior to being averaged across participants. Additionally, the mean cadence per bout was compared to cadence-based thresholds for moderate intensity for older adults (i.e., > 100 spm) (Tudor-Locke et al., 2021) and individuals living with PD (i.e., > 80 spm) (Jeng et al., 2020) to count the number of bouts classified as moderate intensity based on cadence.

To explore if the within-participant variability in the mean HR response to included walking bouts was related to walking characteristics (Objective 5), participants were identified that had a minimum of 10 included walking bouts. Correlations, either Pearson or Spearman depending on normality, were then run within each participant to test if there was an association across all included walking bouts between mean HR per bout and a) mean cadence per bout (total steps per bout/bout duration) and b) bout duration.

All statistical analyses were conducted in Pingouin (Python, Version 3.12) and statistical significance was set at $\alpha < 0.05$. Data are presented as mean (range) unless otherwise noted.

RESULTS

Participant Characteristics

Thirteen PD participants were eligible to participate, and 13 controls were identified because their age fell in the approximate age range of the PD cohort (between ~ 55 and 75 years), as shown in more detail in the participant flow diagram (Figure 4.1). Of the participants who were excluded because of the presence of certain comorbidities, 11 of the control and 3 of the PD participants also self-reported using beta blockers. Demographic characteristics for the included participants are outlined in Table 4.1.

Table 4. 1. Participant characteristics.

	Control (n=13)	PD (n=13)
Age (years)	64 (51-76)	66 (58-75)
Sex (n, % female)	8 (62%)	6 (46%)
Ethnicity (n, %)		
White (European descent)	11 (85%)	10 (77%)
Multiple/Other ^a	2 (15%)	2 (15%)
Prefer not to answer	0	1 (8%)
Education (n, %)		
Completed post-secondary	11 (85%)	11 (85%)
Some post-secondary	2 (15%)	2 (15%)
Did not complete high school	0 (0%)	0 (0%)
MoCA (/30)	26 (23-30)	26 (20-29)
Schwab & England (% independence)		
ON state		92 (80-100)
OFF state		89 (50-100)
Disease Duration (years)		12 (8-18)
LEDD (mg/24-hr)		551 (150-1663)

Data presented as mean (range) unless otherwise noted. *MoCA* Montreal Cognitive Assessment, *LEDD* Levodopa Equivalent Daily Dose

^a Multiple ethnicities or other ethnicities, including South African, Canadian, Caribbean

Objective 1: Determining the volume of analyzable HR data during walking and profiling walking characteristics

The percentage of analyzable HR data across daily life behaviors, including walking, is presented per participant in Figure 4.2. Overall, the mean percentage of analyzable HR data across all participants was 93% (39-99%) for sleep, 86% (51-99%) for sedentary behavior, 59% (6-97%) for non-walking related activity, and 52% (3-95%) for walking. Ten participants (n=4 control, n=6 PD) had < 50% analyzable HR data during walking and non-walking activity, despite > 50% analyzable HR data during sedentary behavior and sleep, suggesting potential impacts of motion on signal quality. While most participants (n=18) had similar percentages of analyzable data during walking and non-walking related activity (i.e., ≤ 10% difference), the percentage of analyzable HR data was considerably lower during walking (i.e., > 10% lower) than during non-walking related activity for 8 participants. In these participants, further investigation is needed to determine if there are specific behaviors related to whole body motion or walking characteristics that are linked to reduced data quality. Two participants (n=1 control and n=1 PD) who had < 10% analyzable HR data during walking were excluded from all subsequent analyses.

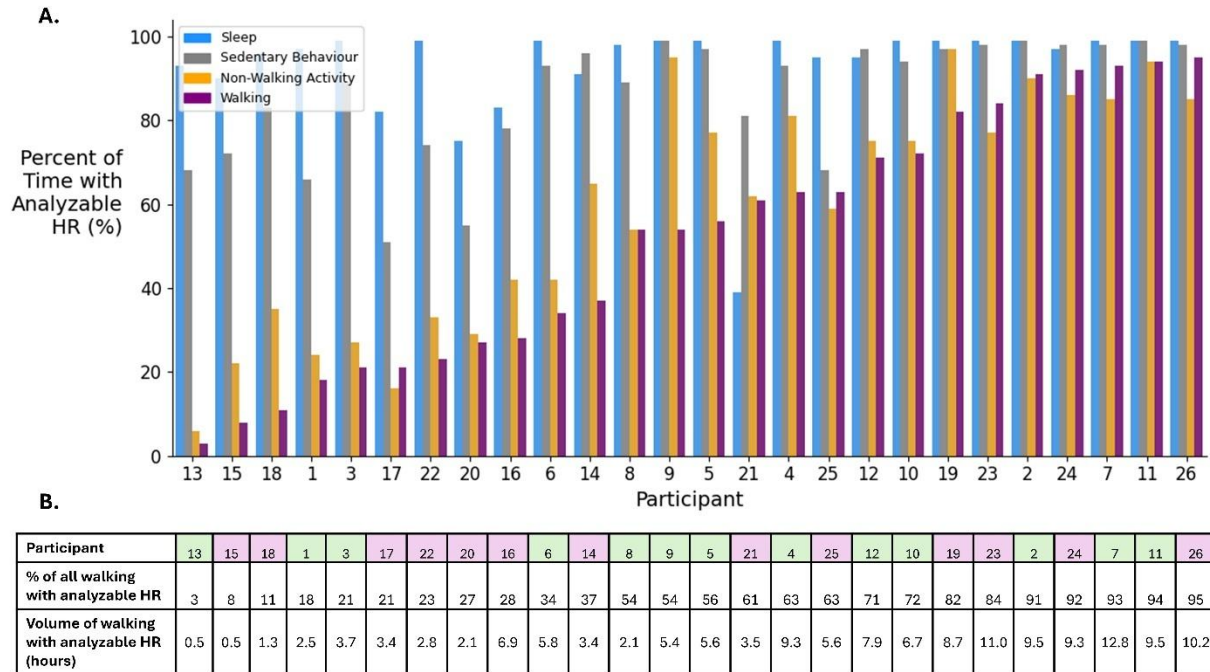


Figure 4. 2. Visualizing the percentage of time with analyzable HR data during sleep, sedentary behavior, non-walking activity, and walking across individual participants. Panel A sorts participants in ascending order from lowest to highest percentage of analyzable HR data during walking. Panel B displays the corresponding total volume of walking with analyzable HR data (expressed as a percentage and in hours) based on the participant order in Panel A, with controls (green) and PD (pink) participants denoted.

The amount of analyzable HR data across daily life behaviors and a summary of walking characteristics are presented in Table 4.2. There were no statistically significant differences between control and PD participants when comparing any of the outcomes related to analyzable HR data or any of the walking characteristics (all $p > 0.05$). Analyzable HR data was available for 4.8 (2-9) and 3.8 (1-9) hours during short (< 30 sec) walking bouts and 1.9 (0.2-8) and 1.8 (0.2-6) hours during medium-long (≥ 30 sec) length walking bouts for control and PD participants, respectively. An average of 44 (2-84)% and 34 (3-80)% of medium-long length walking bouts contained $> 90\%$ analyzable HR data across control and PD participants, respectively.

In terms of volume and characteristics of daily life walking (Table 4.2), control and PD participants took an average of 11,246 (4,644-18,032) and 10,680 (4,993-21,618) steps per day, and completed an average of 116 (30-223) and 147 (25-250) medium-long length walking bouts across the collection period.

Table 4. 2. Volume of analyzable HR data during daily life behaviors and characteristics of daily life walking.

	Control (n=12)	PD (n=12)
Amount of analyzable heart rate (HR)		
Overall percentage of time with analyzable HR data (%)	89.5 (67-98)	78.9 (53-97)
Total volume of analyzable HR data (hours)		
Sedentary Behavior	53.5 (28.7-80.2)	49.5 (24.7-73.9)
Non-walking activity	8.3 (2.3-29.2)	4.7 (0.7-11.2)
Short walking bouts (< 30 sec)	4.8 (1.9-8.6)	3.8 (0.9-8.5)
Medium walking bouts (≥ 30 sec)	1.9 (0.2-7.7)	1.8 (0.2-6.4)
Proportion of all walking bouts with analyzable HR data (%) ^a	75 (28-96)	65 (29-99)
Proportion of medium-long walking bouts (≥ 30 sec) with:		
Any analyzable HR data (%)	70 (22-98)	68 (24-94)
> 90% analyzable HR data (%)	44 (2-84)	34 (3-80)
Daily life walking characteristics		
All Walking		
Total Steps (across days) (steps)	78,689 (27,864-121,122)	77,274 (34,948-172,942)
Total Walking Time (hours)	11.7 (3.8-17.2)	11.7 (5.6-25.2)
Mean Steps per Day (steps)	11,246 (4,644-18,032)	10,680 (4,993-21,618)
Medium-long walking bouts (≥ 30 sec) (n)	116 (30-223)	147 (25-250)
Total Steps (across days) (steps)	27,172 (3,100-54,664)	34,096 (2,624-106,804)
Total Time (hours)	4.2 (0.4-9.1)	5.2 (0.4-15.2)
Mean Cadence per Bout (spm)	106 (97-119)	105 (98-118)
Mean Duration per Bout (min)	2.1 (0.9-3.3)	2.0 (1.1-4.7)
Mean Steps per Bout	234 (97-346)	217 (105-553)
Medium-long walking bouts with > 90% analyzable HR data ^b (n)	45 (2-124)	47 (5-171)
Total Steps (across days) (steps)	8,562 (124-38,452)	6,952 (348-34,694)
Total Time (hours)	1.3 (0.02-6.7)	1.1 (0.06-5.8)
Mean Cadence per Bout (spm)	103 (91-119)	102 (96-116)
Mean Duration per Bout (min)	1.4 (0.6-3.3)	1.2 (0.7-2)
Mean Steps per Bout	147 (62-310)	126 (70-203)

Data presented as mean (range) unless otherwise noted.

^a Walking bouts require at least 3 steps (no other duration criteria applied), with a maximum resting period of 2 seconds in between bouts

^b Referred to as “included” walking bouts when used within analyses associated with objectives 3-5

Objective 2: Characterizing the HR distribution profile of daily life behaviors sampled continuously across the collection in PD and control participants

For both PD and control participants, there was a large within-participant range in HR across each of the daily life behaviors (Table 4.3). For example, the average within-participant range in HR when assessed across all medium-long walking bouts was 57 (32-76) bpm for control participants and 61 (31-88) bpm for PD participants.

Table 4. 3. Characteristics of the HR distribution of daily life behaviors sampled continuously across the collection in control and PD participants.

	Control HR (bpm)			PD HR (bpm)		
	Minimum (1st)	Maximum (99th)	Range	Minimum (1st)	Maximum (99th)	Range
Sedentary Behavior	54 (43-65)	88 (68-98)	34 (22-44)	57 (37-75)	90 (78-100)	33 (21-41)
Activity	61 (52-71)	118 (100-152)	57 (31-89)	55 (38-71)	115 (89-152)	60 (42-84)
Short walking (< 30 sec)	62 (52-75)	115 (100-141)	53 (30-89)	59 (39-72)	114 (90-145)	56 (35-77)
Medium walking (≥ 30 sec)	65 (49-84)	121 (108-135)	57 (32-76)	61 (45-78)	123 (99-158)	61 (31-88)

Data presented as mean (range) calculated across participants.

As seen in Figure 4.3 (A-C), for both PD and control participants, the median HR based on HR pooled across all medium-long walking bouts was significantly greater than the median HR during a) sedentary behavior, b) non-walking related PA, and c) short walking bouts (all $p < 0.005$). Given that the median HR during medium length walking exceeded that of the median HR during short walking bouts, and the desire to focus on walking that excludes ADL-type stepping, all subsequent analyses (Obj 3-5) will focus on medium-long length walking bouts.

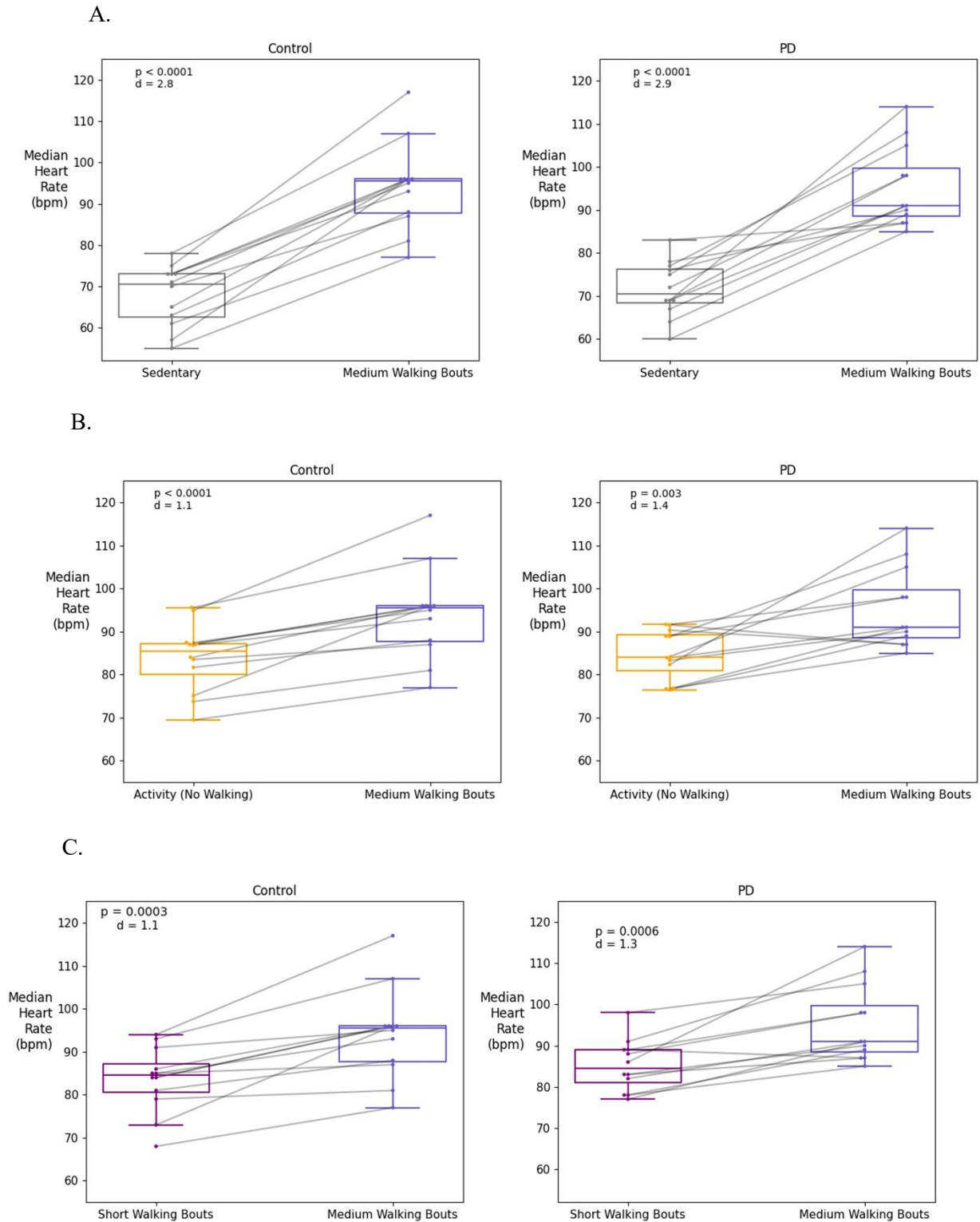
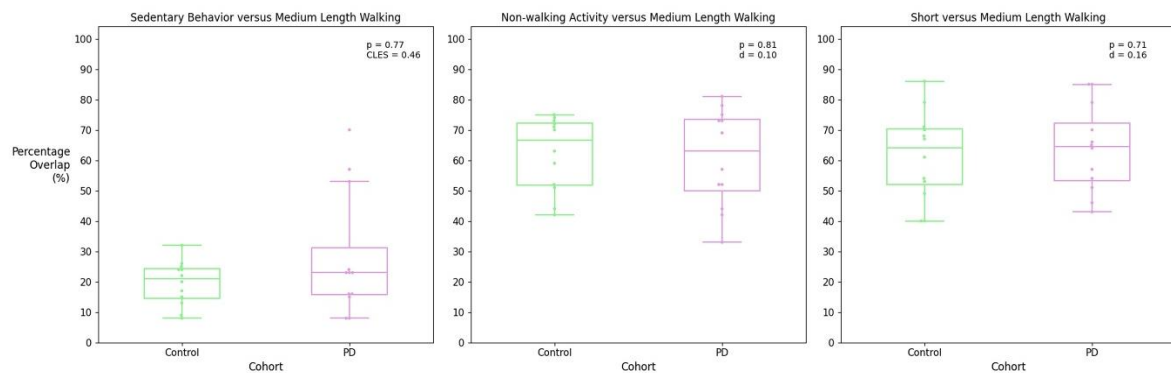


Figure 4. 3. Comparing the median HR during medium walking bouts versus sedentary behavior (A), non-walking related activity (B), and short walking bouts (C) in control (left) and PD (right) participants.

There were no statistically significant differences between control and PD participants, respectively, between the percentage overlaps in the HR distributions of medium-long walking bouts and (i) sedentary behavior (mean overlap (range) [control vs. PD]: 20 (8-32)% vs 28 (8-70)%), (ii) non-walking related PA (62 (42-75)% vs 61 (33-81)%), and (iii) short walking bouts (62 (40-86)% vs 64 (43-85)%) (all $p > 0.05$) (Figure 4.4A). Examples of distribution profiles corresponding to control and PD participants that had “low” or “high” percentage overlaps in their HR distributions between medium-long walking bouts and (i) non-walking related PA (left) or (ii) short length walking bouts (right) are shown in Fig 4.4B.

A.



B.

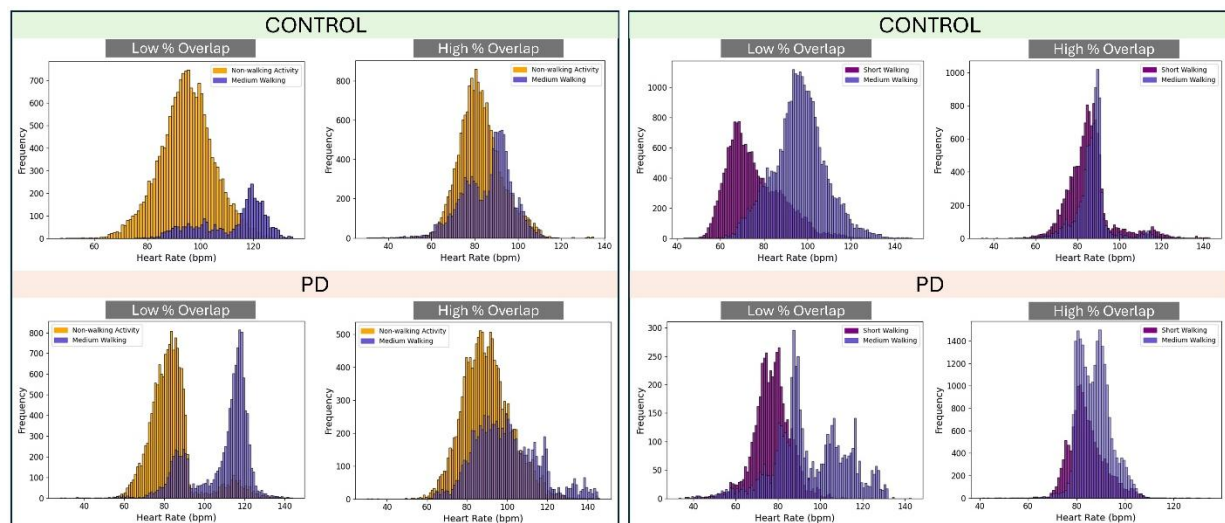


Figure 4. 4. Comparing percentage overlaps in the HR distributions of medium-long walking bouts and sedentary behavior, non-walking related PA, and short walking bouts. Panel A shows that there were no statistically significant differences observed between control and PD participants in any of the percentage overlap categories (all $p > 0.05$). Panel B profiles individual control and PD participants that demonstrated “low” and “high” percentage overlaps in HR distributions between medium-long walking bouts and (i) non-walking related PA (left) or (ii) short length walking bouts (right).

Objective 3: Quantifying and comparing the average and within-participant variability of the HR response to included walking bouts between control and PD participants

There were no statistically significant differences observed between control and PD participants in the grand mean of the mean (Fig 4.5A) or peak (Fig 4.5B) HR response to included walking bouts (when measured in bpm and as %HRR). There was evidence of between-participant variability in both cohorts, with a range in the grand mean HR per bout of 74-106 bpm across control and 81-114 bpm across PD participants. The grand mean of the peak HR per bout for control (41 ± 8 %HRR) and PD (39 ± 9 %HRR) participants was near to the moderate intensity threshold (i.e., 40 %HRR).

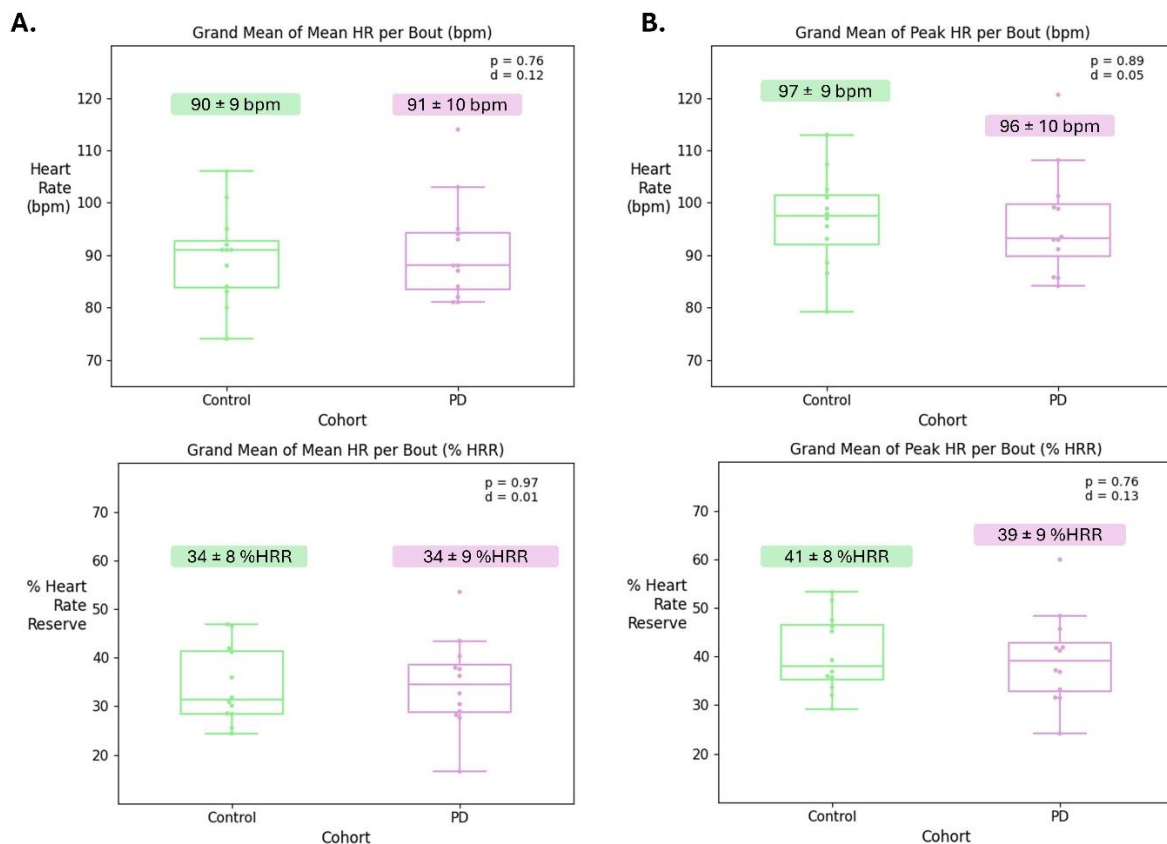


Figure 4. 5. Comparing the relative intensity of included walking bouts between control and PD participants based on the grand mean of the mean HR per bout (A) and peak HR per bout (B). The top row expresses HR in absolute terms (bpm), whereas the bottom row expresses the relative intensity of the HR response (%HRR).

There were no statistically significant differences observed between control and PD participants in the within-participant SD or CV of the mean (Fig 4.6A) or peak (Fig 4.6B) HR per bout (expressed as

%HRR) across included walking bouts. Despite no group-level differences, there was variability observed across participants in both cohorts in the within-participant SD of the (i) mean HR per bout (SD range: 3-15 bpm (control) and 5-26 bpm (PD)) and (ii) peak HR per bout (SD range: 4-16 bpm (control) and 6-26 bpm (PD)) .

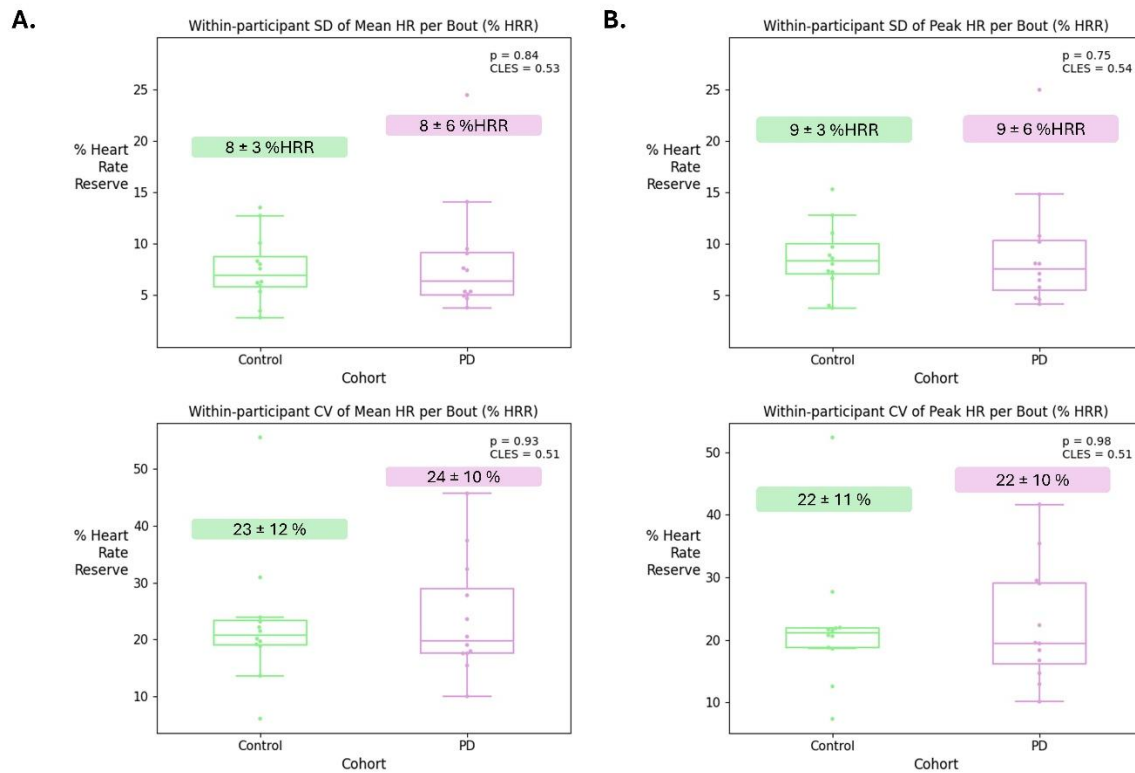


Figure 4. 6. Comparing the within-participant variability in the mean (A) and peak (B) HR response per included walking bout between control and PD participants. Data expressed as %HRR. Within-participant variability in the HR response expressed as standard deviation (SD) (top) and coefficient of variation (CV) (bottom).

The difference between participants in the *degree of* within-participant variability in the mean HR response to included walking bouts, as shown in Figure 4.6A, is visualized per participant within Figure 4.7. Two sample participants are highlighted that have a similar mean relative intensity across walking bouts (mean relative intensity: 47 vs 54 %HRR), but largely different ranges in the mean HR response per bout (range in mean HR response per bout: 26-74 vs 12-95 %HRR).

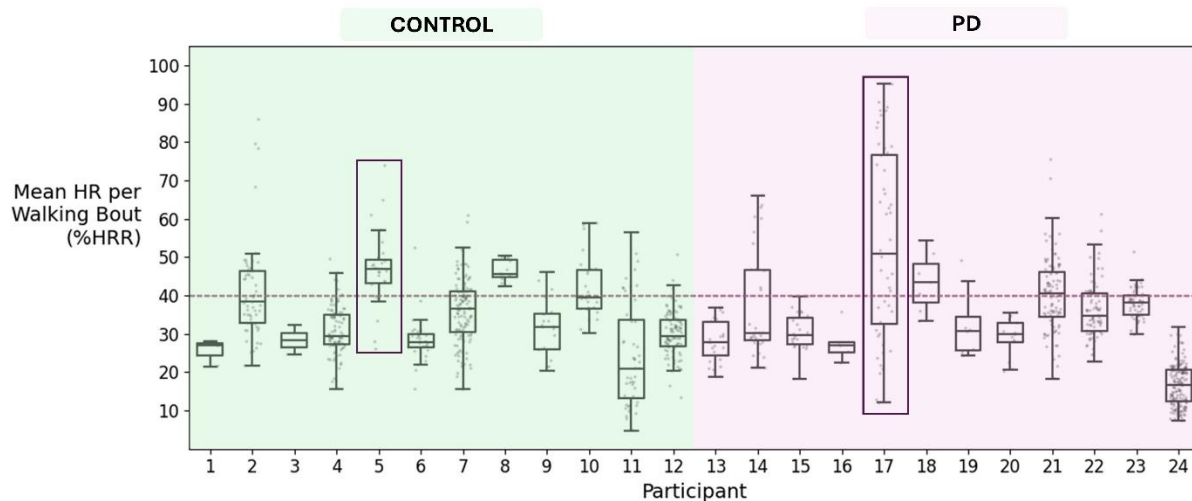


Figure 4. 7. Within-participant variability in the mean HR response per included walking bout visualized across individual control (green) and PD (pink) participants. Mean HR per walking bout expressed as %HRR. Horizontal line indicates the moderate intensity threshold of 40 %HRR. The purple boxes identify two sample participants that have a similar average relative intensity across walking bouts, but largely different ranges in the mean HR response per bout.

Objective 4: Determining the proportion of included bouts that were completed at a moderate intensity

A total of 24% of all included walking bouts (267 out of 1102) had mean HR values > 40 %HRR when pooled across all participants. The mean %HRR per bout across all 1102 bouts was 33 ± 13 %HRR. When assessed per cohort, a total of 24% (130/540) and 24% (137/562) of all included walking bouts had mean HR values > 40 %HRR for control and PD participants, respectively. Using cadence-based thresholds, a total of 57% (310/540) and 99% (556/562) of all included walking bouts were classified as moderate intensity for control and PD participants, respectively. When assessed per participant, the proportion of bouts with mean HR values > 40 %HRR was 29% (range: 0-100%) across control and 25% (range: 0-71%) across PD participants. One control participant had all included bouts with mean HR values > 40 %HRR and seven participants ($n=2$ control, $n=5$ PD) had no included bouts that exceeded this threshold.

Objective 5: Assessing the relationship between the HR response per bout and walking characteristics

Ten control and 9 PD participants had > 10 included walking bouts. The within-participant correlations revealed that there was no consistent positive relationship across all control and PD participants between mean HR per bout and a) mean cadence per bout or b) duration per bout. Specifically, 5 (of 10) control and 4 (of 9) PD participants had statistically significant ($p < 0.05$) weak-moderate positive correlations (r or

$\rho = 0.3-0.6$) between mean HR per bout and mean cadence per bout. Three (of 10) control and 6 (of 9) PD participants had statistically significant ($p < 0.05$) weak-strong positive correlations (r or $\rho = 0.2-0.7$) between mean HR per bout and bout duration. Figure 4.8 overlays the HR and cadence data from the same two sample participants highlighted in Figure 4.7, to illustrate that the mean HR response to walking at similar cadences can differ within a participant and between participants, representing different relative intensity estimates for a given cadence.

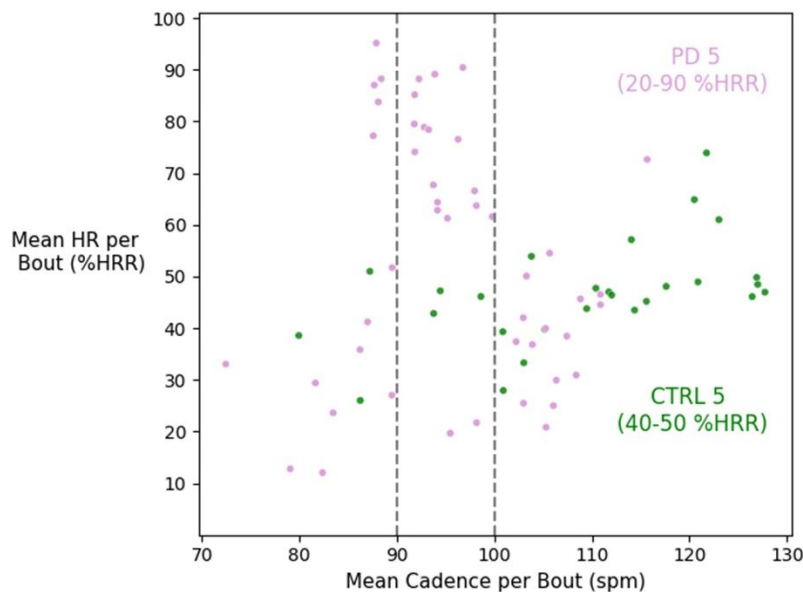


Figure 4. 8. Evidence of similar walking cadences representing differing relative intensities across two sample participants. Relative intensity is expressed as %HRR. The range in %HRR elicited by walking bouts with mean cadences of 90-100 spm are written in text for each of the participants.

DISCUSSION

Participating in daily life PA has been shown to have functional and symptom-relief benefits in PD but requires accurate measurement of PA intensity to appropriately quantify the dose-response relationship. This study suggests that adoption of a robust wearables-based method, which enables free-living HR data to be interpreted in the context of daily life behaviors, may be a promising approach to support deriving relative intensity estimates of daily life walking. Application of this approach in people with and without PD revealed a lack of cohort-level differences but a high degree of between and within-

participant variability in the HR associated with daily life walking behavior, even when restricted to assessment of longer, continuous walking bouts. Furthermore, the variability in the HR response to daily life walking bouts was not shown to be consistently associated with cadence or bout duration across all participants, suggesting that the heterogeneity observed in the HR response to free-living walking may be due to the impact of other person-specific, daily life, or walking-related factors requiring further exploration. Importantly, while many participants were characterized by high volumes of good quality ECG data, a range in the volume of analyzable HR data during daily life walking was observed across participants, suggesting a need to investigate the causes of, or contributors to, walking- or activity-specific degradation of ECG signal quality in some participants. Understanding what factors may relate to the magnitude of the walking-related HR response between and within participants, and confronting determinants of signal quality during daily life PA, will be necessary to continue to advance the use of wearable sensors for remote monitoring of PA intensity in clinical and non-clinical cohorts.

Building upon previous work that has shown a range in HR values per participant across daily life resting conditions (Godkin et al., 2025), the average range in HR across continuously sampled bouts of daily life walking exceeded 50 bpm in control and PD cohorts. Across most participants, there was also a high degree of overlap between the HR distribution profiles of short and medium-long walking bouts. This overlap was somewhat unexpected given the intent to stratify walking by more ADL-type tasks (i.e., < 30 second bouts), which are less likely to yield measurable cardiovascular changes, compared to longer bouts of walking (≥ 30 seconds) that are likely to elicit a higher HR response (del Pozo Cruz et al., 2025). Measuring a high degree of overlap in HR distributions derived from short versus medium-long walking bouts may have been linked to the chosen maximum resting period (MRP) of 2 seconds, which could have resulted in brief pauses in walking (> 2 sec) causing a longer walking period to be segmented into multiple shorter bouts. While an MRP of this length was adopted as a conservative criterion to try to ensure that measured walking periods represented segments of continuous, uninterrupted walking (Barry et al., 2015), previous work assessing daily life walking has been characterized by inconsistency in how

walking bouts are defined (including varied MRP lengths and bout durations) (Del Din et al., 2016). As such, it may be a worthwhile next step to understand how manipulating the MRP (e.g., lengthening the MRP) may change the walking bout classification and associated HR distribution during daily life walking. Visualizing the distribution profile of HR during daily life walking, in the context of other daily life behaviors, also revealed that there was a lack of uniformity across participants in the shape and characteristics of the HR distributions, including some who displayed a bi-modal HR distribution during daily life walking. As such, it may be important to continue to explore approaches that try to describe and understand if characteristics of the daily life walking HR distribution (e.g., data range, volume, shape), when considered in the context of HR distributions of other daily life behaviors (e.g., sedentary behavior), could provide meaningful insight into an individual's daily life profile or pattern of PA.

When constrained to only consider longer, continuous walking periods, no difference was observed between PD and control participants in the grand mean of the mean HR response to, or relative intensity of, medium-long walking bouts (see Fig 4.5). While it has previously been suggested that people with PD may be active at a lower intensity than healthy controls (Pradhan & Kelly, 2019), past conclusions were based on measurements of intensity derived via self-report (van Nimwegen et al., 2011) or accelerometer-based (absolute) intensity thresholds (Correno et al., 2022). This is the first study, to our knowledge, to adopt a multi-device, HR-based method to quantify the magnitude of the HR response and estimate the relative intensity of *daily life* walking in PD. There are several reasons why a lack of difference may have been observed in the average HR response to daily life walking between this cohort of control and PD participants. Firstly, it is possible that this cohort of PD participants had a relatively mild disease severity, based on the reported high levels of functional ability and independence on the Schwab & England ADL Scale, on average, in both the ON and OFF states (i.e., scores averaging ~ 90%) (Bouça-Machado et al., 2022). Although one of the goals of conducting a fully remote data collection protocol was to reduce barriers and enable research participation among individuals who may otherwise be excluded from conventional clinic-based studies, it is possible that those with PD who have complex

needs or moderate-severe dysfunction or disability may not have elected to participate in the HANDDDS-ONT study. A higher level of functioning within this PD cohort may also be reflected by a measured average step count of > 10,000 steps per day, which contrasts previous literature that has shown that (i) those with PD take considerably fewer steps/day (e.g., 30% fewer steps/day) compared to age-matched controls (Lord et al., 2013), or that (ii) only a small proportion of those with PD (i.e., 16%) exceeded a threshold of 7,000 steps per day (Wallén et al., 2015). It is also possible that carefully attending to the adoption of strict inclusion criteria, to try to minimize the impact of confounding conditions or medications on activity-dependent HR responses, resulted in cohorts that may not be reflective of the larger population and cohort sizes that may not have been powered to detect a between-cohort difference (i.e., $n = 13$ per group). Application of this context-dependent ambulatory HR monitoring approach in larger, more heterogeneous cohorts, including those with PD with varied disease severity, is necessary to advance understanding of the existence and/or magnitude of potential differences between PD and controls in the relative intensity of daily life PA, including walking.

Beyond only addressing the lack of between-cohort difference at the group level, it may be of value to consider the person-specific factors that could have contributed to the high degree of *between-participant* variability that was observed in the grand mean of the mean HR response to (or relative intensity of) medium-long walking bouts (see Fig 4.5). Across both cohorts, it is possible that participants with a lower measured relative intensity of daily life walking were those who had higher cardiorespiratory fitness levels, based on the well-accepted phenomena of a lower HR response to a submaximal effort in those with higher fitness (Tulppo et al., 1998). Given that the criterion for daily life walking bout inclusion was based only on duration (i.e., minimum 30 seconds), it is also possible that between-participant differences in walking speed could have contributed to differing HR responses to walking (Waters et al., 1988). There are also several PD-specific reasons as to why HR responses could differ *between individuals*, including the presence of gait dysfunction or motor limitations, which could have resulted in walking requiring an increased energy demand and evoking a higher HR response (Katzel et

al., 2012; Wallén et al., 2015). Conversely, a participant with PD may have been experiencing chronotropic incompetence (CI), which has been reported to occur in 40-50% of people with PD (Panassollo, Mawston, et al., 2024; Speelman et al., 2012). If a participant was experiencing CI, this may have resulted in a blunted HR response to daily life walking, as reflected by a lower relative intensity estimate. Notably, CI also could result in a participant with PD having a lower maximal HR than control counterparts of a similar age (Kanegusuku et al., 2016; Panassollo, Lord, et al., 2024), which could lead to an underestimation of the relative intensity of the activity based on deploying the current age-predicted maximum HR formula. While it is challenging to determine if CI was present based only on the HR response to uncontrolled daily life walking bouts, future inclusion of an in-clinic assessment to measure the HR response to a standardized dose of exercise may permit comparisons to be made between clinical measurement of CI and daily life walking HR responses. Additionally, it is possible that differences between PD participants in the dosing or timing of PD-specific medication intake, as measured by the range in LEDD values across PD participants, may have impacted the walking-related HR response; however, previous in-clinic findings suggest that ON-OFF medication states do not impact the HR response to an acute bout of exercise (DiFrancisco-Donoghue et al., 2009; Panassollo, Mawston, et al., 2024). Further work involving a more robust clinical characterization, which includes measures of fitness and medication timing and the administration of clinical tests or rating scales that measure motor impairments and ANS dysfunction in PD, is necessary to be able to disentangle and isolate the drivers of between-participant variability in the HR response to daily life walking.

Beyond assessing differences between participants in the average HR response summarized across walking bouts, differences were observed between participants in the *within-participant variability* of the mean HR response to medium-long walking bouts (see Fig 4.6). For example, two participants that had similar average estimates of the relative intensity of walking had largely different ranges in the mean HR response across individual bouts (i.e., range of 48 versus 83 %HRR) (see Fig 4.7). This example highlights the potential 1) risk in deriving inferences about an individual's daily life PA intensity level

from a central tendency estimate (e.g., average) or limited snapshot of daily life walking, and 2) value of a multi-device collection that captures per bout responses over an extended monitoring period. These data also reveal the importance of understanding the factors that account for such inter-bout variability, in order to derive outcomes with meaning to support clinical or personal health decision making.

As a first step, exploration into whether the within-participant variability in the mean HR response per walking bout was related to certain walking bout characteristics revealed that approximately half of the participants displayed a positive relationship between mean HR per bout and mean cadence per bout or bout duration. Variability in the HR response to a given cadence was observed within and between participants, resulting in differing relative intensity estimates for a given cadence (see Fig 4.8). These findings suggest that it may not be appropriate to rely on cadence-based measures as a tool for estimating daily life walking intensity in older adults or people with PD. Further evidence of the potential discordance between HR and cadence during daily life walking is highlighted by the fact that there was a considerably lower number of medium-long walking bouts classified as moderate intensity based on the HR- versus cadence-based thresholds for both control (24 vs 57%) and PD (24 vs 99%) cohorts. It is possible that some of this discordance may be the result of adopting “one-size-fits-all” cadence thresholds (Schrack et al., 2018). This could be a specific problem when there is a unique relationship between cadence and energy expenditure during daily life walking that may occur in individuals with movement disorders, such as PD (Jeng et al., 2020). However, it is also possible that the use of age-predicted maximum HR values may have introduced some inaccuracy into the HR-based estimates of relative intensity, particularly if any of the PD participants were experiencing CI, as mentioned previously. A PD-specific alternative for estimating maximal HR was recently proposed (Rosenfeldt et al., 2025) but requires further validation, as application of this equation in the current PD cohort resulted in some participants having HR values measured during daily life walking that exceeded their predicted maximum value. Instead, incorporation of a graded maximal exercise test would allow for direct measurement of an individual’s peak HR (i.e., HR at $\text{VO}_{2\text{peak}}$) and associated HRR, and has been shown to be feasible in

people with PD (Kanegusuku et al., 2016; Panassollo, Lord, et al., 2024; Rosenfeldt et al., 2025), particularly those with mild to moderate disease severity (Katzel et al., 2011). Continuing to confront the relationship between cadence and gait speed during daily life walking, and ensuring that activity-dependent HR measures are anchored to an accurate reference of individual physiological capacity, will be necessary to identify the most suitable approach to monitor daily life PA intensity.

In addition to exploring if walking cadence and bout duration may account for inter-bout variability in HR within a participant, there is also a need to identify and explore other fluctuating or transient real-world factors that may impact the observed HR response to walking bouts in daily life. These factors could include: 1) additional walking bout characteristics such as stride/step length ratio and/or inter-bout step variability, 2) concurrent activities or environmental conditions not currently classified such as carrying external loads, temperature, uneven terrain, and walking location (e.g., indoors vs outdoors), 3) differences in emotional or cognitive state, and 4) pre-bout activity characteristics. Many of these context variables can be captured or inferred from wearable technology. As examples, ongoing work to incorporate GPS can provide information about geospatial context (Beauchamp et al., 2025), analytics of limb trajectory from an IMU can be used to better infer workload changes depending on terrain (e.g., Kowalsky et al., 2021), and a focus on validating the use of speech sensors for assessing voice and speech features in PD (e.g., Dean et al., 2025) could provide insight into concurrent cognitive load. Such work to extend the definition and description of the context to interpret cardiovascular responses during daily life activity using multi-device and -sensor collections remain underway.

While accounting for within-participant variability in the HR response to walking bouts in daily life will be an important next step, these observations also raise the important matter of which data, from all possible bouts of walking within daily collections, should be used to inform clinical or personal health decisions. For example, are all walking bouts required to be included, if they meet specific movement and context conditions? Importantly, answers to these questions will likely be related to the intended use case and goal of collection. For example, if the goal is to determine the total volume and intensity of daily life

PA, it is likely that an extended collection (e.g., week or longer) that captures a high volume of walking bouts is necessary. Conversely, if the intent is to identify a daily life walking bout that may be able to serve as a benchmark (or clinical proxy), perhaps understanding the frequency of naturally occurring walking bouts that may meet specific, clinically relevant criteria (e.g., extended duration, clear arm swing, consistent cadence, nearly complete HR data, etc.) will be most important. Evidence of differences across people in the within-participant variability in the mean HR response to medium length walking bouts also suggests that it might be possible to classify individuals into those with “high” or “low” variability in their responses, to be able to individualize the monitoring paradigm by identifying person-specific collection parameters (e.g., collection duration and/or data volumes) to adequately capture a representative HR response to daily life walking.

Another important consideration when evaluating the potential for HR monitoring to be incorporated into clinical use as a tool for characterizing daily life PA intensity is the quality of the available data. The overall percentage of analyzable time of ~ 90% for control and ~80% for PD participants aligns with previous literature that has revealed amounts of analyzable HR data ranging from 80% (Santala et al., 2021) to > 95% (Goergen et al., 2023; Solomon et al., 2016; Turakhia et al., 2013) of total wear time using single-lead ECG patches or chest straps across multi-day monitoring periods in daily life. However, within these previous investigations, there appears to be a lack of assessment of the volume (or proportion) of analyzable HR data *specific to* periods containing walking, or other daily life physical activities. As such, it is challenging to assess if the seemingly low percentages of analyzable HR data during walking (e.g., < 50% analyzable HR data) experienced by some participants in the present study (Fig 4.2) represent an “expected loss” or if this aligns with what other groups deploying single-lead ECG monitors might have found. Although previous work has not appeared to quantify a total percentage of analyzable HR across repetitive bouts of *daily life* walking, isolated periods of treadmill walking have been shown to result in poorer ECG data quality compared to activities such as cycling, and periods of activity involving movement of the upper body have also been shown to result in increased motion

artifact and signal quality degradation (compared to movement that involves no or minimal engagement of the upper body) (Lindsey et al., 2025). As such, further investigation is required to better profile those in the present study who experienced lower analyzable HR volumes during walking, to understand if there were differences in terms of upper body movement (e.g., arm swing) or walking characteristics (e.g., cadence, duration of bouts, etc.) between included versus rejected ECG data segments. Additionally, the criteria adopted in the present study to define “included” walking bouts, whereby medium-long bouts had to contain $\geq 90\%$ analyzable HR data, resulted in certain participants having considerable attrition in the number of medium-long bouts included in the analysis. Given this attrition, and the potential that some of these longer walking bouts may represent steady state walking, it may also be valuable to explore if and/or how reducing the amount of required analyzable HR data per bout (e.g., only requiring $> 50\%$ analyzable HR data/bout) may change the mean HR estimates per bout and overall volume of included walking bouts.

CONCLUSION

The use of a multi-sensor and multi-device approach, which fuses ECG-derived HR and movement data, holds promise for measuring the intensity of daily life walking. Discrepancies observed in the present study between intensity classifications using HR- versus cadence-based thresholds reinforces the potential importance of adopting a method that expresses the cardiovascular demand of the movement in reference to an individual’s physiological baseline and peak capacity. This may be particularly important in people living with PD because they can experience functional limitations and diverse motor and non-motor symptoms, such as CI, which may impact the energy demand of, and HR response to, a given amount of movement. Future work should look to incorporate a more robust indicator of peak HR and test for cohort-level differences in the relative intensity of daily life walking in larger samples containing more fulsome clinical characterizations (e.g., disease severity, symptom assessments, etc.). To advance the potential clinical utility of this approach, it will also be necessary to further explore the determinants of the between- and within-participant variability in the HR response to walking, as well as of the activity-

dependent degradation in ECG signal quality that was present in some participants. Ultimately, this study suggests that continued refinement and application of context-dependent ambulatory HR monitoring may enable improved monitoring of daily life PA intensity, which has implications for PA prescription and monitoring, and is necessary to continue to advance our understanding of the potentially pleiotropic effects that PA can have in PD and beyond.

CHAPTER 5:

GENERAL DISCUSSION

5.1 Discussion Overview

Ambulatory heart rate (HR) monitoring has been used across research and clinical settings for measuring HR outcomes in daily life and supporting cardiac diagnostics for more than 50 years (Bent et al., 2020; Bouzid et al., 2022; Holter, 1961; Lindsey et al., 2025). While valuable for providing detailed insight into HR rhythm abnormalities and transient HR changes beyond the constraints of a clinic setting, lack of simultaneous measurement of behavioral context represents a critical gap in supporting the interpretation of daily life HR. Despite the more recent advancements in the miniaturization, battery life, convenience, and accessibility of lower profile wearable ambulatory HR monitors, as prominently reflected by the growth in commercial-grade optical sensing devices (Alugubelli et al., 2022; Bayoumy et al., 2021; Soon et al., 2020), interpretation of the HR outcomes derived when deploying these devices in free-living could still be augmented via the provision of additional information about the concurrent behavioral context (e.g., Marino et al., 2024). Concerns about relying on proprietary-based solutions for measuring daily life HR outcomes may also be amplified in cohorts that live with complex health conditions, whereby a lack of transparency about data quality and analysis may make it challenging to assess if the technology is suitable for application to the population of interest (Fuller et al., 2020; Natarajan et al., 2020; Rietz et al., 2024; Speed et al., 2023). Furthermore, if deployed as a single wearable device, within a smartwatch, for example, it is possible that approaches to measurement may be prone to errors when detecting real-world physical activity (e.g., misclassify walking), particularly in those with varied functional abilities (Weber et al., 2023). Instead, an approach that uses multiple sensors and devices worn on specific body locations (Godkin et al., 2022), with access to raw sensor data that can be synchronized across devices and subscribed to customized analytics (Beyer et al., 2024), has the potential to improve the fidelity of free-living behavioral classification by providing robust context for interpreting daily life HR measures. Application of context-based HR outcomes may be particularly relevant to people living with Parkinson's disease, for whom advancing approaches for daily life diurnal HR measurement has the potential to yield insight into ANS dysfunction (Videnovic & Golombek, 2017; Zis et al., 2015), which is an understudied yet problematic phenomenon in PD (Goldstein, 2003;

Gonçalves et al., 2022; Sharabi et al., 2021). Additionally, the diverse symptom profile and heterogeneous movement characteristics that occur in PD may increase the relevance of exploring approaches to monitoring activity intensity that consider the cardiovascular demand of daily life movement (Panassollo, Lord, et al., 2024; Schrack et al., 2018). Despite the potential advantages and possible clinical relevance of adopting context-based ambulatory HR monitoring, a lack of work has deployed multi-sensor and device methods to measure HR across daily life resting and physical activity conditions.

Therefore, the broad aims of this thesis were to 1) advance the development of standard approaches to assess HR from continuously collected data over multiple days and behavioral contexts, and 2) apply these approaches to advance understanding of ANS function and characterization of daily life physical activity profiles among individuals with Parkinson's disease. Through a series of studies, a standardized approach for measuring daily life resting HR that confronts the variability in HR during daily life resting conditions was proposed (Study 1), which laid the foundation for measuring and exploring the relationship between daily life nocturnal HR dipping and ANS dysfunction in PD (Study 2), and for characterizing and quantifying the HR responses and relative intensity of daily life walking in individuals with and without PD (Study 3). The following broad discussion will focus on the study-specific contributions to existing knowledge, as well as review some of the key limitations associated with context-dependent ambulatory HR monitoring, and how current challenges might be addressed via opportunities and recommendations for future work.

5.2 Contributions to Existing Knowledge

The following section summarizes the main findings and research contributions from each study.

Study 1: Proposing a standardized approach for measuring daily life resting HR that confronts the variability in HR during daily life resting conditions

In a cohort of adults who were free of comorbidities known to impact HR, standardized methodology and terminology for describing and measuring HR outcomes during daily life resting conditions (e.g., 'minimum', median, range) were proposed. Criteria were derived based on analysis of

large volumes of high-quality ECG-derived HR data continuously sampled across repeated bouts of sedentary behavior and sleep. When adopting these standards to compare HR outcomes during sleep versus sedentary behavior, no difference in minimum HR values was observed between daily life resting conditions, whereas the median (as a standardized representation of the central tendency) and range in HR values during sedentary behavior were greater than during sleep. Considerable between-day variability in minimum daily HR values was also observed, with the within-participant ranges in minimum HR values as high as 14 bpm for sedentary behavior and sleep. These findings have important implications for recommending wearable technology measurement conditions and optimal collection durations, specifically 1) the need to adopt resting HR measurement approaches that reference the resting behavioral condition (i.e., context-dependent) and criteria used (e.g., minimum, median), and 2) the potential value of performing multi-day collections to avoid deriving RHR estimates from a single day's worth of data. Based on these findings, subsequent thesis studies adopted these daily life resting HR criteria as the foundation for exploring nocturnal HR dipping (Study 2) and when identifying a reference point to be used for quantifying walking-related HR changes (Study 3) in PD and controls. Beyond the direct impact on Studies 2 and 3 of this thesis, this work 1) proposes and adopts a novel approach to characterize the profile and distribution of large volumes of HR data during daily life resting conditions, 2) reveals the potential limitations of conventional, point-in-time ("snapshot") methods of measuring RHR, and 3) serves as a launching point for working towards arriving at a unified, standardized and transparent guideline for RHR measurement in future studies using context-based ambulatory HR monitoring in daily life.

Study 2: Applying resting HR criteria to examine daily life nocturnal HR dipping and explore its association with ANS dysfunction in PD

In a cohort of control and PD participants free of comorbidities known to impact HR, resting HR standards proposed in Study 1 were applied to characterize the differences in resting condition-specific HR outcomes between cohorts. Given the potential clinical relevance of nocturnal HR dipping as an index of ANS dysfunction in PD (Pilleri et al., 2014; Schmidt et al., 2009; Stübner et al., 2013), findings from

Study 1 also informed the pursuit of daily life nocturnal HR dipping indices that: 1) measured median HR differences between sedentary behavior and sleep, and 2) explored the degree of overlap between HR distributions during sedentary behavior and sleep, to try to understand if deriving a measure that considered the spread and/or profile of the HR distribution during daily life resting conditions might meaningfully relate to a relevant health outcome. While no differences were found between PD and controls in resting condition-specific HR outcomes (e.g., minimum sedentary HR, median sleep HR) or daily life measures of nocturnal HR dipping, considerable between-participant variability was observed, which may have been the result of potential heterogeneity in the occurrence of ANS dysfunction within the cohorts. Despite a lack of cohort-level differences, there was a significant association measured between daily life nocturnal HR dipping and the SCOPA-AUT total score in PD. To our knowledge, this was the first study to show a relationship, albeit preliminary, between a clinical measure of ANS dysfunction and a measure of nocturnal HR dipping in daily life in a cohort of PD participants. Measurement of these nocturnal HR dipping indices in a larger PD cohort, accompanied by additional measures of ANS dysfunction via clinically conventional methods, will be necessary to confirm the potential clinical utility of this proposed wearables-based approach. However, the present study may represent an important first step towards identifying novel, accessible, wearable technology-based approaches that leverage context-based HR outcomes to capture meaningful autonomic changes in daily life.

Study 3: Profiling the within-participant HR response to daily life walking in PD, the relationship to walking characteristics, and potential impacts on recommendations for measuring daily life PA

In addition to leveraging the knowledge gained from Study 1 within Study 2 to try to examine if HR profiles during daily life resting conditions could be used as a potential window into ANS dysfunction, it was also important to use the proposed resting HR approach from Study 1 as a reference for quantifying the magnitude of activity-dependent HR changes. Specifically, deriving estimates of the relative intensity of a given activity via use of heart rate reserve (HRR) requires inclusion of a resting HR measurement. In people with PD, for whom diversity in movement characteristics or the presence of ANS

dysfunction may make the use of accelerometer-based absolute intensity estimates less reliable (Katzel et al., 2011; Panassollo, Lord, et al., 2024; Weber et al., 2023), it may be particularly valuable to explore the use of HR-based relative intensity approaches to daily life PA measurement. Accurate measurement of the intensity of daily life PA is necessary to further understand the impact of a particular PA dose on PD symptoms and function. As such, this study set out to characterize and compare the HR response to, and relative intensity of, daily life walking between healthy control and PD participants. Prior to deriving relative intensity estimates, it was necessary to assess the ECG signal quality during daily life walking. Importantly, the negative impact of activity on ECG data quality has been reported in controlled settings (Lindsey et al., 2025) and portable, single-lead ECG systems have assessed ECG data quality overall in daily life (not specific to certain behaviors) (Goergen et al., 2023; Santala et al., 2021; Turakhia et al., 2013); however, there has been a lack of work explicitly examining ECG data quality during PA in daily life. While many participants were characterized by high volumes of good quality ECG data, even during physical activity, there was a wide range in the volume and percentage of analyzable HR data during walking across all participants, suggesting a need to further investigate the factors that impact ECG signal quality in some individuals.

When then measuring the relative intensity of daily life walking, no cohort level differences emerged but there was between- and within-participant variability in the walking-related HR response, even when constrained to longer, continuous walking bouts. Contrary to the hypothesis, walking cadence (and walking bout duration) was not positively associated with the HR response to walking across all participants, suggesting a need to identify and explore other daily life or PD-specific factors that may impact the observed within-participant variability in HR. The discrepancies observed in the present study between HR- and cadence-based intensity classifications also highlights the potential value of adopting a PA measurement approach in PD that accounts for the cardiovascular demand of the movement, including the importance of identifying an accurate reference for both resting and maximal HR. Additionally, observed differences between participants in the within-participant variability of the HR response to

walking may have implications for developing recommendations about the optimal volume of data captured or length of wearable-based collections to ensure that the amount of walking captured aligns with the particular use case. Ultimately, this study suggests that context-dependent ambulatory HR monitoring holds promise as an approach to derive relative intensity estimates of daily life walking, which in turn, may support investigations into the impact of daily life PA on PD outcomes.

5.3 Limitations, Opportunities and Recommendations for Future Work

The following sections address some of the key limitations and opportunities when using context-based ambulatory HR monitoring in daily life, and how some of the current challenges may be addressed or improved upon in future work. These include 1) the potential to continue to advance the fidelity of the behavioral context measured by multiple wearable devices, 2) the opportunity to reference HR data to more robust clinical characteristics and indicators, 3) the opportunity to explore time-varying changes in HR during rest and activity to measure daily life HR outcomes that may reveal ANS function, 4) the limitations of current HR monitoring technology and need to continue to explore new technology and approaches for identifying good quality data, 5) the opportunities to continue to exploit the high within-participant data volumes and limitations of adopting strict inclusion criteria that need to be confronted with future work in larger, more heterogeneous cohorts, and 6) the potential next steps within future work that might be necessary for context-dependent ambulatory HR monitoring to be considered a candidate option for usual or clinical care.

5.3.1 Advancing wearable device-derived behavioral context

As mentioned previously, changes in HR may occur in response to various external factors or internal processes. This includes the ANS-mediated drop in HR during sleep compared to wakeful rest (Mancia, 1993) and increase in HR in response to PA (Coote, 2010), as well as a potential HR increase during wakeful rest as a function of stress (Cannon, 1915; Ulrich-Lai & Herman, 2009). To identify the potential cause of the change in HR or situations of impaired HR responses to tasks or stimuli, particularly in uncontrolled, real-world settings, there is a need for robust detection of the concurrent

behavioral context or resting state. Previous work has shown that it is important to instrument participants at optimal wear locations for detecting certain daily life behaviors, particularly in older adults and people with PD, given that certain single-device wear locations may be susceptible to error in the detection of daily life behaviors (e.g., walking) in these cohorts (Bianchini et al., 2022; Cederberg et al., 2021; Correno et al., 2022; Kim, Hassett, et al., 2019; Packer et al., 2025; Treacy et al., 2017; Weber et al., 2023; Yang & Hsu, 2010). As such, a wearing paradigm that involved multiple devices worn on specific upper- and lower-limb body locations, and thus permitted interpretation of HR in the context of IMU-derived movement data, served as the foundation for the studies in this thesis. While some of the measured behavioral contexts, such as sedentary behavior, did leverage inputs from multiple devices to improve detection, other behaviors, such as sleep and walking, or PD-specific symptoms, may represent candidate targets for continuing to improve detection by integrating data across devices and/or sensor types.

Specific to sedentary behavior, detection was enhanced by removing segments of ankle-detected stepping that were occurring during periods of sedentary behavior defined by the wrist. While this represents an improvement over wrist-only sedentary behavior measurement (Weber et al., 2023), fusion of accelerometer data from multiple synchronized devices (e.g., wrist, ankle, and chest) could also be used to perform full body posture classification and enable more descriptive estimates of sedentary behavior based on body position (e.g., differentiating standing from sitting vs. lying down) (Beyer et al., 2024). Integration of postural information may be particularly important for improving the detection of sedentary behavior in people with PD, for whom wrist-based accelerometer estimates may be susceptible to underestimating sedentary behavior if the manifestation of certain motor symptoms involving isolated wrist/arm movement (e.g., tremor) exceed the sedentary detection thresholds (Kim, Hassett, et al., 2019). If postural integration enabled sedentary behavior to be further stratified into wakeful “sitting” and “lying down” conditions (Tremblay et al., 2017), findings from Chapter 2 (Study 1) could be expanded to generate HR profiles during these conditions and better determine the impact of posture on HR during

daily life wakeful rest. Once posture is controlled for, it may also be possible to better elucidate how HR profiles are impacted by resting state (e.g., sedentary behavior versus sleep) and/or non-motor drivers of HR change (e.g., stress, arousal), both within and between individuals. Improved fidelity of sedentary behavior estimates may also enable determination of the behavioral context surrounding the periods that contain the “minimum” HR during sedentary behavior – such as the duration of the sedentary period, body position, and timing within the period – to inform the value of targeting specific behavioral characteristics when estimating HR during daily life resting conditions.

In terms of sleep, a wrist-based accelerometer approach was used that has been shown to produce sleep estimates that have good agreement with polysomnography-derived parameters (Full et al., 2018; Janssen Daalen et al., 2024; van Hees et al., 2015), instead of relying solely on self-report sleep diaries. Wrist-based actigraphy approaches have been commonly deployed in research as a tool to objectively measure sleep in free-living over the past 30 years; however, they are still susceptible to misclassifying motionless wakeful rest periods as sleep (Boe et al., 2019; de Zambotti et al., 2024), which may be particularly relevant in people with PD who experience decreased sleep quality or nocturnal akinesia (Van de Water et al., 2011; Zampogna et al., 2020). Instead of relying only on accelerometry, it may be possible to take advantage of the high volume of good quality beat-to-beat HR data to improve the detection of sleep (Boe et al., 2019), including calculating heart rate variability (HRV) as a way to estimate sleep stages (Boudreau et al., 2013; de Zambotti et al., 2024; Kerkerling et al., 2022). Previous work has also demonstrated that including data from a skin temperature sensor (on the hand), in addition to HR and accelerometer data, improved the differentiation of sleep versus wake, potentially because distal skin temperature changes mirrored core body temperature changes related to sleep and circadian rhythms (Boe et al., 2019). Given that the limb-worn IMU devices in the present work contain temperature sensors, it may be worthwhile to profile nocturnal skin temperature changes in daily life, alongside accelerometer and HR changes, particularly in those with PD (or at risk of PD) who may have a compromised ability to regulate their nocturnal core body temperature (Raupach et al., 2020; Zhong et al., 2013). If daily life

sleep detection can be improved via integration of other data sources, it may be possible to extend upon the findings from Studies 1 and 2, to re-examine if differences exist within and between control and PD participants in sleeping minimum, median, and range in HR, as well as indices of daily life nocturnal HR dipping. It may also be valuable to consider ankle IMU data during sleeping periods, which could help to characterize the manifestation of sleep disorders such as restless leg syndrome or REM sleep behavior disorder (RBD) in ecologically valid settings (Naismith et al., 2010; Zampogna et al., 2020), including the associated HR response to periodic leg movements (Sicbaldi et al., 2024; Winkelman, 1999).

Moving from the detection of resting behaviors, daily life walking was detected via the ankle-worn device, based on previous work demonstrating improved accuracy in measuring spatiotemporal characteristics (Pacini Panebianco et al., 2018; Storm et al., 2016; Trojaniello et al., 2014) and detecting steps under slower walking conditions (Greene et al., 2010; Treacy et al., 2017) using the ankle compared to other wear locations (e.g., wrist, waist/trunk). The ankle location is additionally advantageous because it can detect lower limb activities such as cycling and whole-body activities such as running (Rhudy & Mahoney, 2018); however, current step-detection methods do not differentiate walking from these other repetitive, rhythmic activities involving the lower limb (Fraccaro et al., 2014; Greene et al., 2010). Within Study 3, manual removal of detected steps that overlapped with periods of self-reported cycling was performed for one participant who logged several hours of cycling that was initially detected as stepping. However, this still may have left some participants with short cycling bouts or segments of running that were misclassified as walking. Moving forward, integration of additional algorithms into the analytical pipeline that automatically identify and feature extract cycling (Mannini et al., 2013) and/or running (Mo & Chow, 2018) based on lower limb IMU data would enable the HR responses specific to periods of daily life walking to be isolated and compared to cycling and running-dependent increases in HR. Given the within- and between-participant variability in the HR response to daily life walking observed in Study 3, it may also be of value to integrate measurement and quantification of arm swing parameters derived from the wrist IMU during walking (Warmerdam, Romijnders, et al., 2020). Measured arm swing could reveal

asymmetries in PD (Warmerdam, Romijnders, et al., 2020), decreases in arm swing amplitude as a function of age (Mirelman et al., 2015) or PD (Katzel et al., 2011), or variable arm swing due to carrying a load or object while walking (Mannini et al., 2013; Weber et al., 2023), and could provide further insight into how arm swing characteristics contribute to the energy demands of walking by examining the associated HR response. Lastly, incorporating an estimate of IMU-derived gait speed/velocity during daily life walking bouts (e.g., Li et al., 2010), instead of relying on cadence, may be particularly relevant in those with PD whose gait could be characterized by small shuffling steps of a higher cadence and smaller stride length than controls (Katzel et al., 2011; Trojaniello et al., 2014). Disentangling walking from other whole-body activity modes involving rhythmic movement of the lower limbs, and including an assessment of arm swing and gait speed, may also permit further exploration into the potential determinants of ECG signal quality degradation during movement.

Beyond measurement of daily life resting and walking conditions, wearing multiple IMUs may also permit HR to be interpreted in the context of additional relevant behaviors and PD-specific motor symptoms (e.g., tremor). Walking was the primary focus of Study 3 because it is the most reported leisure time aerobic PA and a commonly prescribed aerobic exercise within rehabilitation and exercise programs (Dai et al., 2015; Pang et al., 2006), and engaging in daily walking behavior may be viewed as a tool to slow the progression of PD-related disability (Zajac et al., 2021). However, as revealed in Study 3, participants engaged in high volumes of daily life PA that were separate from walking (i.e., “non-walking related PA”), and pooling the non-walking PA bouts within an individual resulted in HR distributions that were distinct or similar to walking-related HR distributions, depending on the participant. Non-walking related PA was determined by isolating the segments classified as light, moderate, and vigorous intensity activity by the wrist (Frayssé et al., 2021; Powell et al., 2017), prior to removing segments that contained concurrent ankle-detected stepping. Next steps could involve distinguishing the PA classification further by assessing wrist-based “light” and “MVPA” segments separately, and comparing wrist-based versus HR-based intensity estimates during these segments, to continue to confront the impact of relying on

wrist-threshold based approaches for intensity classification of daily life PA (Weber et al., 2023). Given that current Canadian 24-hour movement guidelines provide daily and/or weekly volume recommendations specific to sedentary, light and MVPA (Ross et al., 2020), it will be important to continue to advance HR-based PA monitoring methods to ensure that they provide a fulsome picture of the entire daily life movement profile, considering the specific pattern and composition across PA domains.

In addition to profiling PA, wearable IMUs have been used to measure PD-specific motor symptoms, such as tremor (e.g., Salarian et al., 2007), bradykinesia (e.g., Mahadevan et al., 2020), and dyskinesia (e.g., Lopane et al., 2015), most commonly from a single sensor mounted on the trunk or a limb, in short duration data capture in a lab-based or controlled/clinic setting (Maetzler et al., 2013; Packer et al., 2025; Sánchez-Ferro et al., 2016). For example, a single wrist-worn accelerometer was used to monitor and derive clinically meaningful measures of symptom severity for tremor and bradykinesia in individuals with PD during the performance of a series of tasks within a clinic setting (Mahadevan et al., 2020). Assessments beyond the clinic that incorporate multiple IMUs may be important in PD, to minimize the positive (i.e., “Hawthorne effect”) or negative (i.e., stress/anxiety) impact of in-clinic state on performance or symptom manifestation (Morgan et al., 2020; Sica et al., 2021; Warmerdam, Hausdorff, et al., 2020), and to characterize multiple PD-specific features or symptoms that may differentially impact the upper (e.g., tremor) and lower limbs (e.g., gait impairment) as they fluctuate in daily life (Jankovic, 2008). An increasing number of studies are being done in uncontrolled free-living settings to assess the use of wearable technology for PD motor symptom detection (e.g., Del Din et al., 2021; Evers et al., 2020; Knudson et al., 2020; Morgan et al., 2020; Packer et al., 2025; Sica et al., 2021), including work that has used multiple wearable devices to detect motor symptoms (e.g., freezing of gait, tremor, etc.) continuously across several days (e.g., Adams et al., 2021; Fisher, Hammerla, Ploetz, et al., 2016; Mancini et al., 2021), with a recognized need for further testing and continued attention towards validation in daily life (Del Din et al., 2021; Morgan et al., 2020; Sica et al., 2021). Within the present

work, there is the potential to evaluate PD-specific movements more comprehensively by incorporating IMU-based symptom-detection algorithms into the current analytical pipeline (Beyer et al., 2024), and profiling the HR response that is associated with symptom occurrence in daily life. Identifying the feasibility of detecting symptoms in daily life, and the subset of wearable devices necessary to capture key symptoms, may allow for exploration into whether some of the intra- and inter-individual variability in the HR during daily life resting conditions or in response to PA is linked to the manifestation of PD-specific motor symptoms.

5.3.2. Referencing heart rate data to clinical indicators

In addition to the importance of leveraging device-derived behavioral context to interpret daily life HR data, it would be valuable to be able to reference additional clinical measurements or account for the impact of clinical characteristics on HR. One of the strengths of the larger HANDDS-ONT study was that it was a fully remote data collection paradigm and permitted: 1) collection of large volumes of wearables data continuously in ecologically valid settings, compared to point-in-time clinical “snapshots” and 2) exploration into developing and applying quantitative methods for summarizing free-living data in meaningful ways. Despite the potential improved accessibility of this approach, the fully remote nature of the protocol meant that an in-person clinical or laboratory visit did not occur, restricting any characterization of the participants to limited questionnaires or scales that could be completed virtually. Previous work has recognized and suggested that it may not be appropriate to try to validate wearable technology outcomes derived from high-resolution, daily life data against scores from certain clinical assessments or scales due to the inherently different measurement conditions and outcomes (e.g., subjective questionnaire versus objective wearable data, point-in-time assessments versus inclusion of ecological data spanning days/weeks, etc.) (Dorsey et al., 2015; Espay et al., 2016, 2019). Despite this recognition, the utility of technological or wearable endpoints is often still assessed based on comparison to clinical scales or endpoints (Del Din et al., 2021; Goldsack et al., 2020; Mahadevan et al., 2020). Beyond only validation, performing a more fulsome clinical characterization, including the administration

of clinical tests or procedures, could provide complimentary reference points for daily life HR data and enable identification of potential clinical determinants (e.g., medication) of the between and within-participant variability in the HR response to daily life behaviors.

With respect to Study 1, a lack of clinical visit meant that there was no opportunity for HR outcomes measured during sedentary behavior and sleep (e.g., minimum, median) to be compared to a clinical “resting” HR measurement. Given that discrepancies continue to exist with how RHR is measured in-clinic (e.g., average HR during 10-sec supine (Panassollo, Lord, et al., 2024) versus lowest HR during 5-min supine rest (Rosenfeldt et al., 2025)), it may be important to compare the HR outputs from various approaches used to measure RHR clinically to HR distributions during daily life resting conditions. This type of comparison would enable identification of where the in-clinic HR measure(s) fall on the free-living HR distribution, as well as calculation of the magnitude and direction of potential differences between data-driven daily life sedentary and sleep minimum or median HR estimates and clinic-based measurements of RHR. If assessed on a per-participant level, the magnitude of differences exposed between daily life and clinical measures may provide further insight into the impact of in-clinic state on RHR measures (e.g., white coat syndrome). Conducting this type of comparison may also reinforce the importance of addressing RHR nomenclature and standards in a more unified way that is reflective of the specific measurement context and conditions, given the potential impact that adopting varied RHR criteria could have on activity prescription or monitoring and on interpreting the utility of RHR as an indicator of health risk.

In terms of Study 2, one of the goals was to compare daily life nocturnal HR dipping to a clinical measure of ANS dysfunction in PD, given that the measurement of cardiovascular (CV) dysautonomia in PD has conventionally been reliant on the administration of scales or tests done in controlled clinical settings (Goldstein, 2003; Hellman et al., 2015; Zis et al., 2015). With a lack of in-clinic visit included in the study protocol, the only clinical measurement of autonomic dysfunction was the SCOPA-AUT questionnaire (Visser et al., 2004), and this was only available in a sub-set of the larger PD cohort. The

SCOPA-AUT is a validated scale that has been used to assess ANS dysfunction in PD (e.g., Arnao et al., 2020; Mollenhauer et al., 2013); however, it is limited by the fact that it is a self-report questionnaire that does not provide detailed insight into individual symptom severity or a scoring threshold for ANS dysfunction (Stewart et al., 2023), or insight into whether a higher total score reflects increased number or frequency of symptoms. Inclusion of additional clinical measurements specific to the underlying CV dysautonomia and/or the manifestation of associated symptoms, such as testing for cardiac sympathetic denervation and OH or the reporting of orthostatic symptoms (Chaudhuri, 2001; Gonçalves et al., 2022; Hellman et al., 2015), may be an important next step to determine if daily life nocturnal HR dipping indices relate to robust, conventional measures of CV dysautonomia in PD. Beyond measuring CV dysautonomia, if a more fulsome clinical characterization of the PD sample could be included, involving, for example, measurement of indicators of “brain” versus “body” first PD models of progression (Horsager et al., 2020) or information that enabled subtyping of the cohort (e.g., tremor dominant versus postural instability gait disorder (PIGD), non-motor clinical subtypes) (Marras & Chaudhuri, 2016; Titova et al., 2017), it may be possible to determine the impact of models of progression or subtypes on resting HR outcomes and nocturnal HR dipping (Study 2), as well as walking-related HR responses (Study 3).

Most relevant to Study 3, an inability to directly measure peak HR responses to a graded exercise test (GXT) done in a laboratory or clinical setting resulted in the use of age-predicted maximum HR values when calculating HRR as a tool to express the relative intensity of the walking-related HR response. Use of an age-based, generic equation may be particularly problematic in people with PD who may experience chronotropic incompetence, and therefore an inability to achieve a predicted maximum HR, as it may result in an underestimation of the relative intensity of a given activity or an overestimation of a prescribed training intensity (Panassollo, Lord, et al., 2024; Rosenfeldt et al., 2025). If clinical resources are available, it would be optimal to perform a peak effort GXT on all participants to measure peak HR (i.e., HR at VO_2peak) (Katzel et al., 2011; Schumann et al., 2025), as this has been shown to be feasibly completed in older adults with cardiovascular health conditions (e.g., post-stroke) (Tang, Sibley,

Thomas, et al., 2006) and with PD (Kanegusuku et al., 2016; Panassollo, Lord, et al., 2024; Rosenfeldt et al., 2025). This would allow daily life activity-dependent HR responses to be anchored to a direct measurement of an individual's peak physiological response to activity (Brown et al., 2025) and also provide an estimate of aerobic capacity or cardiorespiratory fitness (Garber et al., 2011), which could support the interpretation of resting condition- and activity-specific HR outcomes. However, in situations where there is limited access to resources (e.g., equipment, trained personnel) to perform clinical exercise testing (Tang, Sibley, Bayley, et al., 2006), or where the presence of contraindications or PD-specific impairments preclude safe participation in exercise testing (Katzel et al., 2011), there is a need to continue to advance other methods that may enable efficient estimation of valid “peak” HR values. Given that a multi-device set up worn continuously across a week-long collection period measures a range of daily life physical activities, it may be of value to explore if measured HR responses to daily life walking could be used, alongside clinical data (e.g., disease severity, CI, etc.) or assessment of subjective measures of intensity (e.g., rating of perceived exertion (RPE) or the talk test) (Alberts & Rosenfeldt, 2020; Bishop et al., 2025; Hansen et al., 2022), to extrapolate and predict an individual's peak HR (Matabuena et al., 2019). Application of a valid and reliable approach for estimating an individual's peak HR would enable re-examination of cohort-level differences between PD and controls in the relative intensity of daily life walking. If incorporated alongside the collection of additional clinical data on all PD participants, including a more fulsome characterization of PD severity (e.g., MDS-UPDRS, Hoehn and Yahr), this comparison could be further stratified to examine differences in the HR response to daily life walking between controls and sub-cohorts of PD segmented based on disease severity (e.g., mild, moderate, severe).

5.3.3. Future application: exploring time-varying heart rate in daily life behaviors

In the presence of robust device-derived context and complimentary clinical data, it is possible to extend upon the currently proposed methods of summarizing HR at a more “macro” level, to try to extract meaning from time-varying changes in HR during or in response to known daily life behaviors.

Quantifying transient changes in beat-to-beat HR, when time-locked to periods of daily life rest or walking, provides an opportunity to determine if it is feasible to reliably measure and derive meaning from HR outcomes that have conventionally provided insight into ANS function in clinical settings (e.g., HRV, post-activity HR recovery), when these same measures are recapitulated in real-world settings. Additionally, linking context-based, time-varying HR changes to a more detailed clinical characterization, which includes recordings of medication-taking behavior within and between days, may also allow for direct assessment of the impact of PD-specific and cardiovascular-altering medication on dynamic HR responses in daily life.

Specific to Studies 1 and 2, examination of HR during daily life sedentary behavior and sleep and characterization of the nocturnal HR profile could be extended upon via measurement of HRV. Previous work has measured HRV to assess or screen for CV dysautonomia in PD (Heimrich et al., 2021; Kallio et al., 2004; Mastrocola et al., 1999); however, there have been some inconsistent findings about whether HRV is lower in people with PD compared to healthy controls (Arnao et al., 2020; Maetzler et al., 2009; Miyagi et al., 2022; Niwa et al., 2011; Siepmann et al., 2022; Suzuki et al., 2022). For example, a systematic review and meta-analysis by Heimrich et al., (2021) concluded that people living with PD have lower HRV compared to controls when assessed across short-term windows (< 1 hour) using parameters that reflect parasympathetic activity (e.g., RMSSD); a study by Miyagi et al., (2022) showed no difference (and high variability) between PD and controls in high and low frequency power measures of HRV based on very short term (~ 3 min) supine and standing assessments; and a study by Suzuki et al., (2022) observed decreased 24-hr time-domain HRV measures (i.e., SDNN) in PD compared to controls. Inconsistencies in the literature may be due to considerable methodological heterogeneity across the previously used approaches to measure HRV in PD, including: discrepancies in the type of HRV outcome measures selected (i.e., different time and frequency domain measures used), measurement duration (i.e., short versus long-term), approach for screening and removal of abnormal beats, context or conditions of the measure (e.g., resting state, body position, recency of movement, clinic vs daily life), as well as

differing demographics and PD-characteristics of the study cohort (Arnao et al., 2020; Heimrich et al., 2021; Pursiainen et al., 2002; Shaffer & Ginsberg, 2017). While it is not possible in real-world settings to control for all factors that could impact HRV (e.g., stress, intake of HR-altering substances, temperature, etc.) (Quintana & Heathers, 2014; Uhlig et al., 2020), deploying context-based ambulatory HR monitoring may enable previous HRV comparisons between PD and control participants to be advanced, by controlling and/or accounting for some of the methodological discrepancies. This may involve starting incrementally with some practically feasible constraints, by exerting control over the free-living behavioral context, data quality, and recording length. Specifically, well-defined periods of daily life rest containing beat-to-beat HR data can be isolated, based on criteria specifying resting state (i.e., sleep versus wake), recency of movement (e.g., > 5 minutes post-activity), body position (i.e., sitting versus lying), measurement duration (e.g., 5-minutes), and a consistent approach to artifact screening and/or removal. Then, the reproducibility and consistency of both time and frequency domain HRV metrics, when measured across these short-term, better-defined periods of daily life rest, can be assessed within PD and control participants. This analysis could 1) provide insight into whether there is a short-term HRV index that is stable within an individual across free-living resting periods and/or 2) permit identification of a person-specific baseline for assessing changes in HRV over time or as a function of interventions. Starting with a within-participant design of this nature may help to control for certain between-participant differences that have been shown to impact HRV (e.g., respiration rate, medication usage, etc.) (Quintana & Heathers, 2014). Depending on what is observed, future work may then be able to explore if there are links between potential observed fluctuations in daily life HRV and ANS function, and also further test if there are differences in daily life HRV between PD and controls.

Beyond rest, measuring time-varying changes in the HR response to daily life walking (or other PA) may also extend upon the work in Study 3, by providing a potential window into ANS function. In addition to measuring the mean or peak HR response to walking as an index of the intensity of the activity, measuring HR during the post-exercise recovery period may provide insight into ANS function

(Coote, 2010), and has been shown to have prognostic significance (Lahiri et al., 2008). Specifically, blunted or abnormal HR recovery has been shown to be related to increased risk of mortality, even after submaximal exercise (Cole et al., 2000; Lahiri et al., 2008). Some previous work has used wearable HR monitors to begin to characterize indices of HR recovery to walking and other physical activities (e.g., stair climbing, postural changes), albeit largely based on fixed activity bout windows in controlled or standardized environments (Kim et al., 2021; Sokas et al., 2023; Toosizadeh et al., 2021). The assessment of time-varying HR changes during synchronously detected bouts of daily life walking may allow for measurements of HR recovery to be conducted in unstructured free-living settings. Given that chronotropic incompetence in PD may be the result of impaired parasympathetic and/or sympathetic nervous system activity, it may be of value to explore if these same mechanisms could manifest with impacts to the HR recovery associated with daily life walking bouts. Additionally, instead of constraining the comparison of HR and cadence to average values derived across an entire bout of walking, it may be possible to use the continuous HR data to compare, within a bout (intra-bout) and within a participant, if there is an association between step-to-step changes in cadence and transient, beat-to-beat HR responses (Hausdorff et al., 1992; Yuda & Hayano, 2025). Further quantification of the transient responsiveness of HR (or lack thereof) to changes in activity could potentially provide insight into how movement drives dynamic physiological responses, and into the adaptability of the ANS/CV system within and between individuals.

Across both resting and activity conditions, if a more expansive clinical characterization included detailed medication monitoring (i.e., type, dose, and timestamps), it may be possible to profile the impact of certain medications on time-varying changes in HR in free-living. Specific to PD, this could include exploring the effect of levodopa on HRV at rest or on transient activity-dependent changes in HR, as studies exploring the impact of levodopa on HR have largely been confined to in-clinic measurements and have generated inconsistent findings (Berkebile et al., 2025; DiFrancisco-Donoghue et al., 2009; Noack et al., 2014; Panassollo, Mawston, et al., 2024; Ruonala et al., 2015). Beyond only PD, for any participants

taking medications known to impact HR, such as beta blockers, detailed medication timestamping could allow for more insight into the impact of these medications on HR fluctuations within daily life conditions. This may be accomplished by comparing time-varying HR outcomes within a given behavior (e.g., rest or walking) either a) within a participant taking a certain medication (e.g., examining transient HR response to a walking bout pre- and post- medication intake) or b) between participants who are and are not taking a certain medication (e.g., comparing transient HR response to walking in a participant taking and not taking a beta blocker). Further understanding of the potential impacts of PD-specific and CV-targeting medications on behavioral-specific, time-varying HR responses could help to inform individualized medication titration or management, and recommendations for the need to control or account for certain medications when interpreting daily life HR outcomes.

5.3.4. Technology and approach used to measure and extract daily life heart rate

One of the challenges that faces the field going forward is the decision of which HR devices should be used, ranging from “easy to use” wrist-worn optical (PPG) systems to multi-lead ECG (“gold standard”). Critical to the technology is the importance of extracting valid and reliable analyzable HR data in daily life with the required temporal fidelity. The selection of a research-grade, single-lead ECG device (i.e., Bittium Faros (360) device) was intended to maximize data quality while making the self-application and use of the device possible in older adults. Such technology has been previously deployed as a reference standard within validation studies for other wearable HR monitoring devices (Bent et al., 2020; Kinnunen et al., 2020). This type of portable ECG technology was also selected because it provides access to raw (un-processed) data, continuously collected up to a period of 10 days, without requirements of charging or any engagement of the end user. Access to the raw data enables application of specific, “fit-for-purpose” processing and analytical steps to arrive at beat-to-beat HR outputs, as well as the potential to visualize how ECG waveform properties may be impacted by different types of noise or artifacts (de Zambotti et al., 2024). Specific to this wearable collection paradigm that spanned several days in uncontrolled, free-living settings, particularly relevant sources of noise in the ECG signal may include

skin-electrode impedance, electrode motion, and motion artifact (Rahman et al., 2022; Satija et al., 2018). While it is known that skin preparation prior to electrode attachment has an impact on skin-electrode impedance (Alugubelli et al., 2022; Majumder et al., 2017), it was necessary to scale back on abrasive skin preparation methods given the potential for the extended wear of the electrode adhesive (patch) to result in skin irritation and discomfort, particularly in older adults with reduced skin integrity. If the adhesive was not securely attached, this may have contributed to poor skin-electrode contact or increased electrode motion, which may have been the case for certain participants who appeared to have lower proportions of analyzable HR data across the collection. For other participants who appeared to have activity or walking-specific decrements in ECG signal quality, it is possible that specific features of their movement, such as increased upper body engagement (Lindsey et al., 2025), resulted in more motion artifacts and more ECG signal segments being excluded from subsequent analysis.

While it is valuable to be able to visualize how certain types of noise may manifest in the ECG signal, when processing large volumes of ECG data collected across several days, there is a need to rely on automated signal quality screening methods. The current study relied on a screening approach to classify signal to noise as an index of signal quality. Specifically, the signal quality assessment method utilized in the present work results in an estimate of a continuous signal-to-noise ratio (SNR), which permits segmenting the ECG data into different quality classes (i.e., Q1, Q2, Q3) based on SNR thresholds (Smital et al., 2020). This allows for identification of ECG data segments that are of sufficient quality for specific subsequent analysis, including Q1 segments that permit full waveform analysis and Q2 segments that only enable R-peak detection, and therefore, HR calculation (Smital et al., 2020). Given that the SNR thresholds were chosen to minimize the risk of overestimating the signal quality (i.e., may underestimate the “true” SNR during noisy segments of data), it is possible that this resulted in the exclusion of some segments of ECG data that may contain portions of analyzable signal. As such, it may be of value to explore the suitability of the current SNR thresholds to distinguish between ECG signal quality classes based on continued application into diverse, real-world datasets that have the capacity to

be annotated, or whether there is a need to further refine the thresholds (Lindsey et al., 2025; Rahman et al., 2022). Beyond trying to advance the current signal quality approach, it may also be prudent to explore the adoption of different signal quality screening methods that permit advanced feature extraction of HR during noisy signals (e.g., machine learning approaches) (Satija et al., 2018), to determine if any of the current segments of ECG data that have been discarded (i.e., Q3 segments) contain portions of data that may be recoverable. In addition to a focus on the method used to filter the noise and assess the signal quality, a combined approach to advancing the ECG analysis should also consider the R-peak detection method. The current work used the open-source, NeuroKit peak detection algorithm (NeuroKit2) (Makowski et al., 2021), which has been previously shown to have a relatively fast execution time and to be one of the top R-peak detection methods (i.e., very high degree of accuracy) when tested on datasets containing long-term (up to 24 hours), single-lead ECG signals (Kristof et al., 2024; Sicbaldi et al., 2024). However, this method is still susceptible to peak-detection errors within low-quality ECG data that contains noise and/or time varying changes in QRS waveform morphology (Kristof et al., 2024). Continued comparison to alternative, robust R-peak detection methods, such as wavelet transform-based QRS detection (Elgendi et al., 2014; Kadambe et al., 1999), is warranted to ensure the most accurate and reliable approach to ambulatory R-peak detection is being adopted.

In addition to the possibility of extracting more analyzable data from the current ECG-based approach, near-constant advances in wearable technology for ambulatory HR monitoring presents the opportunity to explore the use of other technologies, such as PPG. Many devices reporting HR, such as smart watches, rely on optical sensing technology and present “easy to use” approaches, but the question that remains is the possible trade-off to data quality. The limitations of using PPG-based commercial systems for research (and/or clinical) use cases have conventionally included a lack of transparency surrounding processing and analytics (i.e., “black-box”), a lack of access to raw data, and concerns about data quality based on a susceptibility to factors that may compromise or alter the contact between the skin and the device (e.g., movement, moisture, personal characteristics such as skin colour, etc.) (Bent et al.,

2020; de Zambotti et al., 2024; Fine et al., 2021; Lindsey et al., 2023; Sana et al., 2020; Schumann et al., 2025). However, emerging advances in analytics hold promise for increasing the research and clinical utility of PPG-based devices, as demonstrated by recent work by Sicbaldi et al., (2025) showing that certain algorithms that fuse accelerometer and PPG data may increase the reliability of PPG-based HR monitoring during periods of dynamic movement when the PPG signal has been corrupted by motion artifact. Coupled with continued recognition about the importance of accessing raw data and/or transparency surrounding data processing and analytics (Brown et al., 2025; Sicbaldi et al., 2025), open-source PPG-based approaches may allow further comparisons to be made between the data quality and performance of ECG versus PPG-based systems for HR detection in daily life conditions. As an example, current attention is being placed, within our lab, on comparing the HR outputs during daily life conditions from research and commercial-grade PPG (e.g., Apple Watch, TicWatch) to portable ECG devices (e.g., Polar H10, Bittium Faros 360), to identify the circumstances where devices may fail and the potential amplitude and temporal differences between devices in HR responses to daily life activities. This work may contribute to understanding particular use cases where deployment of PPG may be suitable, reflecting the need to prioritize feasible ambulatory HR monitoring solutions that consider and try to balance transparency, access to good quality data, and usability.

Beyond thinking of devices or technology in isolation, access to both PPG and ECG data can provide insight into additional cardiovascular outcomes, such as blood pressure (BP) (Allen, 2007; Bard et al., 2019). Hypertension represents a modifiable risk factor for cardiovascular morbidity and mortality that can be targeted with clinical and lifestyle-based strategies (Brook et al., 2015; Landry et al., 2025; Stamler et al., 1993; Stergiou et al., 2022), warranting frequent measurement (Bard et al., 2019). Outside of the clinic, BP has been conventionally assessed in daily life via ambulatory blood pressure monitoring (ABPM), which takes intermittent BP readings at 30-60 minute intervals across the day and night, and enables the measurement of BP outcomes that are 1) associated with an increased risk of CV events and mortality (Fagard et al., 2008; Parati et al., 2013; Staessen et al., 1999) and 2) responsive to BP-targeted

interventions such as isometric training and aerobic exercise (Edwards et al., 2024; Saco-Ledo et al., 2020; Stiller-Moldovan et al., 2012). Despite the clinical utility, ABPM requires the user to wear a brachial cuff and takes measures that could interfere with daily behaviors (e.g., sleep), and cannot capture transient BP changes as they occur during or in response to free-living activities (e.g., walking, body position changes, etc.). Instead, “cuffless” BP monitoring, which can estimate BP based on calculating the time interval between ECG and PPG signal peaks as a measurement of the pulse transit time (Allen, 2007; Majumder et al., 2017), may overcome some of these pragmatic limitations and could be viewed as a convenient, user-friendly tool to aid in the evaluation of BP-lowering strategies. While cuffless approaches have the potential to advance understanding of the clinical significance of BP fluctuations as they occur in daily life, and across broad populations, further validation work is still required to confront concerns regarding accuracy before these approaches can be put into practice (Bard et al., 2019; Bayoumy et al., 2021; Landry et al., 2025; Stergiou et al., 2022).

5.3.5. Volume of daily life heart rate data and participant sample sizes

While it is worth exploring if it is possible to extract more analyzable HR data, particularly during daily life movement-based conditions that were susceptible to data loss, high HR data volumes were still available for each participant during resting conditions and across many participants during movement, providing a robust basis for calculating individual-level metrics. As an example, within Study 1, the number of included 30-second HR epochs per participant averaged approximately 173 000 (range: 103 000-220 000) during sedentary behavior and 162 000 (range: 81 000-220 000) during sleep. As opposed to point-in-time assessments that conventionally capture a “snapshot” and/or are based on a short time window (e.g., < 5 min), repetitive sampling of context-specific HR allows for characterization of within-participant HR distributions across wider time frames in ecologically valid settings. Previous work has shown that using high frequency, objective, and continuously sampled daily life monitoring data to generate participant-specific distributions of outcome measures and individual estimates of variability increases the precision and sensitivity to detect change within a participant over time (Arnold et al., 2024;

Dodge et al., 2015; Espay et al., 2019). Across the studies in this thesis, interpreting HR in the context of pooled bouts of sedentary behavior, sleep, or walking revealed a high degree of within-participant variability in HR, and the potential pitfalls in relying only on estimates of central tendency. Given this observation, it may be valuable to explore adopting “single-case” or “n-of-1” experimental designs (Arnold et al., 2024), whereby these context-specific, within-participant HR distributions serve as the baseline (or reference), prior to an intervention, which is then followed by a repeat, post-intervention monitoring period to assess participant-specific changes (Dodge et al., 2015). For example, this type of context-based continuous HR monitoring could be integrated into the pre-post evaluation structure of an exercise training program, to better elucidate if and/or how the minimum, median, and range in HR values during resting conditions change within a participant as a result of training. It may also be interesting to see if it is possible to cluster participants based on the degree of within-participant variability in HR in a given context (e.g., in the HR response across walking bouts), to potentially distinguish those with “high” versus “low” levels of within-participant variability, and to see if there are specific demographic or behavioral characteristics associated with different variability profiles.

Extending upon the focus on within-participant comparisons, Studies 2 and 3 included an assessment of between-cohort differences, between control and PD participants, based on the application of relatively strict participant inclusion criteria. The decisions to exclude participants with comorbidities or medications known to impact HR (Arnao et al., 2020; Mastrocola et al., 1999; Maurer et al., 2016), and to consider participant age, were made based on an intent to try to isolate the effect of PD on HR during resting conditions and nocturnal HR dipping (Study 2) and activity-dependent HR responses (Study 3). Application of these criteria lead to the inclusion of 13 controls and 13 participants with PD, from an initial sample of 109 control and 62 PD participants with available sensor data. Although a high proportion of participants being excluded may limit the generalizability to the general population of adults or those living with PD, it was important, as a first step, to be able to investigate if cohort-level differences existed in the absence of other confounders and factors that are known to affect the

cardiovascular system, including trying to minimize the impact of pharmacological alteration of HR (Arnao et al., 2020; Kanegusuku et al., 2016; Rosenfeldt et al., 2025). The novelty of the approaches used within this work when generating daily life, context-specific HR indices also made it challenging to identify relevant previous studies to extract appropriate effect size and variance estimates to conduct a priori sample size calculations, in order to ensure that the studies were adequately powered to detect an effect. However, previous work has suggested that participant-specific outcomes derived from data sampled continuously at a high resolution, as occurs across all studies in this thesis, may allow for the use of considerably smaller sample sizes to show desired effects with adequate statistical power (Dodge et al., 2015; Espay et al., 2016). Planned and future studies employing these context-based HR methods to compare across cohorts should still include a greater focus on larger participant sample sizes. Additionally, there is a need to include more heterogeneous cohorts to be able to consider and test the impact of specific demographic characteristics (e.g., age, sex, body composition, race/ethnicity, etc.), clinical comorbidities or characteristics (e.g., CV disease, severity of PD), medication use (e.g., beta blockers), and other relevant factors (e.g., fitness) on measured HR outcomes. There may be opportunity to explore some of these potential drivers of between-participant variability in measured HR outcomes if the proposed approaches from this work are applied within the larger cohort of control and PD participants within the HANDDS-ONT study, as well as across other disease cohorts that are a part of HANDDS-ONT, including individuals living with cerebrovascular disease and other NDDs (e.g., Alzheimer's disease). For example, within the larger PD cohort, comparisons in HR outcomes at rest and/or during PA could be made between those living with and without cardiovascular disease, or even within the broader HANDDS-ONT study sample between those taking and not taking beta blockers. Using systematic approaches to try to understand how various factors may impact daily life resting and activity-dependent HR measures is necessary to be able to determine if and/or how findings from the current work can be extrapolated to more heterogeneous cohorts, and to identify the variables that may need to be accounted or controlled for in future studies examining context-specific HR outcomes.

5.3.6. Embedding context-dependent heart rate monitoring into usual or clinical care

Alongside the need for further testing in larger and more heterogeneous cohorts, considering the possible practical applications of this work beyond research settings involves identifying the steps that might be necessary for remote, context-dependent ambulatory HR monitoring to be considered a candidate option for usual or clinical care. As previously mentioned, the use of a multi-device wearable approach is advocated for across the studies in this thesis as a tool for collecting and connecting robust, continuous, daily life HR data over extended wear periods to reliable movement data that can provide essential behavioral context for profiling how HR varies and identifying context-based HR outcomes. The multi-device set up in this thesis work included the purposeful selection of devices based on certain performance criteria (e.g., raw data access, battery life, data storage, etc.), which were worn on specific body locations based on outcomes of interest. This multi-device paradigm has previously been shown to yield high wear times (compliance) and to be acceptable and tolerable over a week-long collection period within older adult and NDD cohorts (Godkin et al., 2022). The proposed methods for measuring context-dependent HR outcomes within the studies in this thesis can be adopted by others using different wearable device set ups, as long as they include a reliable HR monitoring device that provides access to raw or beat-to-beat HR data, and are able to denote daily life behaviors. From a clinical integration perspective, there is a need to turn attention towards identifying the minimal device number, minimum collection duration, and requisite variables to reliably extract essential context-based HR outcomes. This will likely involve attempting to define a “middle-ground” between 1) conventional Holter monitoring, which is robust but lacks the capacity to provide critical information about behavioral context and involves a multi-lead set-up that may be restrictive, reduce compliance, and preclude extended collections (Hinde et al., 2021; Sana et al., 2020; Santala et al., 2021), and 2) a set up involving instrumentation with several devices that may be comfortable but possibly not pragmatic in environments that are resource-limited (e.g., computationally, financially) or if intending to monitor for extended durations (e.g., months). Continued comparisons between different data collection paradigms (e.g., single versus multi-device) and device types (e.g., research versus commercial, PPG versus ECG) will be needed to enable decisions

about wearable device deployment to be data-driven and guided by empirical evidence and performance criteria, rather than dictated or constrained by the limitations of currently available technologies. A focus on identifying alternative wearable paradigms that continue to minimize potential burden (i.e., unobtrusive, user-friendly, portable) (Boe et al., 2019; Espay et al., 2016; Morgan et al., 2020), without compromising data access and quality (Espay et al., 2019), represents an important next step towards proposing a clinically feasible monitoring approach.

Beyond paring down the number of devices used, proposing a wearables-based approach that has the potential to be integrated into clinical care requires data outputs to provide insights that are clinically meaningful, interpretable and actionable (Bayoumy et al., 2021; Del Din et al., 2021; Espay et al., 2016, 2019). It is possible that an outcome may be deemed clinically important if it addresses a critical knowledge gap or provides additional insight into objective, physiologically relevant changes that are not captured via clinical measurement approaches. For example, applying the approach proposed in Study 3 to profile the pattern and intensity of daily life walking may address a current gap in the assessment of aerobic PA in community settings for people with PD, which has primarily been reliant on self-report questionnaires (Oguh et al., 2014; Silva de Lima et al., 2018; Tsukita et al., 2022). Integrating the HR-based assessment of daily life PA with remote monitoring of PD motor and non-motor symptoms, which can fluctuate erratically on timescales not observed within a conventional clinical exam (Espay et al., 2016; Packer et al., 2025), may also help to elucidate the per-participant relationships between symptoms and PA behavior and could help to guide therapeutic decision making. Importantly, for a wearable-derived measure to be deemed clinically relevant, it must be related to or indicative of a meaningful health outcome and/or reflect a therapeutic target (Espay et al., 2016; Goldsack et al., 2020; Wallén et al., 2015). Specific to the current work, this may necessitate incorporating context-based ambulatory HR monitoring into population level, longitudinal collection protocols that enable associations to be assessed, for example, between resting condition-specific HR measures (e.g., sleeping minimum HR) and risk of adverse health outcomes (e.g., risk of cardiovascular disease, mortality, etc.) (e.g., Nauman et al., 2011;

Vazir et al., 2015). Alternatively, interventional approaches could also be pursued, such as a study that embeds the measurement of daily life nocturnal HR dipping indices, alongside other measures of CV dysautonomia in PD, to assess the responsiveness of nocturnal HR dipping to treatments targeting the ANS (e.g., medication, lifestyle strategies). Beyond demonstrating novel insight and/or a relationship to health outcomes or responsiveness to treatment, for an outcome to be clinically meaningful, it must reflect the priorities or concerns of the end users, including the cohorts and stakeholders of interest (e.g., clinicians, patients) (Del Din et al., 2021; Espay et al., 2016; Godkin et al., 2022; Goldsack et al., 2020; Van Ooteghem et al., 2023). For example, understanding if it is possible to profile ANS dysfunction using daily life HR data was one of the targets of this work because non-motor symptoms, including ANS dysfunction, have been shown to occur as early as the prodromal stages of PD (Mollenhauer et al., 2013; Sharabi et al., 2021), and have been reported by people with PD to negatively impact quality of life (Magerkurth et al., 2005; Martinez-Martin et al., 2011; Witjas et al., 2002), yet have received less measurement attention in daily life than motor symptoms of PD (Janssen Daalen et al., 2024).

If certain outcomes have been shown to have clinical value, focus must shift to ensuring that the relevant stakeholders can interpret the information (i.e., feedback) and/or use the data to inform an appropriate course of action, including for self- or clinical-management. Previous work from our lab used an iterative, participatory approach to develop and implement a method for sharing personalized, wearables-derived information about daily life behaviors (e.g., physical activity, sleep) with older adults and those living with NDDs (Van Ooteghem et al., 2023). Creation of a health behavior feedback report and adoption of an intentional communication strategy, which considered the diverse needs and differing capabilities across the targeted cohorts (e.g., education, data literacy, etc.), resulted in most participants (i.e., > 80%) deeming the feedback to be acceptable and usable (Van Ooteghem et al., 2023). Receipt of this feedback also evoked a behavior change in ~ 60% of participants, suggesting that participants were able to understand their health-related behaviors (self-awareness) and engage in lifestyle-related changes (self-management) (Van Ooteghem et al., 2023). This model may serve as a template for the current thesis

work, in terms of identifying, presenting, and delivering information about context-dependent HR outcomes in a way that supports participant understanding of what is most relevant and if there is a recommended course of action. It will also be important to bring clinician stakeholders to the table, to determine the “what, how, and when” (Espay et al., 2019) – in terms of the types of data outputs included, how they are presented (e.g., visuals), and the frequency or timing of monitoring and feedback delivery – to ensure that any future implementation supports clinical decision making and care. While there is still much additional work to be done to tackle important issues such as cost, accessibility, regulatory policy, and system and clinical workflow integration (Bayoumy et al., 2021; Goldsack et al., 2020), a future that leverages research advances in remote, context-based, ambulatory HR monitoring to inform clinical implementation has the potential to expand the scope and reach of clinical care, including to those who may otherwise have limited access to care and evaluation.

5.4 Conclusions

This dissertation advances the development of, and illustrates the importance of, adopting standardized approaches to measure resting and activity-dependent HR from daily life data collected continuously over multiple days. Throughout this dissertation, the argument has been made that context-based ambulatory HR monitoring has the potential to improve the characterization of free-living behaviors and measurement of HR outcomes that may be of clinical value. This argument has been supported by a series of studies based on the application of a multi-sensor and -device wearable paradigm in daily life, within a cohort of adults with and without Parkinson’s disease. Initially, the measurement of resting HR based on the collection of high volumes of continuous HR data across sedentary and sleeping periods was confronted, and resulted in recommendations for wearables-based, daily life resting HR measures that reference the resting behavioral condition (i.e., sleep versus sedentary behavior) and criteria used (e.g., minimum, median). Application of these recommendations in subsequent thesis studies revealed that context-based ambulatory HR monitoring has the *potential* to 1) provide clinical insight by measuring diurnal HR characteristics as an index of ANS dysfunction in PD, and 2) improve the

characterization of daily life PA intensity, in those with and without PD, by using a relative intensity estimate that provides insight into the cardiovascular demands associated with daily life walking. The high degree of within-participant variation in HR that was observed in daily life resting and physical activity conditions: 1) challenges conventional thinking about the utility of point-in-time (“one-off”) HR measurements, 2) has implications for determining optimal collection lengths to capture representative HR responses, 3) permits exploration into novel free-living HR indices, and 4) supports the need for continued attention towards developing wearables-based, context-dependent HR measurement standards. Beyond the implications for people living with PD, advancing the use of free-living HR has the potential to improve the quality of daily life behavioral measurement and the utility of wearables data across a range of clinical applications and populations.

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Note: This section includes references associated with Chapters 1 (General Introduction), 4 (Study 3) and 5 (General Discussion). Reference lists for Chapters 2 (Study 1) and 3 (Study 2) are included separately, immediately following each manuscript.

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