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Fall Risk-Increasing Drugs and Gait Performance in Community-Dwelling Older Adults: Results from the Gait and Brain Study

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Abstract

Medication use and gait impairment are two of the most important risk factors for falls. Several drug classes have been classified as fall risk-increasing drugs (FRIDs). Gait is an important marker of overall health and independence in older adults. The overall aim of this thesis was to examine the relationship between FRIDs and gait performance in older adults through two studies. Firstly, our systematic review of twenty studies on the association between FRIDs and gait performance found that the use of drugs with sedative properties is associated with reduced gait speed. Secondly, we conducted a cross-sectional analysis of data from the Gait and Brain Study. We found that among community-dwelling older adults aged 65 years old and over, diuretic use was associated with significantly reduced gait speed and statin use was associated with significantly increased stride time variability. Future longitudinal studies are required to determine the clinical relevance of our findings.

Keywords: gait, falls, older adults, psychotropic drugs, cardiovascular drugs

Summary for Lay Audience

Falls in older adults are a major public health concern in older adults. Medication use and gait (walking) impairment are two of the most important risk factors for falls. Several drug classes have been identified as fall risk-increasing drugs. Gait is also an important marker of overall health and independence in older adults therefore the aim of this thesis was to examine the relationship between fall risk-increasing drugs and gait performance in older adults through two studies. Our first study was a systematic review of the current published evidence on the relationship between fall risk-increasing drugs and gait. We found that using drugs with sedative properties is associated with reduced gait speed in older adults. Our second study analyzed data collected from the Gait and Brain Study which is a study of community-dwelling older adults aged 65 years old and over living in London, Ontario. We found that the use of diuretics was associated with significantly reduced gait speed and that statin use was associated with significantly increased stride time variability which is a marker of gait (walking) instability and a predictor of future falls. Future studies following up patients over a period of time are needed to determine the relevance of our findings in a clinical setting.

Co-Authorship Statement

This thesis includes two manuscripts which will be submitted for publication in peer-reviewed academic journals. The co-authorship details for both manuscripts is detailed below. Due to the nature of the integrated article thesis, some duplication of content is inevitable.

Chapter 3: Osman A, Kamkar N, Speechley M, Ali S and Montero-Odasso M.
Fall Risk-Increasing Drugs and Gait Performance in Community-Dwelling Older Adults: A Systematic Review

Abdelhady Osman was responsible for the design and conception of the study, study selection, risk of bias assessments, data extraction, data interpretation and for writing the manuscript and subsequent drafts. Nellie Kamkar assisted as the second reviewer in study selection, risk of bias assessments and data extraction. Dr. Mark Speechley and Dr. Manuel Montero-Odasso contributed to the design and conception of the study. Dr. Mark Speechley, Dr. Shehzad Ali and Dr. Manuel Montero-Odasso were involved in critically revising the manuscript for intellectual content and for editing the manuscript and subsequent drafts.

Chapter 4: Osman A, Speechley M, Ali S and Montero-Odasso M.
Fall Risk-Increasing Drugs and Gait Performance in Community-Dwelling Older Adults: Results from the Gait and Brain Study

Abdelhady Osman was responsible for the design and conception of the study, data exploration, statistical analysis and for writing the manuscript and subsequent drafts. Dr. Shehzad Ali and Dr. Mark Speechley provided statistical and methodological guidance. Dr. Mark Speechley and Dr. Manuel Montero-Odasso contributed to study design and conception. Dr. Montero-Odasso assisted with the interpretation of the results and provided guidance on the clinically-relevant aspects of the study. Dr. Mark Speechley, Dr. Shehzad Ali and Dr. Manuel Montero-Odasso were involved in critically revising the manuscript for intellectual content and for editing the manuscript and subsequent drafts.

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I dedicate this thesis to my late father, Sayed Abdelhady Osman, whom I miss every day.

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Abbreviations

ACEI – Angiotensin-Converting Enzyme Inhibitor

ALSA – Australian Longitudinal Study of Aging

BMI – Body Mass Index

CCB – Calcium Channel Blocker

CCMA – Central Control of Mobility in Aging

CHAMP – Concord Health and Aging in Men Project

CHF – Congestive Heart Failure

CV – Coefficient of Variation

DBI – Drug Burden Index

DBS – Drug Burden Sedative Component

EPESE – Established Populations for Epidemiologic Studies of the Elderly

EUGMS – European Geriatric Medicine Society

FRIDs – Fall Risk-Increasing Drugs

GABA - Gamma-Aminobutyric Acid

GDS – Geriatric Depression Scale

GEMS – Geriatric Multidisciplinary Strategy

MICE - Multiple Imputation by Chained Equations

MMSE – Mini-Mental State Examination

NOS – Newcastle-Ottawa Scale

POMA – Performance-Oriented Mobility Assessment

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT – Randomized Controlled Trial

SD – Standard Deviation

SNRI – Serotonin-Norepinephrine Reuptake Inhibitor

SSRI – Selective Serotonin Reuptake Inhibitor

T-25FW – Timed-25 Foot Walk

TCA – Tricyclic Antidepressant

TIA – Transient Ischemic Attack

TILDA – The Irish Longitudinal Study on Aging

TRAIN - Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors

TUG – Timed Up and Go

WHAS I – Women's Health and Aging Study I

WHI – Women's Health Initiative

WHO – World Health Organization

Chapter 1

1 Introduction

This chapter introduces three concepts: falls, fall risk-increasing drugs and gait. It starts with an overview of falls and their risk factors including a more detailed discussion of fall risk-increasing drugs. The chapter ends with a detailed discussion of gait including the gait cycle, gait assessment methods and the two gait parameters examined in this thesis: gait speed and gait variability.

1.1 Epidemiology of Falls

In 2018, falls were the second leading cause of death due to accidental or unintentional injury worldwide with an estimated 646,000 fatal falls taking place each year[1]. Falls disproportionately affect older adults. In Canada, an estimated 20% to 30% of adults 65 years old and over suffer at least one fall each year and half of those 80 years old and over experience a fall each year[2]. Falls are associated with a range of negative physical and mental health outcomes. Injury and fractures are major consequences of falls. Falls account for 80% to 85% of injury-related hospitalizations and 95% of hip fractures among older adults in Canada[2,3]. One third of Canadian older adults treated for fall-related injury are discharged into long-term care[2]. In addition, falls are also associated with several psychological consequences including fear of falling, avoidance of activity, anxiety and depression[4-7]. Falls are also associated with a significant economic cost. Fall-related costs per capita were almost four times higher for Canadian seniors compared to Canadians under the age of 64[2]. The aging of the population means that falls are going to become a more pressing health, social and economic challenge in future.

1.2 Risk Factors for Falls

Falls are multifactorial. The risk of falls increases with the number of risk factors. It was shown that among community-dwelling older adults, fall risk increases from 8% when no risk factors are present to 78% in the presence of four or more risk factors[8]. Fall risk

factors can be divided into intrinsic factors (such as aging, comorbidities, visual and auditory deficits, balance and gait problems, etc.) and extrinsic factors (such as tripping and slipping hazards, improper usage of assistive devices, etc.). It is thought that many falls result from interactions among different risk factors rather than from simple additive effects[9,10]. An example relevant to this thesis would be comorbidities that cause sensory impairment. These comorbidities result in medications being prescribed, which affect balance and gait, which increases fall risk over that posed by the comorbidities alone. Fall-increasing risk factors were further categorized by the World Health Organization (WHO) into biological, behavioral, environmental and socioeconomic domains[11]. Two of the most important risk factors for falls are medication use and impaired gait performance, which form the core of this thesis.

1.3 Fall Risk-Increasing Drugs (FRIDs)

Medications that are associated with increased fall risk are collectively known as fall risk-increasing drugs (FRIDs). Due to the prevalence of polypharmacy in older adults, the use of FRIDs is common. Older adults are also at risk of prescribing cascades[12]. A prescribing cascade occurs when an adverse drug reaction is misinterpreted as a new medical condition and results in the prescription of additional drugs which may include FRIDs. While no universal evidence-based list of FRIDs has been developed to date, psychotropic and cardiovascular drugs have been identified as the most important FRID classes[13].

The association between these psychotropic drugs and increased fall risk in older adults has been well-established by several systematic reviews and meta-analyses[14-17]. Beers criteria for potentially inappropriate medication in older adults recommends against the use of antipsychotics, antidepressants, benzodiazepines, hypnotics and sedatives in geriatric patients with a history of falls[18]. The evidence for cardiovascular drugs is more mixed. Loop diuretics have been shown to be associated with falls while inconsistent associations have been reported for antihypertensives, beta-blockers and antiarrhythmics[16,17,19,20].

The mechanism of the associations between several FRIDs and increased fall risk is not well understood given the multifactorial nature of fall risk and the involvement of different bodily systems in mobility. Broadly, older adults experience age-associated pharmacokinetic changes including slower metabolism and elimination of drugs as well as increased permeability of the blood-brain barrier[21]. These changes may prolong or augment the effect of medications. Several biological mechanisms for the association between different FRIDs and fall risk have been suggested in the literature.

Antidepressants are thought to contribute to fall risk through sedation, impaired balance, sleep disturbances and orthostatic hypotension[22]. Benzodiazepines have been linked to falls through augmenting the inhibitory effect of GABA[23] in the central nervous system which in turn affects attention and alertness causing sedation. Cardiovascular drugs including diuretics and various classes of antihypertensives are thought to increase fall risk through orthostatic hypotension and syncope. However, these mechanisms have not been extensively studied and are not well established. The body of evidence on the biological mechanisms of the association between FRIDs and fall risk remains limited particularly compared to the consensus on the link between FRIDs and fall incidence.

1.4 Gait

Gait is the medical term that describes walking in healthy adults. Gait is a complex process that requires coordination among various bodily systems including the nervous, sensory, respiratory, cardiovascular and musculoskeletal systems[24]. The normal gait pattern is described by the gait cycle[25] (Figure 1.1)

1.4.1 The Gait Cycle

In a normal gait pattern, the gait cycle represents the time interval between the first heel strike of one foot and the next heel strike of the same foot[26]. The heel strike is the point at which the foot strikes the ground and is also known as the initial contact. Only one foot is considered in the gait cycle and is known as the reference foot. The gait cycle is comprised of two major phases. The stance phase accounts for 60% to 65% of a normal gait cycle and it represents the time interval between the first heel strike of the reference

foot and the point at which the reference foot lifts off the ground. The swing phase accounts for the remaining 40% to 35% of a normal gait cycle and it represents the time interval between the reference lifting off the ground and coming into contact with the ground once again[26].

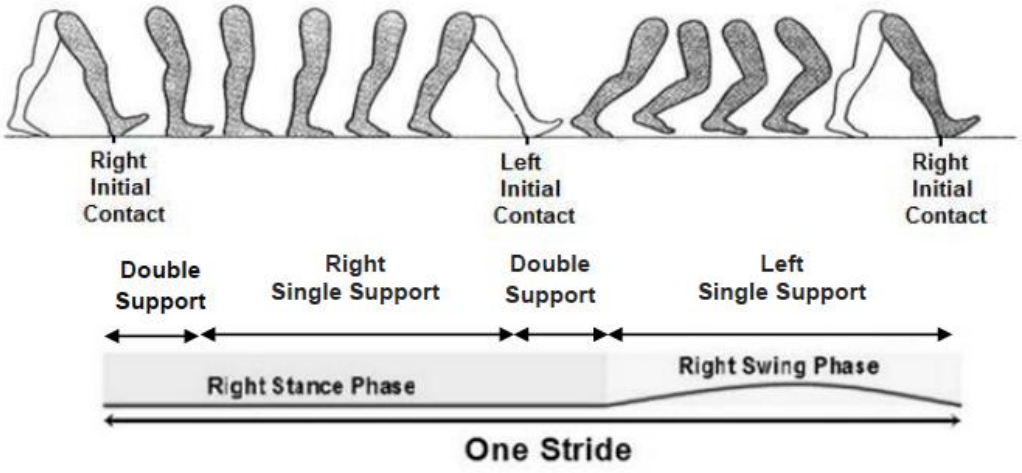

Figure 1.1 The Gait Cycle. Adapted from Montero-Odasso M. (2003)

The gait cycle can be analyzed through several spatial and temporal parameters. Gait (walking) speed is the most commonly assessed gait parameter, and it is quantified by the dividing the distance walked on a smooth surface by unit time. It is often expressed in metres per second (m/s) or centimetres per second (cm/s). The significance of gait speed as a marker of geriatric health is discussed in greater detail later in this chapter. Cadence is a gait parameter that describes the number of steps walked per unit time and provides information about the rhythm of walking[27].

Other temporal parameters are often expressed in seconds and include stride time which describes the time period between two footfalls of the same foot, step time which describes the time period between the heel strike of one foot and the heel strike of the opposite foot and double support time which describes the time in which both feet are in contact with the ground[27].

Commonly-measured spatial parameters of gait are often expressed in metres (Figure 1.2). These include stride length which is equivalent to one gait cycle and describes the distance between two consecutive footfalls of the same foot. Step length describes the

linear distance between the heel strike of one foot and the heel strike of the opposite foot. Step width describes the distance between the midpoint of the footfall from one foot and the midpoint of the footfall from the opposite foot[27].

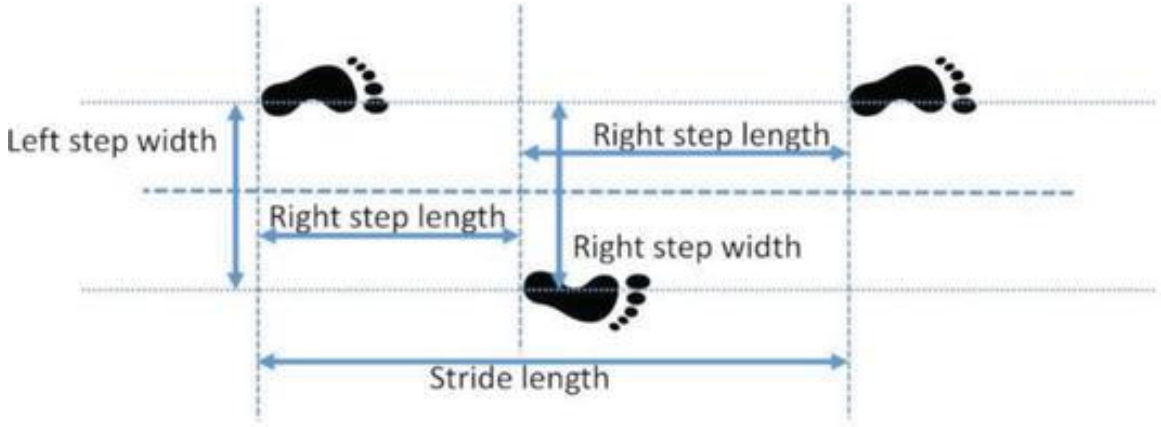

Figure 1.2 Spatial Gait Parameters. Adapted from Pradel G. et al. *An Embedded Gait Analysis System for CNS Injury Patients, Assistive and Rehabilitation Engineering* (2019)[28]

1.4.2 Gait Assessment Methods

Two main methods of gait assessment are observational and instrumental. Observational assessments involve a visual examination of an individual's gait pattern using clinical judgement and expertise[29]. These examinations may be supplemented by tests such as the Timed Up and Go Test (TUG), the Tinetti Performance-Oriented Mobility Assessment (POMA) and the Timed-25 Foot Walk (T25-FW) which capture basic gait parameters such as gait speed and cadence. Instrumental gait assessment methods are more objective and capture several spatiotemporal gait parameters. These instruments include 3D image processing techniques using cameras or wireless sensors, as well as instrumented mats and walkways. One frequently used instrument is the GAITRite® system which consists of a portable walkway with embedded pressure sensors and software that calculates spatiotemporal gait parameters for every footfall based on information transmitted from the sensors[30]

1.4.3 Gait Speed

Gait speed refers to the speed of walking over a smooth surface at a 'usual' pace. While it is a primarily a measure of physical function, gait speed was shown to be a robust predictor of a range of health outcomes including disability, cognitive function, hospitalization, institutionalization, cardiovascular mortality and all-cause mortality[31]. Gait speed is also an important predictor of future falls. Several studies showed that fallers exhibit slower gait speed compared to non-fallers[32-34]. Gait speed is a responsive measure that is appropriate for use in a variety of settings including community, hospital and long-term care settings as well as different populations including healthy and diseased older adults. As a result of the predictive capacity and responsiveness of gait speed, it was termed the 6th vital sign and gait speed assessment is increasingly recommended as part of regular health status examinations[31,35].

1.4.4 Gait Variability

Gait variability is an important quantitative measure of gait performance. Variability refers to the stride-to-stride fluctuations in a walking pattern which are exhibited by older adults as part of the normal aging process and are also manifested in neurodegenerative diseases. It was found that disease-free healthy older adults exhibit stride to-stride fluctuations similar to those exhibited by young children. High stride-to-stride fluctuations are indicative of unstable gait[36].

Variability is quantified by the coefficient of variation (CV) of quantitative gait parameters (CV = standard deviation/mean $\times$ 100)[36]. The use of the CV over the standard deviation (SD) has some advantages. SD measures can be affected by outliers in the data. Additionally, the CV is a unitless measure and allows for comparisons between variabilities of gait parameters that are measured in different units.

There is growing evidence that gait variability may be a more sensitive measure of gait instability and thus a more robust predictor of fall risk than other commonly measured gait parameters such as gait speed[36,37]. Among the different measures of gait variability, stride time variability and swing time variability were found to be closely associated with falls. Fallers were shown to exhibit higher fluctuations in stride time (higher stride time

variability) compared to non-fallers[37] (Figure 1.3). Stride time variability was also found to be most closely associated with the frailty syndrome[38].

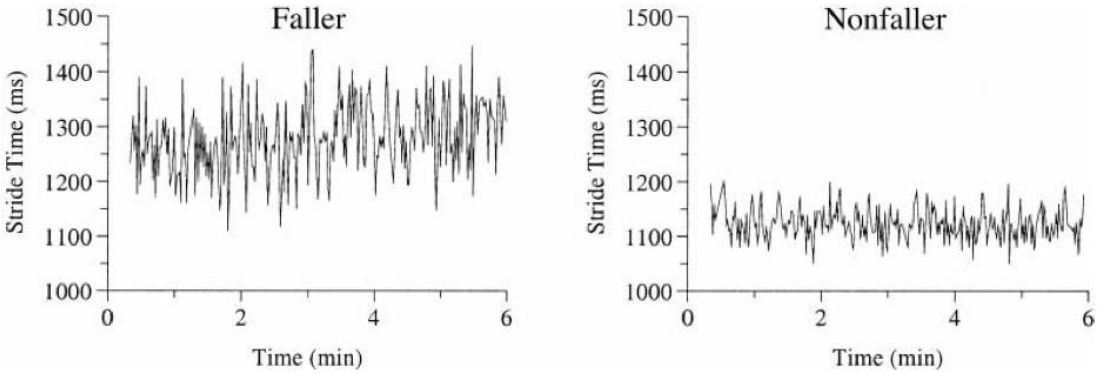

Figure 1.3 Stride time variability patterns in a 78-year old faller compared to an 84-year old non-faller

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Chapter 2

2 Rationale and Objectives

This chapter outlines the rationale for this thesis including the conceptual framework this thesis is based upon. It also outlines the objectives of the thesis

2.1 Rationale

As stated in the previous chapter, the mechanisms of the association between FRIDs and falls are not well understood. It was recently shown that a complex interplay exists between polypharmacy, gait and falls in which the association between polypharmacy and falls in older adults was shown to be partially mediated by gait impairments[1]. The study only considered the total number of medications as an exposure and did not evaluate the impact of individual drug classes on gait. It is plausible that a similar interplay could exist between FRIDs, gait and falls in which gait performance could be an intermediate variable on the causal pathway between FRIDs and falls (Figure 2.1).

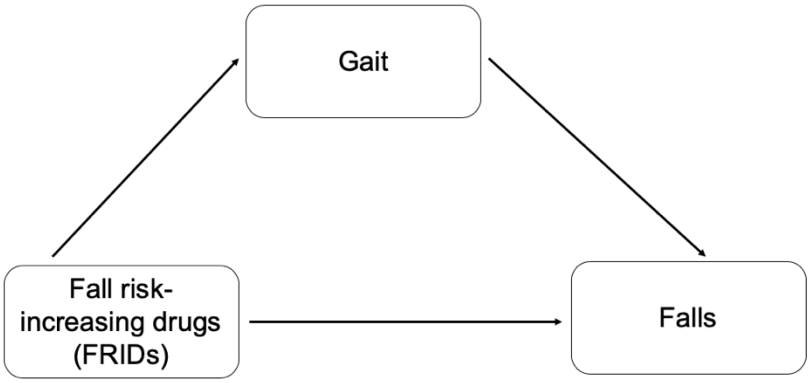

Figure 2.1 The interplay between fall risk-increasing drugs (FRIDs), gait and falls. It is plausible that gait performance could be an intermediate variable on the causal pathway between FRIDs and falls.

In contrast to the body of evidence on the associations between FRIDs and falls as well as gait performance and falls, several knowledge gaps exist when it comes to the relationship between FRIDs and gait. No systematic review focusing on the relationship

between FRIDs and gait performance in community-dwelling older adults has been published to date. Further, the relationship between FRIDs and quantitative gait parameters other than gait speed is understudied. It is important to understand the relationship between FRIDs and parameters such as gait variability which was shown to be associated with increased fall risk and frailty in older adults. In order to address those knowledge gaps, this thesis aims to review the existing evidence on the relationship between psychotropic and cardiovascular FRIDs and investigate the association between these medications and gait performance in a cohort of community-dwelling older adults. The objectives of the thesis are discussed below.

2.2 Objectives

1. To systematically review the published evidence on the association between psychotropic and cardiovascular FRIDs and gait performance in community-dwelling older adults

2. To estimate the cross-sectional association between FRIDs and gait speed in community-dwelling older adults using data from the Gait and Brain Study.

3. To estimate the cross-sectional association between FRIDs and gait variability (quantified by stride time variability) in community-dwelling older adults using data from the Gait and Brain Study.

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Chapter 3

3 Fall Risk-Increasing Drugs and Gait Performance in Community-Dwelling Older Adults: A Systematic Review

3.1 Introduction

Falls are a major public health concern. Falls were the second leading cause of accidental or unintentional injury deaths in 2018 worldwide[1]. In Canada, one third of adults aged 65 years old and over experience at least one fall each year. Falls account for 80% of injury-related hospitalizations among Canadian older adults[2]. In addition, falls are associated with a range of other negative outcomes including fractures, early transition into long-term care, fear of falling, depression and anxiety[2-5]. The economic cost of falls is substantial, both in terms of health system expenditure as well productivity loss; this will become more pressing with the aging of the population[2].

Medication use is one of the main risk factors for falls. Several psychotropic and cardiovascular drugs have been identified as fall risk-increasing drugs (FRIDs). The association between psychotropic drugs and increased fall risk is well-established[6-9]. The evidence on the association between cardiovascular drugs and falls is more mixed; however, associations between the use of diuretics, antihypertensive and antiarrhythmic drugs and falls have been reported in the literature[6,10,11].

The potential underlying mechanisms linking medications with increased fall risk remain unclear. This is due to the large number of prescription drugs, the possibility for drug-drug interactions, and the potential for bias posed by confounding by indication. This is made more complex by the highly multifactorial nature of falling. For these reasons, studying an intermediate variable on the causal pathway such as gait performance may help elucidate the means by which medications increase fall risk.

Gait is a complex process that involves coordination between the nervous, sensory, cardiorespiratory and musculoskeletal systems[15]. Quantitative gait performance measures including gait speed and gait variability have been shown to be robust predictors of fall

risk[12-14]. It is plausible, therefore, that FRIDs may increase fall risk by causing gait impairments.

Despite the large body of research on the association between FRIDs and falls, no systematic review has yet examined the evidence on the effect of FRIDs on gait performance in community-dwelling older adults. A previous literature review from 2013 examined the evidence on the association between FRIDs and postural control in both young and older subjects. It captured only two studies that analyzed gait performance[16]. Therefore, the aim of this systematic review is to evaluate the most up-to-date evidence on the association between FRIDs and quantitative gait performance measures in community-dwelling older adults.

3.2 Methods

The protocol for this systematic review was pre-registered with the PROSPERO – International Prospective Register of Systematic Reviews (ID: CRD42020193949) after the search but prior to study screening. We followed the PRISMA reporting guidelines for systematic reviews[17].

3.2.1 Identification of Studies

Two separate systematic searches were performed in Medline, Embase, PsycINFO and CINAHL. The first search contained the following key concepts: “Gait”, “Psychotropic drug” and “Older adult”. The concept “psychotropic drug” included all psychotropic drug classes identified as potentially fall risk-increasing in the 2019 Beers Criteria for Potentially Inappropriate Medication in Older Adults and by the European Geriatric Medicine Society’s (EuGMS) Task Force on Falls[18,19].

The second search contained the following key concepts: “Gait”, “Cardiovascular drug” and “Older adult”. The concept “Cardiovascular drug” included all cardiovascular drug classes identified as potentially fall risk-increasing by the EuGMS Task Force on Falls[19].

A customized search strategy was created for each database including keywords and MeSH terms. Additional studies were identified by searching grey literature in the Web

of Science Core Collection and the ProQuest Global Theses and Dissertations Database. The reference lists of included articles were checked to identify any missing studies. No date restrictions were applied in any of our searches. We restricted our search to English language studies. The psychotropic search was performed in January 2020 and updated in June 2020. The cardiovascular search was performed in June 2020. The full search strategy is provided in Appendices 3A and 3B for psychotropic FRIDs and cardiovascular FRIDs respectively.

3.2.2 Study Selection

One author (A.O.) screened all titles and abstracts. After this initial screening, two authors (A.O. and N.K.) independently screened full texts. Disagreements were resolved by discussion and a senior author (M.S. or M.M.O.) was consulted when necessary. We included RCTs, observational studies including cohort, case-control, cross-sectional and case-crossover studies that investigated the association between medication use and gait performance. Gait performance was defined as any quantitative gait performance parameter which included the following: gait speed, any measure of gait variability, step time, step width, step length, stride time, stride width, stride length, double support time or cadence.

We included studies with community-dwelling participants who were all aged 60 years and older or in which the mean age of participants was 60 years and older. Studies were excluded if participants had neurodegenerative or neurological diseases that impair mobility. We also excluded studies in which participants were hospitalized or institutionalized as well as studies that assessed falls, balance or postural control without assessing gait performance. Conference abstracts, case reports/case studies, case series, systematic reviews and meta-analyses were also excluded. In the case of different studies using the same cohort, the study with the larger sample size was included.

3.2.3 Quality and Risk of Bias Assessments

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies[20]. The NOS scale was chosen because it assesses several criteria in three domains:

selection, comparability and outcome and it has been used in previous systematic reviews on related topics such as the association between FRIDs and falls which made it easily adapted to this review. A copy of the adjusted scale is provided in Appendix 3C. Each study was given a score between 0 and 9. Studies with a score of 0-3 were considered "low" quality, 4-6 "intermediate" quality and 7 or above "high" quality. In addition, risk of bias assessments were conducted for RCTs included in our review using the Cochrane risk-of-bias tool for randomized trials[21]. Quality assessment and risk of bias assessments were performed independently by two reviewers (A.O. and N.K.). Disagreements were resolved by discussion with the involvement of a senior author (M.S. or M.M.O.) when necessary. Quality and risk of bias assessment results for all studies are provided in the Appendix.

3.2.4 Data Extraction

The following information was extracted from each included study: author, year of publication, study design, country, cohort used, participant characteristics (number of participants, sex and mean age), medication class, gait assessment protocol, quantitative gait performance measures assessed and effect size for each quantitative gait performance measure assessed. Data extraction was performed by the primary author (A.O.) and verified by a second reviewer (N.K.)

3.2.5 Data Synthesis

Study characteristics and findings were summarized using a descriptive approach broken down by drug class. In cases where studies provided both unadjusted and adjusted effect estimates, adjusted estimates were reported in the evidence table and qualitative synthesis. A meta-analysis was not conducted due to the considerable heterogeneity in gait assessment protocols (e.g. distance walked, usual vs. fast pace) as well as different statistical effect measures reported (e.g .regression coefficients, mean differences, etc.) In addition, there was an insufficient number of studies for most drug classes considered to conduct a meta-analysis for each drug class.

3.3 Results

Our first search was conducted to identify studies assessing the association between psychotropic FRIDs and gait performance. This search identified 3187 studies. After removal of duplicates and title and abstract screening, 32 studies underwent full-text screening for eligibility. Twelve studies met the final inclusion criteria (Figure 3.1). Our second search was conducted to identify studies assessing the association between cardiovascular FRIDs and gait performance. This search identified 5568 studies. After removal of duplicates and title and abstract screening, 25 studies underwent full-text screening for eligibility. Eight studies met the final inclusion criteria (Figure 3.2). In total, 20 studies were included in our qualitative synthesis. The characteristics and findings of studies included are outlined below and described in greater detail in table 3.1 for psychotropic FRIDs and table 3.2 for cardiovascular FRIDs.

3.3.1 Characteristics of Included Studies

3.3.1.1 Psychotropic FRIDs

Twelve studies assessed the association between a psychotropic drug class and gait performance in community-dwelling older adults. Of those, eight were cross-sectional studies, two were prospective cohort studies, one was an open-label trial and one was a randomized-controlled crossover trial. Studies were performed in the United States (4), France (4), Australia (2), Finland (1), France (1), Italy (1), Israel (1) and Japan (1).

Psychotropic drug classes assessed included sedatives (5), antidepressants (3), benzodiazepines (3) and antipsychotics (1). Across the twelve studies, gait assessment was conducted over varying distances ranging from 2 m to 10 m. Ten studies assessed normal pace walking while two assessed fast pace walking. All studies assessed gait speed as an outcome except for one study that assessed gait variability only. In addition to gait speed, studies assessed additional quantitative gait performance measures including stride length (3), cadence (3), step width (1), stride time (1) and double support phase (1). Measures of gait variability were assessed in two studies. All studies assessed single-task gait performance. In addition, one study assessed dual-task gait performance

and one study assessed obstructed gait performance.

Quality assessment results for all included studies are provided in the Appendix. In summary, two studies were rated as “high” quality, seven as “intermediate” quality and one as “low” quality (Appendix 3D). One RCT included in our review (Draganich et al.) was assessed to have an overall “low” risk of bias. One open-label trial included in our review (Palecau et al.) was assessed to have an overall “high” risk of bias (Appendix 3F)

3.3.1.2 Cardiovascular FRIDs

Eight studies assessed the association between a cardiovascular drug class and gait performance. Of those, four were prospective cohort studies, three were cross-sectional studies and one was a RCT. Studies were performed in the United States (5), Japan (2) and France (1)

Cardiovascular drug classes assessed included angiotensin-converting enzyme (ACE) inhibitors (3), statins (3), calcium-channel blockers (1) and one study assessed both ACE inhibitors and statins (1). Across the eight studies, gait assessment was conducted over varying distances ranging from 4 m to 20 m. All studies assessed normal pace walking and one study also assessed fast pace walking. All studies assessed gait speed as an outcome. In addition to gait speed, only one study assessed additional quantitative measures of gait performance including stride length, swing time and gait variability. All studies assessed single-task gait performance and none assessed dual-task performance.

Quality assessment results for all included studies are provided in the appendix. In summary, five studies were rated as “high” quality and two were rated as “intermediate” quality (Appendix 3E). One RCT included (Cesari et al.) was assessed to have an overall “unclear” risk of bias (Appendix 3F)

Figure 3.1 PRISMA flowchart for study selection (Psychotropic FRIDs)

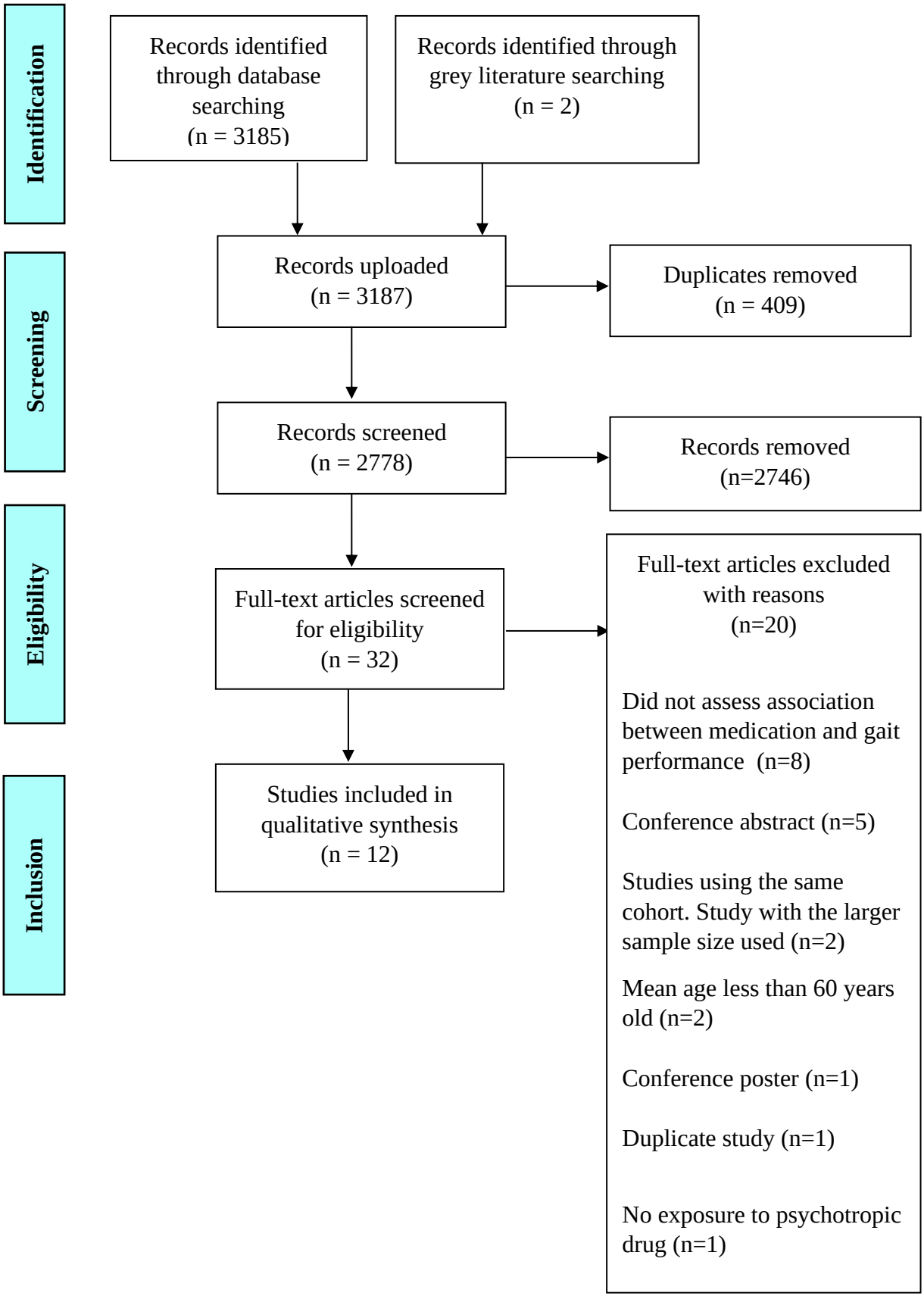
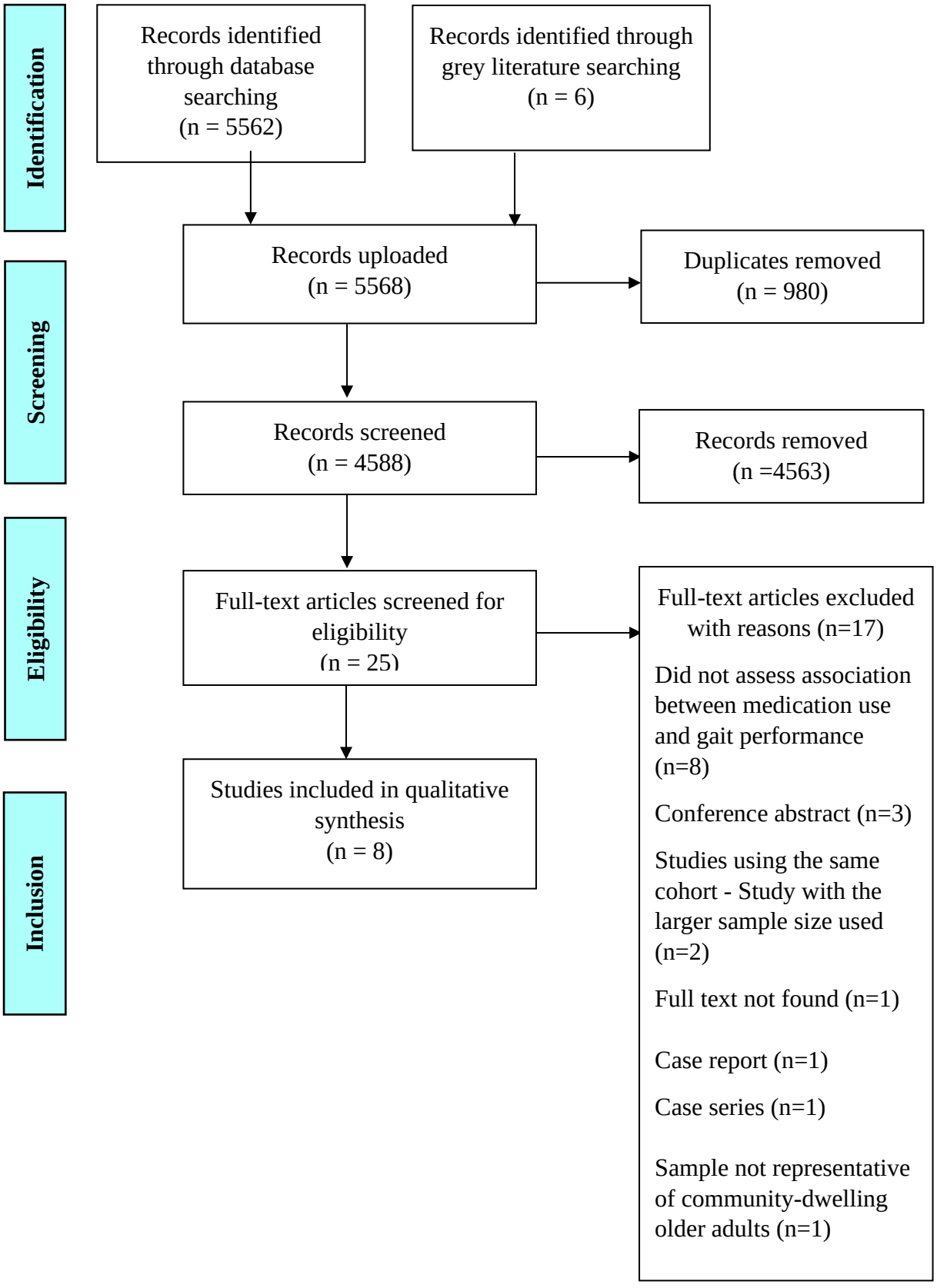


Figure 3.2 PRISMA flowchart for study selection (Cardiovascular FRIDs)



3.3.2 Summary of Findings

3.3.2.1 Psychotropic FRIDs

Antidepressants

Four studies assessed the association between antidepressant use and gait performance. In a crossover RCT, Draganich et al. assessed the impact of single doses of amitriptyline (a tertiary-amine tricyclic antidepressant (TCA)), desipramine (a secondary-amine TCA) and paroxetine (selective serotonin reuptake inhibitor (SSRI)) on unobstructed and obstructed gait performance (n=12)[22]. Obstructed gait performance was assessed by having participants step over obstacles. No significant associations were reported between unobstructed gait performance measures and any of the three drugs. Compared to placebo, amitriptyline significantly reduced obstructed gait speed by as much as 8% and obstructed cadence by as much as 4.9%. No significant associations were reported for either desipramine or paroxetine.

In a cross-sectional study with a large sample size (n=1998), Donoghue et al. found that after adjustment for confounders, non-specific antidepressant use was associated with a significant reduction in gait speed (β = -7.51 cm/s) and stride length (β = -6.78 cm) during single-task walking[23]. Antidepressant use was also associated with significant reductions in gait speed and stride length during dual-task walking. Notably, while antidepressant use was associated with an increase in both stride length coefficient of variation (CV) and stride time CV during single-task walking, it was associated with a decline in both of those measures during dual-task walking; however none of those associations were statistically significant after adjustment.

A cross-sectional study by Poujol et al. assessed the association between the use of antidepressants or benzodiazepines on stride time CV only (n=179)[24]. The study found that, after adjustment for confounders, antidepressant or benzodiazepine use was associated with a significant increase in stride time CV which is a marker of gait instability. However, it is important to note that the authors did not report separate findings for antidepressants and benzodiazepines and analyzed a combined independent

variable for the use of either drug classes. In addition, the authors acknowledged that their cohort consisted of older adults who showed a greater interest in health issues than the general population of older adults.

In contrast to those findings, an open-label label trial by Palecau et al. (n=19) found that SSRI and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant therapy in older adults diagnosed with clinical depression was significantly associated with a 10% increase in gait speed as well as a 9.8% increase in stride length[25]. The study also found that antidepressant therapy significantly reduced stride time variability by 8% which indicates improved gait performance.

Benzodiazepines

Three studies assessed the association between benzodiazepine use and gait performance. In a prospective cohort study with a large sample (n=885), Gray et al. evaluated the association between benzodiazepine use and physical function in community-dwelling older women[26]. They found that after adjustment for confounders, benzodiazepine use was associated with a significant decline in gait speed over four years of follow-up (β = -0.34 m/s). Although no specific figures were provided, the authors reported that they found a dose-response relationship in which higher-than-recommended doses of benzodiazepine were associated with greater declines in overall physical performance. Gray et al. also found that overall physical performance declined significantly more among long-term users of benzodiazepines than short-term users.

A cross-sectional study by Landi et al. found no significant association between benzodiazepine use and gait speed after adjustment in community-dwelling adults aged 80 years and over in a small (n=31) study[27]. Similarly, another cross-sectional study by Eto et al. (n=25) found no significant difference in mean gait speed between users and non-users of benzodiazepines among regular attendees aged 65 years and older of a day care service[28]. The study found that mean step length was 12% lower in benzodiazepine users than non-users. It is worth noting, however, that this study did not adjust for any confounding factors.

Sedatives

Five studies assessed the association between sedative use and gait performance. A prospective cohort study with a large (n=2172) sample by Hilmer et al. assessed the association between Drug Burden Index (DBI) – a measure of overall exposure to medications with anticholinergic and sedative properties – and physical performance in community-dwelling older adults[29]. The study found that at baseline, DBI was significantly associated with slower usual gait speed after adjustment. Greater DBI remained associated with significantly slower gait speed after three and five years of follow-up although the effect size was small (β = -0.01 m/s)

A recent cross-sectional study with a large (n=2087) sample by Lim et al. assessed the association between sedative medication use and physical function in community-dwelling older men [30]. They found that mean gait speed was significantly lower in sedative users than non-users after adjustment for confounders, although the effect size was modest (mean difference = -0.05 m/s).

Similarly, Gnjidic et al. assessed the association between DBI and physical function in community-dwelling older men (n=1705)[31]. They found that the sedative component of the DBI (DBS) was associated with significantly slower gait speed after adjustment for confounders, with a modest effect size (Mean difference = -0.08 m/s).

Furthermore, a cross-sectional study by Taipale el al. (n=700) assessed the association between sedative load – a three-level measure of the cumulative effect of taking multiple drugs with sedative properties – and physical function in a cohort of community dwelling older adults[32]. Notably, the study found consistently lower mean gait speed scores in women than men across all sedative loads (0, 1 and 2). After adjustment for confounders, participants with a sedative load of 1 or 2 had significantly lower mean gait speeds than those with a sedative load of 0. There were no significant differences in mean gait speed between those with sedative loads of 1 or 2.

Finally, a cross-sectional study by Cao et al. (n=932) assessed the association between sedative use and physical function in community-dwelling older women[33]. In contrast to

the aforementioned studies, this study found no significant association between sedative use and gait speed after adjustment for confounders.

Antipsychotics

No study assessed antipsychotics exclusively, although Landi et al. assessed gait performance in a subgroup of participants who used antipsychotics only in their cross-sectional study of the association between anticholinergic drugs and physical function[27]. They found no significant association between antipsychotic use and gait speed after adjustment for covariates although the sample size was small (n=11)

Table 3.1 Characteristics of studies included (Psychotropic FRIDs)

Author (Year of Publication)	Study Design	Participant Characteristics	Drug Class	Gait Assessment Protocol	Quantitative Gait Performance Measures	Summary of Findings
Draganich et al. (2001)[22]	Randomized-controlled crossover trial Washout period: 6 days	n=12 Mean age: 66.9 Country: United States	Antidepressants: Amitriptyline (tertiary-amine TCA) Despiramine (secondary-amine TCA) Paroxetine (SSRI)	Normal walking pace over 9.5-m (Unobstructed) Normal walking pace over 9.5-m encountering obstacles of 3 different heights (Obstructed)	Gait speed, stride length and cadence	Unobstructed gait measures were unaffected by any of the three antidepressants Amitriptyline significantly reduced obstructed gait speed by 8.0% (P=0.028) and cadence by 4.9% (P=0.012)
Paleacau et al. (2007)[25]	Open-label-controlled trial Follow-up period: 10 weeks	n=19 Mean age: 68.6 Clinically depressed Country: Israel	Antidepressants : SNRI (venlafaxine) : 2 participants SSRIs (various) : 17 participants	Normal pace walking over 2-m	Gait speed, stride length, stride time, stride time variability	Antidepressant therapy significantly increased gait speed (pre-therapy: 1.02 m/s post-therapy: 1.13 m/s. P=0.033) and stride length (pre-therapy: 1.12 m to post therapy: 1.23 m. P=0.006). It also significantly decreased stride time variability (pre-

						therapy: 36 ms to post-therapy: 33 ms. P=0.036)
Donoghue et al. (2015)[23]	Cross-sectional	n=1998 Mean age: 68.2 Country: Ireland Cohort: The Irish Longitudinal Study on Aging (TILDA)	Antidepressants	Two normal pace walks over 4.88-m GAITRite walkway followed by two walks under cognitive dual-task conditions	Gait speed, stride length, cadence, step width, double support phase, stride length CV and stride time CV	Antidepressant use was associated with a significant decline in gait speed (β= -7.51 cm/s, P=<0.001) and stride length (β= -6.78 cm, P<0.001) during single-task walking. Associations remained significant in dual-task walking
Poujol et al. (2010)[24]	Cross-sectional	n=179 Mean age: 71.7 County: France	Antidepressant or benzodiazepine	Unspecified	Gait variability (CV of stride time)	Antidepressant or benzodiazepine use was significantly associated with increased gait variability (β=1.56, P=0.002)
Eto et al. (1998)[28]	Cross-sectional	n=53 Age: 65 years old and over Country: Japan	Benzodiazepine	Fast pace walking over 10-m	Gait speed, step length and cadence	Benzodiazepine users had a significantly lower mean step length (38.2 cm) than non-users (41.4 cm) (P=0.04). No adjustment for confounders

Gray et al. (2003)[26]	Prospective cohort Follow-up period: 4 years	n=885 (women only) Mean age: 77.7 Country: United States Cohort: Established Populations for Epidemiologic Studies of the Elderly (EPESE)	Benzodiazepine	Normal pace walking over 2.4-m	Gait speed	Benzodiazepine use was associated with a significant decline in gait speed over 4 years (β: -0.34 m/s) (P=0.002)
Landi et al. (2007)[27]	Cross-sectional	n=364 Mean age: 85.8 Country: Italy Cohort: Study of Aging and Longevity in Sirente (ilSIRENTE)	Benzodiazepine (n=31) Antipsychotics (n=11)	Normal pace walking over 4-m	Gait speed	Mean gait speed was unaffected by benzodiazepine or antipsychotic drug use
Cao et al. (2008)[33]	Cross-sectional	n=932 (women only) Median age: 78 Country: United States Cohort: Women's Health and Aging Study I (WHAS-I)	Sedatives	Normal pace walking over 4-m.	Gait speed	No significant association was observed between sedative and gait speed

Gnijdic et al. (2009)[31]	Cross-sectional	n=1705 (men only) Mean age: 76.9 Country: Australia Cohort: Concord Health and Aging in Men Project (CHAMP)	Sedatives	Normal pace walking over 6-m.	Gait speed	Sedative drug burden was significantly associated with reduced gait speed (P<0.01)
Hilmer et al. (2009)[29]	Prospective cohort Follow-up period: 5 years	n=2172 Mean age: 73 Country: United States Cohort: Health, Aging and Body Composition Study	Sedatives	Normal pace walking over 4-m.	Gait speed	Cumulative exposure to sedative and anticholinergic medications over five years was significantly associated with a decline in gait speed in the sixth year of follow-up (β = -0.01 m/s) (P=0.004)
Taipale et al. (2012)[32]	Cross-sectional	n=700 Mean age: 81.3 Country: Finland Cohort: Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS)	Sedatives	Fast pace walking over 10-m	Gait speed	Exposure to higher sedative load was associated with slower gait speed (P=0.0003)

Lim et al. (2019)[30]	Cross-sectional	n=2087 Mean age: 78.2 Country: Australia Cohort: Australian Longitudinal Study of Aging (ALSA)	Sedatives (n=235)	Normal pace walking over 2.4-m	Gait speed	Sedative drug users had a significantly lower gait speed compared to non-users (Mean difference: -0.05 m/s, P<0.0038)

3.3.2.2 Cardiovascular FRIDs

Angiotensin-Converting Enzyme Inhibitors (ACEI)

Four studies assessed the association between angiotensin-converting enzyme inhibitors (ACEI) and gait performance. A RCT by Cesari et al. assessed the effect of ACEI administration on physical function in a cohort of older adults with a high cardiovascular risk profile (n=257)[34]. After a 6-month long administration of the ACEI fosinopril, no significant difference in mean gait speed was observed between the fosinopril and placebo groups.

A prospective cohort study with a large sample size by Gray et al. (n=5777) assessed the association between ACEI use and physical function in participants in community-dwelling older women[35]. After adjustment for confounders, no significant association was found between ACEI use and gait speed at baseline or during follow-up. It is worth noting however that ACEI use at baseline was significantly associated with reduced mean grip strength which is a measure of frailty status.

A prospective cohort study by Onder et al. also evaluated the association between ACEI use and physical function in a cohort of community-dwelling older women with hypertension (n=641)[36]. They found that after adjustment and, mean 3-year decline in gait speed was 87% lower in continuous than intermittent ACEI users, 89% lower than continuous/intermittent users of other antihypertensives and 90% lower than never users of any antihypertensive drugs. These findings were statistically significant.

A recent cross-sectional study by George and Verghese also assessed the association between ACEI use and gait performance in a cohort of community-dwelling older adults with hypertension (n=281)[37]. In contrast to the study by Onder et al., this study found that ACEI use was associated with significantly reduced gait speed after adjustment for confounders (β = -7.29 cm/s) . Further, the study also assessed additional quantitative gait performance measures including stride length, stride time, stride length variability and stride time variability. ACEI use was associated with significantly reduced stride length after adjustment (β = -6.86 cm) . No significant associations were found between ACEI use and the other gait performance measures assessed.

Statin

Four studies assessed the association between statin use and gait performance. A prospective cohort study with a large (n=5777) sample size by Gray et al. assessed the association between ACEI use and physical function in community-dwelling older women[35]. After adjustment for covariates, no significant association was found between statin and gait speed at baseline or during the 5-year follow-up period. Similarly, another prospective cohort study of community-dwelling older adults by Lo-Ciganic et al. (n=2405) found no significant association between the use of any statin and gait speed over 5-years of follow-up[38]. The authors did report, however, that the use of low-dose statins was associated with slower gait speed decline over 5 years compared to non-use after adjustment for confounders. The authors defined gait speed decline as a decrease of 0.1 m/s or greater in one-year. Further, a recent cross-sectional study by Kawai et al (n=1022) found no significant association between statin use and gait speed in a cohort of community dwelling-older adults[39].

Finally, a prospective cohort study by Dumurgier et al. assessed the association between statin use and the decline in fast walking gait speed in a cohort of community dwelling older adults[40]. In contrast to the rest of the included studies, this study found that statin use was associated with significantly slower gait speed decline over 10 years of follow-up after adjustment for a large number of relevant confounders. The authors did note however that the clinical relevance of their findings was uncertain due to the modest effect size observed (β = 0.67 m/s)

Calcium-channel blockers (CCB)

A cross-sectional study by Deguchi et al. assessed the association between polypharmacy and gait speed in a cohort of older outpatients (n=31)[41]. This study also examined the relationship between gait speed and prescription contents. It was found that mean gait speed among CCB users was 19% lower than among non-users. No differences in mean gait speed were found between users and non-users of other antihypertensives or other vasodilators. It is important to note however the number of CCB users in the sample was small (n=19).

Table 3.2 Characteristics of studies included (Cardiovascular FRIDs)

Author (Year of Publication)	Study Design	Participant Characteristics	Drug Class	Gait Assessment Protocol	Quantitative Gait Performance Measures	Summary of Findings
Onder at al. (2002)[36]	Prospective cohort Follow-up period: 3 years	n=641 (women only) Hypertensive Mean age: 78.9 Country: United States Cohort: Women's Health and Aging I (WHAS-I)	ACE inhibitor (ACEI)	Normal walking pace over 4-m	Gait speed	Mean 3-year decline in gait speed was significantly lower in continuous ACEI users (-1.7 cm/s) than that of either intermittent ACEI users (-13.6 cm/s) (P=0.015) or never users of any drug (-17.9 cm/s) (P=0.001)
Cesari et al. (2009)[34]	Randomized-controlled crossover trial Follow-up period: 6 months Washout period: 3 months	n=257 Mean age: 65.7 Country: United States Cohort: TRAIN Study	ACEI (Fosinopril)	Normal walking pace over 4-m	Gait speed	No significant difference in mean gait speed between drug and placebo groups after 6 months of ACEI administration.
Gray et al. (2012)[35]	Prospective cohort Follow-up period: 6 years	n=5777 (women only) Mean age: 70 Country: United States	ACEI	Normal walking pace over 6-m	Gait speed	No significant differences in mean gait speed between users and non-users at baseline. No difference in mean annual change in gait

		Cohort: Women's Health Initiative (WHI)				speed between users and non-users during follow up.
			Statins	Normal walking pace over 6-m	Gait speed	No significant differences in mean gait speed between users and non-users at baseline. No difference in mean annual change in gait speed between users and non-users during follow up.
George and Verghese (2016)[37]	Cross-sectional	n=281 Hypertensive Mean age (users): 76 Mean age: (non-users): 77.2 Country: United States Cohort: Central Control of Mobility in Aging (CCMA) Study	ACEI	Normal walking pace over 20-ft GAITRite walkway	Gait speed, stride length, swing time, stride length variability, swing time variability	ACEI use was associated with significantly lower mean gait speed (91.7 cm/s) than non-use (97.3 cm/s) (P=0.016). ACEI use was also associated with significantly lower stride length (109.9 cm) than non-use (114.4 cm) (P=0.006)
Dumurgier et al. (2013)[40]	Prospective cohort Follow-up period: 10 years	n=4009 Mean age: 73.4 Country: France Cohort: The Three-City Study	Statins	Normal walking pace over 6-m. Fast walking pace over 6-m	Gait speed	Statin use at baseline was associated with a slower decline in fast walking speed over 10 years of follow-up (β=0.67 m/s, P= <0.001)

Lo-Ciganic et al. (2014)[38]	Prospective cohort Follow-up period: 5 years	n=2405 Mean age: 74.6 Country: United States Cohort: Health, Aging and Body Composition Study	Statins	Normal walking pace over 20-m	Gait speed	Statin use was not associated with gait speed decline over the follow-up period
Kawai et al. (2018)[39]	Cross-sectional	n=1022 Mean age: 73.4 Country: Japan	Statins	Normal walking pace over 6-m. Fast walking pace over 6-m	Gait speed	No significant association was observed between statin use and normal gait peace
Deugchi et al. (2019)[41]	Cross-sectional	n=31 Mean age: 79 Country: Japan	Calcium channel-blockers	Normal walking pace over 5-m	Gait speed	Users of calcium channel-blockers had a significantly lower gait speed (0.93 m/s) than non-users (1.15 m/s) (P=0.02)

3.4. Discussion

This systematic review investigated the current evidence on the association between cardiovascular and psychotropic FRIDs and gait performance in community-dwelling older adults. The drug classes examined were those identified as fall risk-increasing by the Beers Criteria as well as the EuGMS Task Force on Falls[18,19]. A total of 20 studies were included in this review: 12 assessed the association between psychotropic FRIDs and gait performance, and eight assessed the association between cardiovascular FRIDs and gait performance. Overall, our review suggests that the use of drugs with sedative properties is associated with reduced gait speed in community-dwelling older adults, with the interesting exception of one open-label pre-post study that found that antidepressant therapy was associated with increased gait speed and stride length, and decreased stride time variability among older adults with clinical depression.[25] We also found that statin use is not associated with impaired gait performance in community-dwelling older adults across the included studies with the exception of a large cohort study that showed slower declines in fast walking speed among those taking statins at baseline. The evidence on other drug classes was mixed. Additionally, there was an insufficient number of studies that assessed quantitative gait parameters other than gait speed to be able to draw conclusions about the effects of these drugs on these specific aspects of gait that are emerging as sensitive prognostic indicators of fall risk and other health outcomes. A discussion of the review findings for each drug classes is provided below

Our review suggests that the use of drugs with sedative properties is associated with a decline in gait speed in community-dwelling older adults. This association was reported in four of the five studies included in our review that examined the association between sedative use and gait performance. These findings are consistent with the known effects of sedatives on psychomotor slowing. It is important to note that sedatives are a broad drug class comprising several drugs with sedative properties, which could be assessed as stand-alone exposures such as benzodiazepines, antidepressants and hypnotics among others. In order to account for this, we observed that studies have used aggregate measures of sedative exposure such as the drug burden index (DBI) and the sedative load model. The DBI incorporates the usage of drugs with anticholinergic properties and those

with sedative properties[42]. The sedative load model assigns a sedative rating to each drug based on its own sedative properties. A cumulative sum of those sedative ratings then produces the sedative load.[43] Importantly, only one of the five included studies was longitudinal which supports the need for more studies to establish causality between sedative use and reduced gait speed over time. Additionally, given that one study found that female sedative users had lower gait speeds than male users, further research is required to confirm if sex differences exist in the impact of sedative use on physical function. Our review also supports the need for research on the association between sedative use and quantitative gait performance measures other than gait speed since none of the included studies assessed those parameters. The increasing availability of electronic walkways and accelerometer-based wearables should enable more studies of these parameters than the first studies of gait speed which could be done using only a stop watch and a measured course.

Three studies assessed the association between antidepressant use and gait performance and only one of those had a large sample size. It is plausible that due to the now well-established association between antidepressant use and falls, physicians have become less likely to prescribe antidepressants for older adults or are more likely to encourage older adults to discontinue antidepressant use. Additionally, although there are several subclasses of antidepressants, only one of three included studies that examined antidepressant use reported separate results for different subclasses of antidepressants. Donoghue et al. reported that non-specific antidepressant use was associated with reduced gait speed and stride length during both single and dual-task walking[23]. In contrast, Draganich et al. found that amitriptyline – a tertiary amine TCA – significantly reduced obstructed gait speed and cadence while unobstructed gait was not affected by TCAs or SSRIs[22]. This is consistent with evidence that TCAs may have a stronger effect on psychomotor and cognitive function than SSRIs due to their greater sedating properties[44]. Our review supports the need for further investigation into the differential effects of subclasses of antidepressants on gait performance.

Our review also suggests that the presence of depression should be taken into account when considering the impact of antidepressants on gait performance. The open-label trial

by Palecau et al. showed that antidepressant use improved gait speed and gait variability in community-dwelling older adults diagnosed with clinical depression[25]. Although the study has a high risk of bias due to its open-label design, its findings are consistent with evidence showing that depression is associated with gait impairment therefore depressed older adults are likely to have lower baseline gait performance[45]. One interpretation of this study is that any possible pharmacologic effects of antidepressant therapy on slowing gait are more than offset by the effects of the drug on treating depression.

The evidence on the association between benzodiazepine use and gait performance was inconclusive which was notable given that benzodiazepines have sedative properties and share similar adverse effects on psychomotor functioning with tricyclic antidepressants. This can be attributed to several factors. Similar to antidepressants, only three studies examined the effect of benzodiazepine use on gait in older adults in our review. Of those, only one assessed the effect of benzodiazepine use in a large cohort of community-dwelling older women[26]. The two remaining studies assessed the effect of benzodiazepine use in small subgroups of benzodiazepine-only users from a larger cohort and a random sample of patients in a day clinic respectively[27,28]. Additionally, the only study that found an association between benzodiazepine use and gait was a longitudinal study. Our review thus supports the need for well-designed longitudinal studies to produce more conclusive evidence on the association between benzodiazepine use and gait performance. Similar to antidepressants, there exist different subclasses of benzodiazepines. There is evidence that long-acting benzodiazepines have a greater fall risk-increasing effect than short-acting ones thus there is a need for more research into the differential effects of benzodiazepine subclasses on gait performance[7].

Our review suggests that there is no association between statin use and gait speed decline in community-dwelling older adults. Although Dumurgier et al. found that statin use at baseline was associated with a slower reduction in gait speed over ten years of follow-up, the authors highlighted that the clinical relevance of their finding was uncertain[40]. Additionally, de Vries et al. found in their meta-analysis that statin use had a protective effect on fall risk in older adults[10]. These findings along with the findings herein are remarkable given the known adverse effects of statin on muscle function and

structure[46,47]. One potential explanation is that because of those potential adverse effects, physicians are less likely to prescribe statins for frail older adults who are clearly at risk of reduced physical function. Nonetheless, given the prevalence of statin use among older adults in general, our review supports the need for research into the association between statin use and quantitative gait parameters other than gait speed.

Our review highlights the conflicting evidence on the association between ACEI use and gait performance in older adults. Particularly, the impact of ACEI use on gait in hypertensive patients is of interest given that hypertension was shown to be associated with impaired gait performance[48,49]. In a cross-sectional study, George and Verghese found that ACEI use was associated with reduced gait speed among hypertensive community-dwelling older adults[37]. In contrast, Onder et al. found in a longitudinal study that ACEI use was associated with slower gait speed decline in hypertensive older women over 3 years[36]. Given the difference between study designs, it is plausible that the positive effect of ACEI in slowing gait speed decline in the longitudinal study can be attributed to their therapeutic effect on hypertension over time. The two other included studies in our review, one of which was a RCT, found no association between ACEI use and gait performance[34,35]. Given this inconclusive evidence, our review supports the need for further research in this area particularly through clinical trials in both hypertensive and non-hypertensive older adults.

3.4.1 Strengths and Limitations

To the best of our knowledge, this is the first systematic review to focus specifically on the association between FRIDs and gait performance in community-dwelling older adults. We searched four databases as well as two sources of grey literature, without date restrictions. Our review does have potential limitations. With respect to generalizability, our findings are restricted to community-dwelling older adults without neurodegenerative or neurological diseases. The effects of medications on gait is a relatively recently emerging topic and there is a of lack of consensus on drug classes that are considered fall risk-increasing. We relied on guidelines such as the Beers criteria as well as the EuGMS position paper on FRIDs to identify drug classes for inclusion in our search strategy. As a

result, studies of gait performance in drug classes that were not identified as FRIDs in those guidelines were not included in our review. As stated earlier, a meta-analysis was not possible due to the inconsistency in statistical effect measures, insufficient number of studies for each drug class and heterogeneity in gait assessment protocols. The lack of meta-analysis means that evidence of potential publication bias cannot be examined using symmetrical funnel plots. Importantly, while the majority of observational studies included in our review adjusted for known strong confounders, residual confounding and confounding by indication cannot be ruled out. Several studies included in our review also did not consider important pharmacologic factors such as dosage, duration of use and medication adherence. Finally, the restriction of study selection to English language studies means that potentially relevant non-English studies would have been missed.

3.5. Conclusion and Implications for Practice and Research

Our systematic review examined the current evidence on the association between psychotropic and cardiovascular FRIDs and gait performance in community-dwelling older adults. We found that the use of drugs with sedative properties is associated with reduced gait speed in older adults. Due to the myriad of adverse events associated with slowing gait in older adults , including falls and fracture, caution should be taken in clinical settings when prescribing those medications to older patients. Our review also shows that statin use is not associated with gait speed reduction in older adults, although further research is needed to assess the impact of statin use on other quantitative gait performance measures.

Importantly, our review also identified several knowledge gaps to be addressed in future research. In contrast to the large body of evidence on the association between FRIDs and falls in older adults, the current evidence on the association between FRIDs and gait performance in older adults is limited and conflicting. This is particularly true for cardiovascular FRIDs. With the exception of statins and ACEI, our review did not identify studies that examined the impact of other cardiovascular FRIDs on gait performance. This might be attributed to the current lack of consensus over which cardiovascular drug classes qualify as FRIDs and to the fact that gait performance has not

traditionally been considered as an outcome of interest in studies of cardiovascular drugs. More broadly, there is a need for more longitudinal research on the association between FRIDs and changes in gait performance. Longitudinal research is important not only to establish temporality but also to discern the impact of factors such as long-term use and medication adherence.

Our review also identified knowledge gaps in gait assessment. Only six studies included in the review assessed quantitative gait parameters other than gait speed. This made it difficult to draw any conclusions about the impact of FRIDs on gait parameters other than gait speed for any of the drug classes assessed. These parameters are important indicators of gait performance and provide information about rhythm and pace of gait. Additionally, only two studies assessed gait performance under dual-task or obstructed conditions. Our findings support the need for more research in those areas in order to produce more conclusive evidence on the association between FRIDs and gait performance in older adults which will in turn help elucidate the causal mechanisms linking FRIDs with increased fall risk in older adults.

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Chapter 4

4 Fall Risk-Increasing Drugs and Gait Performance in Community-Dwelling Older Adults: Results from the Gait and Brain Study

4.1 Introduction

Falls in older adults are a major public health concern worldwide. Falls were the second-leading cause of death from unintentional injury in 2018[1]. One-third of adults aged 65 years old and over fall at least once each year[2]. In addition, falls are associated with a range of negative health outcomes including fractures, anxiety, depression, disability and accelerated transition into long-term care as well as a significant economic cost[2-6]. Falls will become a more urgent challenge with the aging of the population.

Prescription medication use is a major risk factors for falls. Several psychotropic and cardiovascular drug classes have been identified as fall risk-increasing drugs (FRIDs) in older adults[7-9]. Clinical guidelines such as the Beers criteria recommend against the use of psychotropic drugs in older adults with a history of falls or fractures[10].

Gait impairment is another major risk factor for falls in older adults. Gait performance can be assessed through quantitative gait parameters that correspond to different phases of the gait cycle. Gait speed, usually measured at usual walking pace over a measured course, has been shown to be a robust predictor of future falls as well as several health outcomes including cognitive function, disability, and mortality[11,12]. Gait variability is another aspect of gait performance which quantifies stride-to-stride fluctuations in gait parameters such as stride time and step width during walking. High gait variability is a marker of gait instability and was shown to be associated with increased fall risk and the frailty syndrome[13,14]. Gait control is a complex process that involves coordination between different bodily systems including the nervous, cardiorespiratory and musculoskeletal systems. It is therefore plausible that gait control is affected by FRID use. Given that gait impairment could be an intermediate variable on a causal pathway

between FRID use and increased fall risk, it is important to better understand the impact of FRID use on gait performance.

There is a large body of existing evidence on the association between FRIDs and falls in older adults, and a growing literature on the effects of gait performance on fall risk. By contrast, evidence on the association between FRIDs and gait performance is limited. A small number of previous studies have shown that the use of sedative drugs is associated with reduced gait speed in community-dwelling older adults[16-18]. With the exception of statins and angiotensin-converting enzyme inhibitors (ACE inhibitors), the evidence on the association between cardiovascular FRIDs and gait performance in older adults is scarce. In addition, there remains a knowledge gap on the impact of FRIDs on gait parameters other than gait speed such as stride time variability.

The aim of this study was to evaluate the cross-sectional associations between FRID use and gait performance measures including gait speed and stride time variability in community-dwelling older adults using data from Gait and Brain Study.

4.2 Methods

4.2.1 Study Population and Data Collection

The study analyzed baseline data collected from participants enrolled in the Gait and Brain Study, an ongoing prospective cohort study with up to 15 years of follow-up designed to investigate whether gait impairments can predict falls, frailty, cognitive impairment and progression to dementia. Study design and logistics have been described in detail elsewhere[19]. After obtaining written consent, participants underwent demographic, functional, neuropsychological and gait assessments at baseline. To be included in the study, participants had to be community-dwelling older adults 65 years or older and able to walk 10 m independently without a gait aid. Exclusion criteria included lack of English proficiency, Parkinson's disease or any neurological disorder with motor deficits and active major depression. Ethics approval was obtained from the University of Western Ontario Health Sciences Research Ethics Board. Data collection occurred between July 2007 and June 2016.

4.2.2 Gait Assessment

Gait performance was assessed using the GAITRite electronic walkway (GAITRite system, 600 cm long and 64 cm wide; CIR Systems Inc, Franklin, NJ). Assessments were based on a validated and standardized gait protocol. Start and endpoints were marked on the floor 1 m from the start and end of the walkway to avoid recording the acceleration and deceleration phases. Every participant performed a practice trial on the walkway prior to the assessment. Gait variability was assessed in addition to gait speed. Gait variability was measured as the coefficient of variation (CV) of stride time [Stride time CV = (standard deviation of mean stride time/mean stride time) x 100]. Stride time CV was chosen as a measure of gait variability because it was shown to be robust predictor of falls[13,14].

4.2.3 Medication Ascertainment

Medications taken by each participant at baseline were recorded using validated questionnaires and verified using participants' electronic medical records. For the purposes of the Gait and Brain Study, the trade name of each medication was manually looked up and classified by the study assessors under one of the following classes: neuroleptics, antidepressants, benzodiazepines, alpha-blockers, beta-blockers, vasodilators, diuretics, statin and aspirin.

4.2.4 Covariates

Factors that could potentially confound the association between drug use and gait performance were identified based on clinical judgement and a review of the literature. Data was collected at baseline on demographic variables including age, sex and years of education. Body mass index (BMI) was calculated using self-reported weight and height. Cognitive function was assessed using the Mini-Mental State Examination (MMSE). The presence of depressive symptoms was assessed using the Geriatric Depression Scale (GDS). Physical activity level was determined based on self-reported general activity. In addition, presence of the following co-morbidities at baseline was ascertained through self-report: osteoarthritis, osteoporosis, congestive heart failure (CHF), history of

myocardial infarction, angina, atrial fibrillation, hypertension, lung disease, diabetes mellitus, history of stroke, history of transient ischemic attack (TIA), vision impairment and hearing impairment.

4.3 Statistical Analysis

The frequency of use for each drug class (percentage) was determined. Descriptive statistics were generated using mean and standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. Multiple linear regression models were created to assess the association between each drug class and each of the two gait performance outcomes, mean gait speed in cm/sec. and stride time CV [Stride time CV = (standard deviation of mean stride time/mean stride time) x 100]. The drug classes tested included antidepressants, benzodiazepines, beta-blockers, alpha-blockers, vasodilators, diuretics, statin and aspirin. Each drug class was assessed separately. In each model, age and sex interactions with the drug were tested. We did not run models testing the association between neuroleptics and gait performance due to small cell size (n=4). The stride time CV variable was log-transformed in order to satisfy the normality assumption for the linear regression analysis. All statistical analyses were run using Stata 16.

Each crude (unadjusted) model was adjusted for age, sex, years of education, BMI, MMSE score, GDS score, general activity level, and use of other FRIDs. In addition, to minimize confounding by indication, a comorbidity propensity score was created for each drug class using logistic regression. The propensity score model was created using the drug class (exposure) as the dependent variable and the comorbidities associated with that drug class as well as those associated with the gait variable (outcome) as independent variables. The propensity score was then included as a covariate in the multiple linear regression model testing the association between the drug class of interest and the gait variable of interest. This adjusted for the conditional probability that the drug was used given the presence of the specified comorbidities. Confounding by indication and propensity scoring are discussed conceptually in greater detail in the following sections

4.3.1 Confounding by Indication

Confounding by indication is a common source of bias in pharmaco-epidemiological observational studies. It is defined as distortion of an association between an exposure and an outcome the presence of an indication for the exposure which happens to be the true cause of the outcome[20]. In a clinical context, it arises when the clinical indication for a specific treatment also affects the outcome. More specifically, in our study, confounding by indication arises due to the presence of comorbidities that are potentially associated with impaired gait performance (Figure 4.1). Several of those comorbidities could also be indications for FRIDs. For example, there is evidence that depression is associated with impaired gait performance in older adults[21]. At the same time, depression is also an indicator for antidepressant use. As a result, an association between antidepressant use and an impaired gait performance measure (e.g. reduced gait speed) could be distorted by the presence of depression.

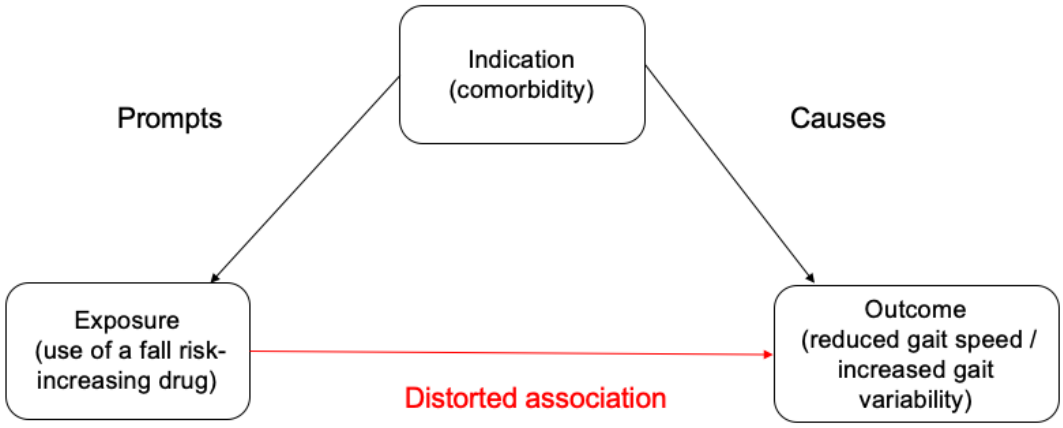

Figure 4.1 The principle of confounding by indication. The figure shows the general principle along with an example of how it arises in our study. A comorbidity that is a clinical indication for a fall risk-increasing drug can distort an association between the drug and the gait outcome.

Confounding by indication cannot be eliminated in observational studies because treatment assignment is based on clinical indications rather than randomization however it can be minimized in statistical analyses. In our study, we opted to use propensity score adjustment to adjust for confounding by indication due to comorbidities.

4.3.2 Comorbidity Propensity Scoring

Propensity scoring is commonly used to control for confounding variables in pharmaco-epidemiological studies[22,23]. The propensity score was first defined by Rosenbaum and Rubin as the conditional probability of assignment to a particular treatment given the vector of observed covariates[24].

$$PS(X) = \Pr(Z = 1 | X)$$

$$PS(Comorbidity) = \Pr(FRID\ use = 1 \mid Comorbidity)$$

Figure 4.2. The propensity score (PS). The top line illustrates the general propensity score function. The bottom line illustrates the function in the context of the study. The comorbidity propensity score is conditional probability of FRID use given the comorbidities specified in the propensity score model.

In our study, we generated a "comorbidity propensity score" for each drug class of interest. These scores were generated using logistic regression models in which the drug class of interest was the dependent variable and the comorbidities were the independent variables. In generating a propensity score model, Rubin recommended the inclusion of variables that are strongly related to the outcome[25]. Similarly, Brookhart et al, recommended the inclusion of variables that are related to the outcome regardless of whether or not they were related to the exposure[26].

Since different comorbidities were associated with gait speed and gait variability, we generated two sets of comorbidity propensity score models. One for the association between every FRID class and gait speed (Appendix 4A) and another for the association between every FRID class and stride time variability (Appendix 4B). In generating our comorbidity propensity score models, we included comorbidities that were associated with either the a) the drug class of interest (exposure) or b) the gait variable of interest (outcome). The models were generated using the PSCORE command in Stata (Figure 4.3). This command verifies that the balancing property of the propensity score model is satisfied and provides a warning when it is not. We also calculated a c-statistic and

conducted a Hosmer-Lemeshow good-of-fitness test to ensure model fit for each of the comorbidity propensity score models we generated.

```
pscore T0_SSRI T0_oa T0_chf T0_angina T0_dm T0_vision T0_Hear T0_htn T0_depress, logit pscore(SSRIpsc
ore)
```

Estimation of the propensity score

```
Iteration 0:   log likelihood = -127.97957
Iteration 1:   log likelihood = -104.44435
Iteration 2:   log likelihood = -97.409352
Iteration 3:   log likelihood = -97.321202
Iteration 4:   log likelihood = -97.320979

Logistic regression                               Number of obs   =        319
                                                  LR chi2(8)      =      61.32
                                                  Prob > chi2     =     0.0000
Log likelihood = -97.320979                       Pseudo R2       =     0.2396
```

T0_SSRI	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_oa	.832234	.3796338	2.19	0.028	.0881653	1.576303
T0_chf	.0911159	.9819039	0.09	0.926	-1.83338	2.015612
T0_angina	-.6524121	.8822377	-0.74	0.460	-2.381566	1.076742
T0_dm	.2393716	.4976909	0.48	0.631	-.7360847	1.214828
T0_vision	-.2958052	.4241601	-0.70	0.486	-1.127144	.5355333
T0_Hear	.4401872	.3798645	1.16	0.247	-.3043336	1.184708
T0_htn	.6562622	.3908907	1.68	0.093	-.1098695	1.422394
T0_depress	2.518229	.3915911	6.43	0.000	1.750725	3.285734
_cons	-3.74678	.4724779	-7.93	0.000	-4.67282	-2.820741

Description of the estimated propensity score

Estimated propensity score

	Percentiles	Smallest		
1%	.0172493	.0139971		
5%	.0172493	.0172493		
10%	.0230498	.0172493	Obs	319
25%	.0334712	.0172493	Sum of Wgt.	319
50%	.0546221		Mean	.137931
		Largest	Std. Dev.	.1645857
75%	.1788209	.655589		
90%	.4021975	.6682171	Variance	.0270885
95%	.5109657	.6880993	Skewness	1.566521
99%	.655589	.7189994	Kurtosis	4.352252

```
************************************************************
Step 1: Identification of the optimal number of blocks
Use option detail if you want more detailed output
************************************************************

The final number of blocks is 4

This number of blocks ensures that the mean propensity score
is not different for treated and controls in each block


************************************************************
Step 2: Test of balancing property of the propensity score
Use option detail if you want more detailed output
************************************************************

The balancing property is satisfied
```

Figure 4.3 Estimation of comorbidity propensity score on Stata. The example shown here is for antidepressants (SSRIs). The PSCORE command is used to generate a logistic regression model using the drug as the dependent variable and comorbidities associated with the drug or gait speed as independent variables.

The comorbidity propensity score was then included as a covariate in the multiple linear regression analysis testing the association between the drug class of interest and the gait variable of interest. This adjusted for the conditional probability that the drug was used given the presence of the specified comorbidities. For example, the comorbidity propensity score for statin was included as a covariate in the linear regression model testing the association between statin and gait speed. This adjusted for the conditional probability that statin was used given the presence of comorbidities associated with either statin or gait speed.

4.3.3 Sensitivity Analysis

Regression diagnostics were run to ensure model fit and that regression assumptions were satisfied. 90% of participants in the study had complete data for the all the variables used in our analysis. For our main analysis, we conducted a complete case analysis. To account for potential bias due to missing data, multiple imputation was conducted and regression models were re-run using imputed values. We used multiple imputation by chained equations (MICE) on Stata 16. Sensitivity analysis results are shown in Appendix 4C.

4.4 Results

4.4.1 Characteristics of the Study Population

Baseline characteristics of the study population are shown in table 4.1 A total of 345 participants were assessed (mean age: 72 years old, S.D.: 6.55). The prevalence of polypharmacy (five or more medications) among the participants was 66%. The prevalence of each comorbidity among the participants is shown in table 4.1. The most common comorbidity was hypertension (45%). Frequency of FRID use is shown in table 4.2. Statin was the most commonly used drug class among study participants (41%) followed by aspirin (31%) and vasodilators (22%).

4.4.2 The Association between FRID Use and Gait Speed

In the crude model (model 1), statistically significant associations between FRID use and reduced gait speed were found for SSRIs, aspirin, statin, beta-blockers and diuretics. After adjustment for demographic confounders (age, sex and years of education) (model 2), these associations remained statistically significant for SSRIs, statin and diuretics. In the fully adjusted model (model 3), only diuretic use was significantly associated with reduced gait speed. Notably, after adjustment for confounders, there was an association between vasodilator use and increased gait speed however this association was not statistically significant. No statistically significant age or sex interactions were observed for any of the drug classes thus those terms were dropped from the models. Full results for the associations between FRID use and gait speed are shown in table 4.3

4.4.3 The Association between FRID Use and Stride Time Variability (Stride Time CV)

In the crude model (model 1), statistically significant associations between FRID use and increased stride time variability were found for statin and alpha-blockers. After adjustment for demographic confounders (model 2), statin use was significantly associated with increased stride time variability. This association remained statistically significant in the fully adjusted model (model 3). No statistically significant age or sex interactions were observed for any of the drug classes thus those terms were dropped from the models. Full results for the associations between FRID use and stride time variability are shown in table 4.4

Table 4.1 Baseline Characteristics of the Study Population, n=345

Demographic characteristics	
Age, mean (SD)	72.4 (6.6)
Years of education , mean (SD)	14.6 (3.2)
Female, n (%)	198 (58.6)
Health-status characteristics	
Body Mass Index (BMI), mean (SD)	28.1 (5.4)
Mini-Mental State Examination (MMSE) score , mean (SD)	27.5 (2.2)
Geriatric Depression Scale (GDS) score, mean (SD)	2.4 (2.7)
Number of falls within the past year, mean (SD)	0.6 (1.4)
Polypharmacy, n (%)	228 (66.1)
Suffered falls within the past year, n (%)	109 (32.3)
Fear of falling, n (%)	45 (13.4)
Smoking, n (%)	104 (31.3)
General activity level, n (%)	
Vigorously Active	141 (42.0)
Moderately Active	144 (43.0)
Seldom Active	46 (13.0)
Comorbidities	
Number of comorbidities , mean (SD)	5.1 (2.7)
Comorbidities, n (%)	
Depression	88 (26.4)
Cardiac diseases	52 (15.4)
Myocardial infarction	20 (5.9)
Angina	19 (5.6)

Hypertension	155 (45.9)
Lung disease	21 (6.2)
Stroke or Transient ischemic attack	35 (10.4)
Osteoarthritis	126 (37.3)
Osteoporosis	53 (15.7)
Diabetes milletus	51 (15.1)
Visual impairment	116 (34.3)
Hearing impairment	122 (36.1)
Cancer	78 (23.1)

Table 4.2 Medication Use in the Study Population

Drug class	**n (%)**
Neuroleptics	4 (1.2)
Antidepressants	45 (13.3)
Benzodiazepines	20 (5.9)
Beta-blockers	55 (16.3)
Alpha-blockers	25 (7.4)
Vasodilators	73 (21.7)
Diuretics	62 (18.3)
Statin	139 (41.1)
Aspirin	104 (30.8)

Table 4.3 The Associations between FRID use and Gait Speed (cm/s)

	Model 1		Model 2		Model 3	
Drug class	**Coefficient (95% CI) (cm/s)**	**P-value**	**Coefficient (95% CI) (cm/s)**	**P-value**	**Coefficient (95% CI) (cm/s)**	**P-value**
Antidepressants	-10.06 (-16.91, -3.21)	**0.004**	-7.23 (-13.59, -0.87)	**0.026**	-1.90 (-8.68, 4.88)	0.582
Benzodiazepines	-2.93 (-12.91, 7.04)	0.563	-1.79 (-11.13, 7.56)	0.707	-1.29 (-10.21, 7.62)	0.776
Diuretics	-10.91 (-16.88, -4.94)	**<0.001**	-10.49 (-15.98, -5.00)	**<0.001**	-7.97 (-13.94, -2.00)	**0.009**
Statin	-9.50 (-14.18, -4.82)	**<0.0001**	-6.64 (-11.14, -2.14)	**0.004**	-1.47 (-6.23, 3.30)	0.546
Vasodilators	-2.20 (-7.93, 3.53)	0.45	0.27 (-5.02, 5.57)	0.919	4.83 (-0.66, 10.31)	0.084
Beta-blockers	-7.59 (-13.96, -1.21)	**0.02**	-5.82 (-11.77, 0.13)	0.055	-3.13 (-9.42, 3.16)	0.328
Alpha-blockers	-5.77 (-14.74, 3.21)	0.207	-3.29 (-11.93, 5.36)	0.455	-6.20 (-14.59, 2.20)	0.147
Aspirin	-5.34 (-10.41, -0.27)	**0.039**	-3.18 (-7.98, 1.62)	0.194	-0.14 (-4.96, 4.68)	0.954

Model 1 is unadjusted (crude)
Model 2 is adjusted for age, sex and years of education
Model 3 is adjusted for age, sex, years of education, Body Mass Index (BMI), Geriatric Depression Scale (GDS) score, Mini-Mental State Examination (MMSE), general activity level, other FRID use and comorbidity propensity score.

Table 4.4 The Associations between FRID Use and Stride Time Variability (Stride Time CV)

	Model 1		Model 2		Model 3	
Drug class	**Coefficient (95% CI)**	**P-value**	**Coefficient (95% CI)**	**P-value**	**Coefficient (95% CI)**	**P-value**
Antidepressants	0.11 (-0.03, 0.25)	0.127	0.09 (-0.05, 0.23)	0.221	0.01 (-0.15, 0.17)	0.905
Benzodiazepines	0.07 (-0.14, 0.27)	0.511	0.11 (-0.10, 0.31)	0.31	0.12 (-0.09, 0.32)	0.270
Diuretics	0.03 (-0.10, 0.15)	0.658	0.04 (-0.09, 0.16)	0.553	-0.05 (-0.18, 0.09)	0.515
Statin	0.16 (0.06, 0.26)	**0.001**	0.14 (0.04, 0.24)	**0.004**	0.13 (0.02, 0.24)	**0.026**
Vasodilators	0.04 (-0.08, 0.16)	0.504	0.01 (-0.10, 0.12)	0.861	-0.05 (-0.17, 0.08)	0.491
Beta-blockers	0.07 (-0.06, 0.21)	0.267	0.07 (-0.06 0.20)	0.27	0.09 (-0.05, 0.24)	0.209
Alpha-blockers	0.20 (0.02, 0.38)	**0.034**	0.16 (-0.03, 0.35)	0.096	0.15 (-0.05, 0.34)	0.144
Aspirin	0.07 (-0.04, 0.17)	0.21	0.04 (-0.06, 0.15)	0.447	-0.01 (-0.12, 0.11)	0.898

Model 1 is unadjusted (crude)
Model 2 is adjusted for age, sex and years of education
Model 3 is adjusted for age, sex, years of education, Body Mass Index (BMI), Geriatric Depression Scale (GDS) score, Mini-Mental State Examination (MMSE), general activity level, other FRID use and comorbidity propensity score

4.5 Discussion

In this cohort of 345 community-dwelling older adults, diuretic use was associated with reduced gait speed and statin use was associated with increased stride time variability. These associations remained statistically significantly after adjustment for covariates. Although the associations were not statistically significant, we found that vasodilator use was associated with increased gait speed and reduced stride time variability both of which are markers of improved gait performance.

To the best of our knowledge, ours is the first study to report an association between diuretic use and reduced gait speed in older adults. This association is consistent with existing evidence on the association between diuretic use and increased fall risk. Longitudinal research is required to establish whether this association between diuretic use and reduced gait speed in older adults is causal. Loop diuretics have a greater natriuretic effect than thiazide diuretics and they can generate hypovolemia therefore they may have a greater fall risk-increasing effect. Future research should consider whether loop diuretics would have a more detrimental effect on gait performance than thiazide diuretics[27]. The biological mechanisms behind diuretic use and gait performance and increased fall risk are not well understood. Besides the hypovolemic effect of loop diuretics which can exacerbate postural blood pressure changes, thiazide diuretics can cause hypokalemia and hyponatremia both of which were shown to be associated with reduced alertness and increased fall risk[28].

We found no statistically significant association between statin use and reduced gait speed. This is consistent with several previous studies[29,30,31]. While one study found that statin use was associated with a slower decline in fast-walking speed over 10 years of follow-up, the authors noted that the clinical relevance of their finding was uncertain[32]. In contrast, we found that statin use was associated with increased stride time variability which is an indicator of gait instability and increased fall risk. Statin is associated with adverse effects on muscle structure and function, including increased risk of myopathy, which may explain this finding[33,34]. We did not find any published studies that investigated the association between statin and gait variability measures therefore further

research is needed to corroborate our findings and determine their clinical relevance. This is particularly important given the high prevalence of statin use among older adults which was also reflected in our study. Statin was the most commonly-used drug class in our cohort (41% of participants in our study were statin users).

We found that after adjustment for demographic variables (age, sex and years of education), vasodilator use was associated with increased gait speed. This association was not statistically significant in the fully adjusted model. Similarly, vasodilator use was associated with reduced stride time variability in the fully adjusted model. This association was also not statistically significant and the effect size was relatively modest. While those findings are non-significant, the associations between vasodilator use and improved gait performance parameters are notable. There is conflicting evidence on the impact of vasodilators such as angiotensin-converting enzyme inhibitors (ACE inhibitors) on gait speed and physical function in older adults[35-37]. A previous study with a small sample size (n=31) found that calcium-channel blockers users had a significantly lower mean gait speed than non-users[38]. Given that confounding by indication cannot be ruled out in observational studies, positive effects of vasodilators reported in previous studies could still be attributed to their therapeutic effects on underlying conditions such as hypertension which is a risk factor for impaired gait performance[39,40]. We recommend further research into this question, preferably using randomized-controlled trials (RCTs), and focusing on subclasses of vasodilators since this is a broad drug class.

We found no statistically significant associations between either beta-blocker or alpha-blocker use and gait performance. Our cohort had a relatively large number of aspirin users (n=104) however we found no statistically significant associations between aspirin and gait performance. The existing evidence on the association between those drug classes and gait performance is scarce and further research is needed into this topic to better understand the impact of those widely-used drug classes on gait performance in older adults. Notably, a recent meta-analysis found that beta-blocker use had a protective effect on falls which was attributed by the authors to the potential cardioprotective effect of those drugs[27].

Remarkably, we also found no statistically significant associations between either antidepressant use or benzodiazepine use and gait performance. It is worth noting that when the multiple regression model for the association between benzodiazepine use and gait speed was re-run after multiple imputation, the regression coefficient was positive as opposed to negative in the complete case analysis. The association was not statistically significant in either analysis. This is possibly explained by the small number of benzodiazepine users in our study (n=20).

Antidepressant use was associated with reduced gait speed after adjustment for demographic confounders but it did not remain significant in the fully adjusted model. This is in contrast to the well-established association between antidepressant use and falls as well as previous studies that reported an association between antidepressant use and reduced gait performance in older adults[41,42]. Our results could potentially be explained by the small number of antidepressant users in our cohort (n=45) and the fact they were all users of SSRIs (selective serotonin reuptake inhibitors). There is evidence that SSRIs may be less sedating than tricyclic antidepressants[43]. A previous RCT showed that the SSRI paroxetine did not affect unobstructed or obstructed gait performance in healthy older adults however the study also had a small sample size (n=12)[44].

Strengths of our study include a large and well-characterized cohort of community-dwelling older adults who underwent instrumented in-person assessments of several gait performance parameters by experienced staff. Importantly, our study helps to address a knowledge gap in the literature on the association between cardiovascular FRIDs and gait performance particularly on gait parameters other than gait speed. To the best of our knowledge, ours is the first study to report an association between diuretic use and reduced gait speed as well as between statin use and increased gait variability in community-dwelling older adults. Our analyses controlled for strong known demographic and health status confounders. We aimed to minimize confounding by indication by adjusting for comorbidity using propensity scores. Propensity scoring is increasingly used in pharmaco-epidemiological studies and there is evidence that it yields comparable results to those obtained by including individual covariates in the regression model[45,46].

Our study is not free of limitations. Due to the cross-sectional design of the study, we were unable to assess temporality of the associations. The clinical relevance of those associations is also uncertain. We were unable to study subclasses of broader drug classes such as vasodilators which limits our ability to draw more specific conclusions. We did not consider the impact of pharmacological factors such as dosage, duration of use, adherence to medication and drug-drug indications. Finally, although we aimed to minimize confounding by indication by adjusting for propensity scores, confounding by indication cannot be eliminated due to the observational nature of the study. Additionally a limitation of propensity scoring is its inability to account for unmeasured confounders which results in residual confounding bias.

4.6 Conclusion

In our cohort of community-dwelling older adults, diuretic use was associated with reduced gait speed and statin use was associated with increased stride time variability. Further longitudinal research is needed to establish the causality of those associations. Given our finding and the existing evidence on the association between diuretic use and falls in older adults, clinicians should use caution when prescribing these medications to older adults.

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Chapter 5

5 Synthesis and Conclusion

This chapter synthesizes the findings of the two studies conducted in this thesis. It provides a summary of the findings from both studies and outlines the contributions of those findings to the existing knowledge body. Finally, this chapter notes some of the limitations of this thesis and directions for future research identified by this thesis.

5.1 Summary of Studies

The main aim of this thesis was to contribute to the knowledge body on the relationship between medication use and gait performance in older adults. This was achieved through two studies. First, we conducted a systematic review of the existing evidence on the association between psychotropic and cardiovascular fall risk-increasing drugs (FRIDs) and gait performance in community-dwelling older adults (Chapter 3). This review identified several knowledge gaps on the association between FRIDs and gait performance. Second, we attempted to address those knowledge gaps through a cross-sectional study of the association between FRID use and gait performance among community-dwelling older adults using medication use data from the Gait and Brain Study (Chapter 4). Specifically, we analyzed gait speed and stride time variability (quantified as the coefficient of variation of stride time).

Our systematic review found that drugs with sedative properties are associated with a decrease in gait speed among community-dwelling older adults. An exception to this was an open-label trial that found that antidepressant therapy improved gait performance in patients with clinical depression[1]. Our review also found that in all studies reviewed except one, gait speed was not affected by statin use. The exception was a large cohort study in which statin use reduced gait speed decline in older adults over 10 years of follow-up; however the authors noted that the clinical relevance of this finding was uncertain due to the modest effect size observed[2]. Our review identified several knowledge gaps. With the exception of ACE inhibitors and statins, no studies assessed the association between other cardiovascular drugs and gait performance in older adults.

Additionally, there was an insufficient number of studies on the impact of FRIDs and gait performance measures other than gait speed.

Our cross-sectional study found that among a cohort of community-dwelling older adults (65 years old and over) living in London, Ontario,, after adjustment for covariates, diuretic use was associated with reduced gait speed (B = -7.97 m/s, P= 0.009). We also found that, after adjustment, statin use was associated with increased stride time variability (B = 0.13, P=0.026). Notably, we also found that vasodilator use was associated with increased gait speed and reduced stride time variability, both of which are indicators of improved gait performance. However those associations were not statistically significant after adjustment for covariates.

5.2 Contributions to Research

This thesis provides important contributions to the existing literature on the relationship between medication use and gait performance. To the best of our knowledge, our systematic review is the first review to focus specifically on the association between FRIDs and gait performance in community-dwelling older adults. A previous literature review conducted in 2013 examined the evidence on the relationship between FRIDs and postural control, although it included both young and older adults[3]. Our study of the association between medication use and gait performance in the Gait and Brain Study addresses some of the knowledge gaps identified by our systematic review. To the best of our knowledge, ours is the first study to report an association between diuretic use and reduced gait speed, as well as between statin use and increased gait variability in community-dwelling older adults. We also assessed the associations between cardiovascular drugs including beta-blockers, alpha-blockers, aspirin and gait performance.

5.3 Limitations

The studies included in this thesis have a number of limitations. In terms of generalizability, this thesis focused on community-dwelling older adults so its findings cannot be generalized to nursing home residents or hospitalized patients. This thesis also excluded patients with neurological or neurodegenerative diseases that impair mobility.

Given that the relationship between medication use and falls is a recently emerging topic, there is no consensus on the drug classes that can be classified as fall risk-increasing. This has implications for both our systematic review and our cross-sectional study. For our systematic review, we relied on current guidelines such as the Beers criteria and previous systematic reviews by the EuGMS Task Force on Falls to inform our search strategy[4,5,6]. Studies of gait performance involving drug classes that were not identified as FRIDs in those resources were not included in our review. In our own study, we assessed the impact of drug classes such as aspirin, beta-blockers and alpha-blockers, although there is no consensus on whether those drug classes can be classified as fall risk-increasing due to the inconsistent evidence reported in the literature. We could not perform a meta-analysis due to the small number of studies for each drug class, inconsistency in statistical effect measures reported and heterogeneity in gait assessment protocols.

An important limitation in the observational studies included in our systematic review as well as our own study is confounding by indication. Studies attempted to minimize this by adjusting for confounders identified through clinical judgement, the literature and statistical methods such as bivariate analyses or stepwise regression. For our own study, we adjusted for known demographic and health-related confounders based on clinical judgement and a review of the literature. We also adjusted for comorbidities by creating a comorbidity propensity score for each drug class (based on the comorbidities associated with both the drug class and the gait performance measure being examined) and including the propensity score as a covariate in our models. Nonetheless, confounding by indication and residual confounding cannot be completely eliminated in observational studies. Other limitations of our study include the cross-sectional design which limits our ability to establish the temporality of the associations we found. We did not have information on drug-drug interactions or dosage recorded in our database so we could not consider the impact of those factors in our study.

5.4 Future Directions

The findings of this thesis provide several ideas for future research. Broadly, the existing literature on the association between FRIDs and gait performance in community-dwelling older adults is relatively limited in contrast to the large body of knowledge on the association between FRIDs and falls. This was shown in our systematic review which retrieved a total of 20 studies for both psychotropic and cardiovascular FRIDs. Gait performance is an important predictor of future health outcomes in older adults including future falls, cognitive impairment and progression to dementia therefore more research is needed to expand the knowledge base on the relationship between medication use and gait. There is a particular need for more research on the association between cardiovascular FRIDs and gait performance given the high prevalence of cardiovascular conditions among older adults. Additionally, more research is needed to discern the impact of FRIDs on gait performance measures other than gait speed such as gait variability. These measures are important markers of gait performance and provide information on gait stability.

Given that drug classes are often broad, further research is required to see whether subclasses of drugs have differential effects on gait performance. For example, we found an association between diuretic use and reduced gait speed in older adults. Future studies could look into the potential differential effects of loop diuretics and thiazide diuretics and gait. This also applies to other drug classes including SSRI and TCA antidepressants as well as short and long-acting benzodiazepines.

Finally, future research on the relationship between FRID use and gait performance should be conducted through clinical trials if possible. Clinical trials can eliminate the risk of bias arising from confounding by indication and residual confounding in observational studies. They can also help establish the clinical relevance of associations reported in observational studies.

5.5 Conclusion

This thesis examined the association between psychotropic and cardiovascular FRIDs and gait performance in community-dwelling older adults through a systematic review and a cross-sectional study. Our systematic review found that in the majority of studies reviewed, the use of drugs with sedative properties was associated with reduced gait speed in community-dwelling older adults. Our review also identified several knowledge gaps including the association between cardiovascular drugs and gait performance. We conducted a cross-sectional study on the association between FRIDs and gait performance in community-dwelling adults aged 65 years old and over using medication use data from the Gait and Brain Study. We found statistically significant associations between diuretic use and reduced gait speed as well as statin use and increased stride time variability. Further research is required to establish causality and determine the clinical relevance of those findings. Broadly, the findings of this thesis suggest that, given the multifactorial nature of falls, caution should be exercised when prescribing drugs with sedative properties as well as diuretics to older adults at an increased risk of falls. Further research is required to confirm our finding on the association between statin and increased stride time variability.

5.6 References

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Appendices

Appendix 1A: License to reuse Figure 1.3

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Appendix 3A: Search Strategy - Psychotropic FRIDs

a) Database search

The following search was run on January 28th, 2020 and updated on June 19th, 2020. A separate search was run in each of Ovid MEDLINE® (1946 to 2020), Ovid EMBASE (1947 to 2020), Ovid APA PsycINFO (1806-2020) and EBSCOhost CINAHL (1981-2020). Every search strategy included database-specific subject headings and a general keyword search.

MEDLINE

1. exp Gait Analysis/ or exp Gait/ or exp Gait Disorders, Neurologic/
2. limit 1 to (english language and humans)
3. (gait or gait disorder* or gait deficit* or gait impairment* or walk*).ti,ab,tw.
4. limit 3 to (english language and humans)
5. 2 or 4
6. exp "Aged, 80 and over"/ or exp Aged/
7. limit 6 to (english language and humans)
8. (Aged or older adult* or elder*).ti,ab,tw.
9. limit 8 to (english language and humans)
10. exp benzodiazepines/ or exp psychotropic drugs/ or exp antidepressive agents/ or exp antipsychotic agents/ or exp "hypnotics and sedatives"/ or exp Anticonvulsants/
11. limit 10 to (english language and humans)
12. (psychotropic* or antiepileptic* or neuroleptic* or antidepressant* or benzodiazepine* or anxiolytic* or hypnotic* or sedative*).ti,ab,tw.
13. limit 12 to (english language and humans)
14. 7 or 9
15. 11 or 13
16. 5 and 14 and 15

Total records uploaded to Mendeley: 473

EMBASE

1. exp Gait Analysis/ or exp Gait/ or exp Gait Disorders, Neurologic/
2. limit 1 to (english language and humans)
3. (gait or gait disorder* or gait deficit* or gait impairment* or walk*).ti,ab,tw.
4. limit 3 to (english language and humans)
5. 2 or 4
6. exp "Aged, 80 and over"/ or exp Aged/

7. limit 6 to (english language and humans)

8. (Aged or older adult* or elder*).ti,ab,tw.

9. limit 8 to (abstracts and english language and humans)

10. exp benzodiazepines/ or exp psychotropic drugs/ or exp antidepressive agents/ or exp antipsychotic agents/ or exp hypnotic agent/ or exp sedative agent/ or exp anticonvulsive agent/

11. limit 10 to (english language and humans)

12. (psychotropic* or antiepileptic* or neuroleptic* or antidepressant* or benzodiazepine* or anxiolytic* or hypnotic* or sedative*).ti,ab,tw.

13. limit 12 to (english language and humans)

14. 7 or 9

15. 11 or 13

16. 5 and 14 and 15

Total records uploaded to Mendeley: 1904

APA PsycINFO

1. exp Gait/ or exp Motor Processes/ or exp Walking/ or exp Movement Disorders/

2. limit 1 to (human and english language)

3. (gait or gait disorder* or gait deficit* or gait impairment* or walk*).ti,ab,tw.

4. limit 3 to (human and english language)

5. exp Antidepressant Drugs/ or exp Psychopharmacology/ or exp Neuroleptic Drugs/ or exp Benzodiazepines/ or exp Hypnotic Drugs/ or exp Sedatives/ or exp Anticonvulsive Drugs/

6. limit 5 to (human and english language)

7. (psychotropic* or antiepileptic* or neuroleptic* or antidepressant* or benzodiazepine* or anxiolytic* or hypnotic* or sedative*).ti,ab,tw.

8. limit 7 to (human and english language)

9. exp Geriatric Patients/ or exp Aging/ or exp Geriatrics/

10. limit 9 to (human and english language)

11. (Aged or older adult* or elder*).ti,ab,tw.

12. limit 11 to (human and english language)

13. 2 or 4

14. 6 or 8

15. 10 or 12

16. 13 and 14 and 15

Total records uploaded to Mendeley: 795

CINAHL

S10 S7 AND S8 AND S9

S9 S5 OR S6

S8 S3 OR S4

S7 S1 OR S2

S6 ""older adults OR elderly OR seniors OR geriatrics"" Limiters - English Language; Publication Type: Abstract; Age Groups: Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over; Language: English

S5 (MH "Aged+") OR (MH "Aged, 80 and Over+") Limiters - English Language; Human; Age Groups: Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over

S4 ""benzodiazepine* OR antidepressant* OR antiepileptic* OR psychotropic* OR neuroleptic* OR hypnotic* OR sedative*"" Limiters - English Language; Publication Type: Abstract; Age Groups: Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over;

S3 (MH "Psychotropic Drugs+") OR (MH "Antidepressive Agents+") OR (MH "Antianxiety Agents, Benzodiazepine+") OR (MH "Antipsychotic Agents+") OR (MH "Hypnotics and Sedatives+") OR (MH "Anticonvulsants+") Limiters - English Language; Age Groups: Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over

S2 ""gait OR gait disorder* OR gait deficit* OR gait impairment* OR OR walk*"" Limiters - Human; Publication Type: Abstract; Age Groups: Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over; Language: English

S1 (MH "Gait+") OR (MH "Gait Disorders, Neurologic+") OR (MH "Gait Analysis") OR (MM "Walking Speed") Limiters - Human; Age Groups: Middle Aged: 45-64 years, Aged: 65+ years, Aged, 80 and over; Language: English

Total records uploaded to Mendeley: 13

b) Grey Literature search

WEB OF SCIENCE

(TS=(gait or gait disorder* or gait deficit* or gait impairment* or walk*) .) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article)

AND

(TS=(psychotropic* or antiepileptic* or neuroleptic* or antidepressant* or benzodiazepine* or anxiolytic* or hypnotic* or sedative*) .) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article)

AND

(TS=(Aged or older adult* or elder*)) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article)

Total records uploaded to Mendeley: 2

PROQUEST DISSERTATIONS & THESIS GLOBAL

ab(gait OR gait disorder* OR gait deficit* OR gait impairment* OR walk*) AND ab(psychotropic* or antiepileptic* or neuroleptic* or antidepressant* or benzodiazepine* or anxiolytic* or hypnotic* or sedative*) AND ab(Aged or older adult* or elder*)

Total records uploaded to Mendeley: 0

Appendix 3B: Search Strategy - Cardiovascular FRIDs

a) Database search

The following search was run on June 15th, 2020. A separate search was run in each of Ovid MEDLINE® (1946 to 2020), Ovid EMBASE (1947 to 2020), Ovid APA PsycINFO (1806-2020) and EBSCOhost CINAHL (1981-2020). Every search strategy included database-specific subject headings and a general keyword search.

MEDLINE

1. exp Gait Analysis/ or exp Gait/ or exp Gait Disorders, Neurologic/
2. limit 1 to (english language and humans)
3. (gait or gait disorder* or gait deficit* or gait impairment* or walk*).ti,ab,tw.
4. limit 3 to (english language and humans)
5. exp Diuretics/
6. limit 5 to (english language and humans)
7. exp Vasodilator Agents/
8. limit 7 to (english language and humans)
9. exp Adrenergic beta-Antagonists/
10. limit 9 to (english language and humans)
11. exp Adrenergic alpha-Antagonists/
12. limit 11 to (english language and humans)
13. exp Calcium Channel Blockers/
14. limit 13 to (english language and humans)
15. exp Angiotensin-Converting Enzyme Inhibitors/
16. limit 15 to (english language and humans)
17. exp Angiotensin II Type 1 Receptor Blockers/
18. limit 17 to (english language and humans)
19. exp Antihypertensive Agents/
20. limit 19 to (english language and humans)
21. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
22. limit 21 to (english language and humans)

23. exp cardiac glycosides/
24. limit 23 to (english language and humans)
25. exp Cardiovascular Agents/
26. limit 25 to (english language and humans)
27. exp "Aged, 80 and over"/ or exp Aged/
28. limit 27 to (english language and humans)
29. (Aged or older adult* or elder*).ti,ab,tw.
30. limit 29 to (english language and humans)
31. (diuretic* or vasodilator agent* or antihypertensive agent* or Adrenergic beta-Antagonist* or beta blocker* or Alpha-adrenoceptor antagonist* or alpha blocker* or ACE inhibitor* or angiotensin II inhibitor* or Hydroxymethylglutaryl-CoA Reductase Inhibitor* or statin* or calcium antagonist* or calcium channel blocker* or cardiac glycoside* or cardiovascular agent*).ti,ab,tw.
32. limit 31 to (english language and humans)
33. 2 or 4
34. 6 or 8 or 10 or 12 or 14 or 16 or 18 or 20 or 22 or 24 or 26 or 32
35. 28 or 30
36. 33 and 34 and 35

Total records uploaded to Mendeley: 1608

EMBASE

1. exp Gait Analysis/ or exp Gait/ or exp Gait Disorders, Neurologic/
2. limit 1 to (human and english language)
3. (gait or gait disorder* or gait deficit* or gait impairment* or walk*).ti,ab,tw.
4. limit 3 to (human and english language)
5. exp diuretic agent/
6. limit 5 to (human and english language)
7. exp vasodilator agent/
8. limit 7 to (human and english language)
9. exp alpha adrenergic receptor blocking agent/
10. limit 9 to (human and english language)
11. exp beta adrenergic receptor blocking agent/
12. limit 11 to (human and english language)
13. exp calcium channel blocking agent/
14. limit 13 to (human and english language)
15. exp calcium antagonist/
16. limit 15 to (human and english language)
17. exp dipeptidyl carboxypeptidase inhibitor/

18. limit 17 to (human and english language)
19. exp angiotensin II antagonist/
20. limit 19 to (human and english language)
21. exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
22. limit 21 to (human and english language)
23. exp cardiovascular agent/
24. limit 23 to (human and english language)
25. exp antihypertensive agent/
26. limit 25 to (human and english language)
27. exp cardiac glycoside/
28. limit 27 to (human and english language)
29. (diuretic* or vasodilator agent* or antihypertensive agent* or Adrenergic beta-Antagonist* or beta blocker* or Alpha-adrenoceptor antagonist* or alpha blocker* or ACE inhibitor* or angiotensin II inhibitor* or Hydroxymethylglutaryl-CoA Reductase Inhibitor* or statin* or calcium antagonist* or calcium channel blocker* or cardiac glycoside* or cardiovascular agent*).ti,ab,tw.
30. limit 29 to (human and english language)
31. exp "Aged, 80 and over"/ or exp Aged/
32. limit 31 to (human and english language)
33. (Aged or older adult* or elder*).ti,ab,tw.
34. limit 33 to (human and english language)
35. 2 or 4
36. 6 or 8 or 10 or 12 or 14 or 16 or 18 or 20 or 22 or 24 or 26 or 28 or 30
37. 32 or 34
38. 35 and 36 and 37

Total records uploaded to Mendeley: 3301

APA PsycINFO

1. exp Gait/ or exp Motor Processes/ or exp Walking/ or exp Movement Disorders/
2. limit 1 to (human and english language)
3. exp Vasodilator Drugs/
4. limit 3 to (human and english language)
5. exp Antihypertensive Drugs/
6. limit 5 to (human and english language)
7. exp Adrenergic Blocking Drugs/
8. limit 7 to (human and english language)
9. exp Channel Blockers/
10. limit 9 to (human and english language)

11. exp Statins/

12. limit 11 to (human and english language)

13. exp digoxin/

14. limit 13 to (human and english language)

15. exp "Side Effects (Drug)"/

16. limit 15 to (human and english language)

17. (diuretic* or vasodilator agent* or antihypertensive agent* or Adrenergic beta-Antagonist* or beta blocker* or Alpha-adrenoceptor antagonist* or alpha blocker* or ACE inhibitor* or angiotensin II inhibitor* or Hydroxymethylglutaryl-CoA Reductase Inhibitor* or statin* or calcium antagonist* or calcium channel blocker* or cardiac glycoside* or cardiovascular agent*).ti,ab,tw.

18. limit 17 to (human and english language)

19. exp Geriatric Patients/ or exp Aging/ or exp Geriatrics/

20. limit 19 to (human and english language)

21. (Aged or older adult* or elder*).ti,ab,tw.

22. limit 21 to (human and english language)

23. (gait or gait disorder* or gait deficit* or gait impairment* or walk*).ti,ab,tw.

24. limit 23 to (human and english language)

25. 2 or 24

26. 4 or 6 or 8 or 10 or 12 or 14 or 16 or 18

27. 20 or 22

28. 25 and 26 and 27

Total records uploaded to Mendeley: 391

CINAHL

S15 S12 AND S13 AND S14

S14 S10 OR S11

S13 S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9

S12 S1 OR S2

S11 "Aged" OR "older adult*" OR "elder*" Limiters - English Language; Human

S10 (MH "Aged+") OR (MH "Aged, 80 and Over+") Limiters - English Language; Human

S9 "diuretic*" OR "vasodilator agent*" OR "antihypertensive agent*" OR "Adrenergic beta-Antagonist*" OR "beta blocker*" OR "Alpha-adrenoceptor antagonist*" OR "alpha blocker*" OR "ACE inhibitor*" OR "angiotensin II inhibitor*" OR "Hydroxymethylglutaryl-CoA Reductase Inhibitor*" OR "statin*" OR "calcium antagonist*" OR "calcium channel blocker*" OR "cardiac glycoside*" OR "cardiovascular agent*" Limiters - English Language; Human

S8 (MH "Statins+") Limiters - English Language; Human

S7 (MH "Cardiac Glycosides+") Limiters - English Language; Human

S6 (MH "Angiotensin-Converting Enzyme Inhibitors+") OR (MH "Angiotensin II Type I Receptor Blockers+") Limiters - English Language; Human

S5 (MH "Adrenergic Alpha-Antagonists+") OR (MH "Adrenergic Beta-Antagonists+") OR
(MH "Calcium Channel Blockers+") Limiters - English Language; Human

S4 (MH "Vasodilator Agents+") Limiters - English Language; Human

S3 (MH "Diuretics+") OR (MH "Diuretics, Thiazide+") Limiters - English Language; Human

S2 "gait" OR "gait disorder*" OR "gait deficit*" OR "gait impairment*" OR "walk*" Limiters - English Language; Human

S1 (MH "Gait+") OR (MH "Gait Disorders, Neurologic+") OR (MH "Gait Analysis") OR (MM "Walking Speed") Limiters - English Language; Human

Total records uploaded to Mendeley: 262

b) Grey Literature search

WEB OF SCIENCE

(TS=(gait or gait disorder* or gait deficit* or gait impairment* or walk*) .) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article)

AND
(TS=(diuretic* or vasodilator agent* or antihypertensive agent* or Adrenergic beta-Antagonist* or beta blocker* or Alpha-adrenoceptor antagonist* or alpha blocker* or ACE inhibitor* or angiotensin II inhibitor* or Hydroxymethylglutaryl-CoA Reductase Inhibitor* or statin* or calcium antagonist* or calcium channel blocker* or cardiac glycoside* or cardiovascular agent*)) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article)

AND

(TS=(Aged or older adult* or elder*)) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article)

Total records uploaded to Mendeley: 6

PROQUEST DISSERTATIONS & THESIS GLOBAL

ab(gait or gait disorder* or gait deficit* or gait impairment* or walk*) AND ab(diuretic* or vasodilator agent* or antihypertensive agent* or Adrenergic beta-Antagonist* or beta blocker* or Alpha-adrenoceptor antagonist* or alpha blocker* or ACE inhibitor* or angiotensin II inhibitor* or Hydroxymethylglutaryl-CoA Reductase Inhibitor* or statin* or calcium antagonist* or calcium channel blocker* or cardiac glycoside*r cardiovascular agent*) AND ab(Aged or older adult* or elder*)

Total records uploaded to Mendeley: 0

Appendix 3C: The Newcastle-Ottawa Scale for quality assessment of cohort and cross-sectional studies. The scale was adjusted to fit the review topic

Criteria	Acceptable (* awarded)	Unacceptable (* not awarded)
Selection		
1) Representativeness of the exposed cohort	• Truly representative of the average older persons in the community * • Somewhat representative of the average older persons in the community *	• Selected group of users (e.g. nurses, volunteers) • No description of the derivation of the cohort
2) Selection of the non exposed cohort	• Drawn from the same community as the exposed cohort *	• Drawn from a different source • No description of the derivation of the non-exposed cohort
3) Ascertainment of exposure	• Medication ascertained through secure records* • Medication ascertained through interviews*	• Medication ascertained through self-reports • No description
4) Demonstration that outcome of interest was not present at start of study	• Yes*	• No
Comparability		
1) Comparability of cohorts on the basis of the design or analysis	• Controlled for age and other factors* * • Controlled for age only *	• No description

Outcome		
1) Assessment of outcome	• Independent gait assessment * • Gait parameters in medical record *	• Self-report (retrospective) • No description
2) Was follow-up long enough for outcomes to occur (N/A for cross-sectional studies)	• Yes*	• No
3) Adequacy of follow up of cohorts (N/A for cross-sectional studies)	• Complete follow-up – all subjects accounted for * • Subjects loss to follow-up unlikely to introduce bias – small number lost to follow-up *	• Subjects lost to follow-up likely to introduce bias • No statement

Appendix 3D: Quality assessment for observational studies included using the Newcastle-Ottawa scale (NOS) (Psychotropic FRIDs)

Author (Year of Publication)	Selection				Comparability	Outcome			Total Score (/9)
	1) Representative-ness of the exposed cohort (*)	2) Selection of non-exposed cohort (⋆)	3) Ascertainment of exposure (*)	4) Demonstration that outcome of interest was not present at start of study (*)	1) Comparability of cohorts on the basis of the design or analysis (**)	1) Assessment of outcome (*)	2) Was follow-up long enough for outcomes to occur (*) (N/A for cross-sectional studies)	3) Adequacy of follow up of cohorts (*) (N/A for cross-sectional studies)	
Donoghue et al (2015)	*	*	-	-	**	*	N/A	N/A	5
Poujol et al (2010)	-	*	-	-	**	*	N/A	N/A	4
Eto et al (1998)	*	*	-	-	-	*	N/A	N/A	3
Gray et al (2003)	*	*	*	-	**	*	*	*	8
Landi et al (2007)	*	*	*	-	**	*	N/A	N/A	6
Cao et al (2008)	*	*	*	-	**	*	N/A	N/A	6

Gnijdic et al (2009)	*	*	*	-	**	*	N/A	N/A	6
Hilmer et al (2009)	*	*	*	-	**	*	*	*	8
Taipale et al (2012)	*	*	*	-	**	*	N/A	N/A	6
Lim et al (2019)	*	*	-	-	**	*	N/A	N/A	5

Appendix 3E: Quality assessment for observational studies included using the Newcastle-Ottawa scale (NOS) (Cardiovascular FRIDs)

Author (Year of Publication)	Selection				Comparability		Outcome		Total Score (/9)
	1) Representative-ness of the exposed cohort (*)	2) Selection of non-exposed cohort (⋆)	3) Ascertainment of exposure (*)	4) Demonstration that outcome of interest was not present at start of study (*)	1) Comparability of cohorts on the basis of the design or analysis (**)	1) Assessment of outcome (*)	2) Was follow-up long enough for outcomes to occur (*) (N/A for cross-sectional studies)	3) Adequacy of follow up of cohorts (*) (N/A for cross-sectional studies)	
Onder at al (2002)	*	*	*	-	**	*	*	*	8
Gray et al (2012)	*	*	*	-	**	*	*	*	8
George and Verghese (2016)	*	*	*	-	**	*	N/A	N/A	6
Dumurgier et al (2013)	*	*	*	*	**	*	*	*	9
Lo-Ciganic (2014)	*	*	*	*	**	*	*	*	9

Kawai et al (2018)	*	*	*	-	**	*	N/A	N/A	6
Deugchi et al (2019)	*	*	*	*	**	*	N/A	N/A	7

Appendix 3F: Risk of bias assessment for clinical trials included using the Cochrane risk-of-bias tool

Author (Year of Publication)	Risk of bias domains						
	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity	Summary bias
Draganich et al (2001)	Low	Low	Low	Low	Low	Low	Low risk
Paleacau et al (2007)	High	High	High	Low	Low	Low	High risk
Cesari et al (2009)	Unclear	Unclear	Low	Low	Low	Low	Unclear risk

Appendix 4A: Comorbidity propensity score models for the association between FRIDs and Gait Speed

1) SSRI

Estimation of the propensity score

```
Iteration 0:   log likelihood = -127.97957
Iteration 1:   log likelihood = -104.44435
Iteration 2:   log likelihood = -97.409352
Iteration 3:   log likelihood = -97.321202
Iteration 4:   log likelihood = -97.320979

Logistic regression                             Number of obs   =        319
                                                LR chi2(8)      =      61.32
                                                Prob > chi2     =     0.0000
Log likelihood = -97.320979                     Pseudo R2       =     0.2396
```

T0_SSRI	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_oa	.832234	.3796338	2.19	0.028	.0881653	1.576303
T0_chf	.0911159	.9819039	0.09	0.926	-1.83338	2.015612
T0_angina	-.6524121	.8822377	-0.74	0.460	-2.381566	1.076742
T0_dm	.2393716	.4976909	0.48	0.631	-.7360847	1.214828
T0_vision	-.2958052	.4241601	-0.70	0.486	-1.127144	.5355333
T0_Hear	.4401872	.3798645	1.16	0.247	-.3043336	1.184708
T0_htn	.6562622	.3908907	1.68	0.093	-.1098695	1.422394
T0_depress	2.518229	.3915911	6.43	0.000	1.750725	3.285734
_cons	-3.74678	.4724779	-7.93	0.000	-4.67282	-2.820741

Logistic model for T0_SSRI, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0230	0	1.3	61	59.7	61
2	0.0265	0	0.1	4	3.9	4
3	0.0388	1	1.4	39	38.6	40
4	0.0435	1	1.3	29	28.7	30
5	0.0546	5	1.5	24	27.5	29
6	0.0722	2	2.2	31	30.8	33
7	0.1172	2	2.4	25	24.6	27
8	0.2711	4	6.4	29	26.6	33
9	0.4022	13	11.6	19	20.4	32
10	0.7190	16	15.8	14	14.2	30

```
      number of observations =       319
            number of groups =        10
     Hosmer-Lemeshow chi2(8) =     11.73
                     Prob > chi2 =      0.1634

7 . lroc

Logistic model for T0_SSRI

number of observations =      319
area under ROC curve   =   0.8378
```

2) Benzodiazepine

Estimation of the propensity score

```
Iteration 0:   log likelihood =  -69.22908
Iteration 1:   log likelihood = -65.772356
Iteration 2:   log likelihood = -65.207729
Iteration 3:   log likelihood = -65.201852
Iteration 4:   log likelihood =  -65.20185

Logistic regression                               Number of obs   =        319
                                                  LR chi2(7)      =       8.05
                                                  Prob > chi2     =     0.3278
Log likelihood =  -65.20185                       Pseudo R2       =     0.0582
```

T0_Benz	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_oa	.0180104	.5134175	0.04	0.972	-.9882694	1.02429
T0_angina	-.4540788	1.096506	-0.41	0.679	-2.603191	1.695033
T0_dm	.5920873	.5848789	1.01	0.311	-.5542543	1.738429
T0_vision	-.0521816	.5422736	-0.10	0.923	-1.115018	1.010655
T0_Hear	.0708832	.5140291	0.14	0.890	-.9365954	1.078362
T0_htn	.8900118	.538899	1.65	0.099	-.1662108	1.946234
T0_depress	.9244075	.5088951	1.82	0.069	-.0730086	1.921823
_cons	-3.740826	.5502528	-6.80	0.000	-4.819301	-2.66235

Logistic model for T0_Benz, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0224	1	0.7	32	32.3	33
2	0.0232	0	1.0	41	40.0	41
3	0.0240	1	0.6	23	23.4	24
4	0.0386	0	0.8	30	29.2	30
5	0.0546	3	2.6	46	46.4	49
6	0.0564	3	1.3	21	22.7	24
7	0.0584	2	1.8	29	29.2	31
8	0.0676	1	1.5	23	22.5	24
9	0.1271	2	3.9	36	34.1	38
10	0.2235	5	3.9	20	21.1	25

```
      number of observations =       319
            number of groups =        10
  Hosmer-Lemeshow chi2(8) =         6.10
                  Prob > chi2 =     0.6356
```

```
. lroc

Logistic model for T0_Benz

number of observations =       319
area under ROC curve   =    0.6884
```

3) Alpha-blockers

Estimation of the propensity score

```
Iteration 0:   log likelihood = -80.054583
Iteration 1:   log likelihood = -76.127536
Iteration 2:   log likelihood = -75.468192
Iteration 3:   log likelihood = -75.460441
Iteration 4:   log likelihood = -75.460437

Logistic regression                             Number of obs     =        319
                                                LR chi2(6)        =       9.19
                                                Prob > chi2       =     0.1633
Log likelihood = -75.460437                     Pseudo R2         =     0.0574
```

T0_Alpha	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_oa	-.2496679	.4786949	-0.52	0.602	-1.187893	.6885568
T0_angina	.7512572	.7030123	1.07	0.285	-.6266215	2.129136
T0_dm	.1708621	.556713	0.31	0.759	-.9202753	1.262
T0_vision	.412775	.4622005	0.89	0.372	-.4931214	1.318671
T0_Hear	.6281225	.4562262	1.38	0.169	-.2660645	1.522309
T0_htn	.8023848	.4936588	1.63	0.104	-.1651686	1.769938
_cons	-3.502815	.4841898	-7.23	0.000	-4.45181	-2.55382

Logistic model for T0_Alpha, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)
(There are only 9 distinct quantiles because of ties)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
2	0.0292	2	2.1	76	75.9	78
3	0.0345	0	0.7	19	18.3	19
4	0.0435	3	1.5	31	32.5	34
5	0.0534	2	1.7	31	31.3	33
6	0.0629	0	2.5	40	37.5	40
7	0.0786	4	1.9	21	23.1	25
8	0.1075	1	2.6	27	25.4	28
9	0.1299	5	3.7	26	27.3	31
10	0.2874	5	5.4	26	25.6	31

```
      number of observations =       319
            number of groups =         9
    Hosmer-Lemeshow chi2(7) =      9.47
                Prob > chi2 =    0.2209

. lroc

Logistic model for T0_Alpha

number of observations =      319
area under ROC curve   =   0.6856
```

4) Beta-blockers

Estimation of the propensity score

```
Iteration 0:   log likelihood =  -141.8359
Iteration 1:   log likelihood =  -121.4888
Iteration 2:   log likelihood = -119.06842
Iteration 3:   log likelihood = -118.21978
Iteration 4:   log likelihood = -118.21498
Iteration 5:   log likelihood = -118.21498

Logistic regression                             Number of obs   =        319
                                                LR chi2(9)      =      47.24
                                                Prob > chi2     =     0.0000
Log likelihood = -118.21498                     Pseudo R2       =     0.1665
```

T0_Beta	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_oa	.1839064	.3545455	0.52	0.604	-.51099	.8788029
T0_chf	-1.133077	1.126303	-1.01	0.314	-3.34059	1.074437
T0_angina	.4956956	.658597	0.75	0.452	-.7951307	1.786522
T0_dm	.5946408	.4315459	1.38	0.168	-.2511735	1.440455
T0_vision	-.586301	.3939873	-1.49	0.137	-1.358502	.1858999
T0_Hear	.0357361	.3534262	0.10	0.919	-.6569665	.7284388
T0_htn	.9187964	.3604599	2.55	0.011	.2123079	1.625285
T0_atria	.7613944	.59119	1.29	0.198	-.3973167	1.920105
T0_mi	2.509732	.632554	3.97	0.000	1.269949	3.749516
_cons	-2.486371	.3381152	-7.35	0.000	-3.149064	-1.823677

Logistic model for T0_Beta, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0527	2	1.7	35	35.3	37
2	0.0768	3	4.2	53	51.8	56
3	0.0794	2	1.7	19	19.3	21
4	0.0909	3	2.6	26	26.4	29
5	0.1040	2	1.9	17	17.1	19
6	0.1310	3	3.6	27	26.4	30
7	0.1726	5	5.7	29	28.3	34
8	0.2004	6	6.5	29	28.5	35
9	0.3087	10	7.2	19	21.8	29
10	0.9516	16	17.1	13	11.9	29

```
      number of observations =       319
            number of groups =        10
    Hosmer-Lemeshow chi2(8) =      2.44
                Prob > chi2 =    0.9645
```

```
. lroc

Logistic model for T0_Beta

number of observations =      319
area under ROC curve   =   0.7566
```

5) Vasodilators

Estimation of the propensity score

```
Iteration 0:   log likelihood = -165.28075
Iteration 1:   log likelihood = -139.40137
Iteration 2:   log likelihood = -137.32197
Iteration 3:   log likelihood = -137.29028
Iteration 4:   log likelihood = -137.29025

Logistic regression                             Number of obs   =        319
                                                LR chi2(8)      =      55.98
                                                Prob > chi2     =     0.0000
Log likelihood = -137.29025                     Pseudo R2       =     0.1694
```

T0_Vaso	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_oa	.3712561	.3106969	1.19	0.232	-.2376987	.9802108
T0_chf	1.33923	.8412988	1.59	0.111	-.3096858	2.988145
T0_dm	.4433659	.3866659	1.15	0.252	-.3144853	1.201217
T0_vision	.4395009	.3137372	1.40	0.161	-.1754127	1.054415
T0_Hear	.3608706	.3076611	1.17	0.241	-.2421342	.9638753
T0_htn	1.784297	.3478295	5.13	0.000	1.102563	2.46603
T0_Lung	.4313613	.5489947	0.79	0.432	-.6446485	1.507371
T0_mi	.5283543	.5368255	0.98	0.325	-.5238043	1.580513
_cons	-3.036737	.3600073	-8.44	0.000	-3.742339	-2.331136

Logistic model for T0_Vaso, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0458	3	2.2	46	46.8	49
2	0.0644	1	1.3	19	18.7	20
3	0.0688	1	1.8	27	26.2	28
4	0.0907	2	2.6	32	31.4	34
5	0.1341	3	3.4	29	28.6	32
6	0.2223	8	7.3	26	26.7	34
7	0.2929	5	7.9	22	19.1	27
8	0.3889	16	12.8	20	23.2	36
9	0.4303	14	11.1	14	16.9	28
10	0.7913	15	17.6	16	13.4	31

```
      number of observations =       319
            number of groups =        10
     Hosmer-Lemeshow chi2(8) =      5.85
                Prob > chi2 =      0.6645
```

```
. lroc

Logistic model for T0_Vaso

number of observations =      319
area under ROC curve   =   0.7813
```

6) Statin

Estimation of the propensity score

```
Iteration 0:   log likelihood = -216.69065
Iteration 1:   log likelihood =  -188.6368
Iteration 2:   log likelihood = -187.71207
Iteration 3:   log likelihood = -187.67993
Iteration 4:   log likelihood = -187.67982

Logistic regression                             Number of obs   =        319
                                                LR chi2(8)      =      58.02
                                                Prob > chi2     =     0.0000
Log likelihood = -187.67982                     Pseudo R2       =     0.1339
```

T0_Stat	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_oa	.0875999	.2645408	0.33	0.741	-.4308906	.6060903
T0_chf	-.6150833	.9538486	-0.64	0.519	-2.484592	1.254426
T0_dm	1.342472	.3926159	3.42	0.001	.572959	2.111985
T0_vision	-.1022368	.2723415	-0.38	0.707	-.6360163	.4315428
T0_angina	.0709777	.6308255	0.11	0.910	-1.165418	1.307373
T0_Hear	.2516711	.2596418	0.97	0.332	-.2572174	.7605596
T0_htn	.9250163	.2552467	3.62	0.000	.4247419	1.425291
T0_mi	2.332794	.8431407	2.77	0.006	.6802691	3.98532
_cons	-1.160306	.2259621	-5.13	0.000	-1.603183	-.7174281

Logistic model for T0_Vaso, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0458	3	2.2	46	46.8	49
2	0.0644	1	1.3	19	18.7	20
3	0.0688	1	1.8	27	26.2	28
4	0.0907	2	2.6	32	31.4	34
5	0.1341	3	3.4	29	28.6	32
6	0.2223	8	7.3	26	26.7	34
7	0.2929	5	7.9	22	19.1	27
8	0.3889	16	12.8	20	23.2	36
9	0.4303	14	11.1	14	16.9	28
10	0.7913	15	17.6	16	13.4	31

```
      number of observations =       319
            number of groups =        10
  Hosmer-Lemeshow chi2(8) =         5.85
                  Prob > chi2 =     0.6645

. lroc

Logistic model for T0_Vaso

number of observations =      319
area under ROC curve   =   0.7813
```

7) Aspirin

Estimation of the propensity score

```
Iteration 0:   log likelihood = -199.91101
Iteration 1:   log likelihood = -178.10715
Iteration 2:   log likelihood =   -177.333
Iteration 3:   log likelihood = -177.32523
Iteration 4:   log likelihood = -177.32523

Logistic regression                             Number of obs     =        319
                                                LR chi2(9)        =      45.17
                                                Prob > chi2       =     0.0000
Log likelihood = -177.32523                     Pseudo R2         =     0.1130
```

T0_Aspirin	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_oa	-.1937871	.2782979	-0.70	0.486	-.7392409	.3516667
T0_chf	1.736649	.8439056	2.06	0.040	.0826245	3.390674
T0_angina	.5341405	.5610786	0.95	0.341	-.5655534	1.633834
T0_dm	.3545816	.3715671	0.95	0.340	-.3736766	1.08284
T0_vision	.5044155	.2707385	1.86	0.062	-.0262222	1.035053
T0_Hear	.3070366	.2711871	1.13	0.258	-.2244804	.8385536
T0_htn	.8117077	.2709468	3.00	0.003	.2806616	1.342754
T0_depress	-1.305004	.3618675	-3.61	0.000	-2.014251	-.5957567
T0_mi	.4924493	.5570267	0.88	0.377	-.599303	1.584202
_cons	-1.289208	.2463129	-5.23	0.000	-1.771972	-.8064432

Logistic model for T0_Aspirin, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0922	4	2.4	29	30.6	33
2	0.1850	5	6.0	35	34.0	40
3	0.2160	8	10.6	42	39.4	50
4	0.2358	1	1.7	6	5.3	7
5	0.2820	11	8.7	21	23.3	32
6	0.3382	9	9.7	21	20.3	30
7	0.3925	11	12.1	21	19.9	32
8	0.4584	16	14.2	16	17.8	32
9	0.5798	15	16.3	17	15.7	32
10	0.9334	22	20.3	9	10.7	31

```
      number of observations =       319
            number of groups =        10
  Hosmer-Lemeshow chi2(8) =         4.58
                  Prob > chi2 =     0.8017
```

```
. lroc

Logistic model for T0_Aspirin

number of observations =      319
area under ROC curve   =   0.7270
```

8) Diuretics

Estimation of the propensity score

```
Iteration 0:   log likelihood = -154.21682
Iteration 1:   log likelihood = -122.99868
Iteration 2:   log likelihood = -118.75433
Iteration 3:   log likelihood = -118.52009
Iteration 4:   log likelihood = -118.51724
Iteration 5:   log likelihood = -118.51724

Logistic regression                             Number of obs     =        319
                                                LR chi2(7)        =      71.40
                                                Prob > chi2       =     0.0000
Log likelihood = -118.51724                     Pseudo R2         =     0.2315
```

T0_Diu	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_oa	.2498586	.3409722	0.73	0.464	-.4184346	.9181518
T0_chf	2.535948	.9324416	2.72	0.007	.7083963	4.3635
T0_angina	-1.362293	.7282007	-1.87	0.061	-2.78954	.0649544
T0_dm	.5350809	.3959329	1.35	0.177	-.2409333	1.311095
T0_vision	.01174	.3457639	0.03	0.973	-.6659448	.6894249
T0_Hear	.0257762	.3315311	0.08	0.938	-.6240128	.6755652
T0_htn	2.769139	.462992	5.98	0.000	1.861692	3.676587
_cons	-3.51284	.4635452	-7.58	0.000	-4.421372	-2.604308

Logistic model for T0_Diu, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0289	0	1.5	54	52.5	54
2	0.0293	1	0.6	20	20.4	21
3	0.0297	1	0.6	20	20.4	21
4	0.0373	2	1.5	41	41.5	43
5	0.0484	0	0.9	23	22.1	23
6	0.3222	16	12.2	35	38.8	51
7	0.3279	11	8.8	16	18.2	27
8	0.3790	7	8.1	16	14.9	23
9	0.4480	7	11.9	23	18.1	30
10	0.9294	15	13.7	11	12.3	26

```
      number of observations =       319
            number of groups =        10
  Hosmer-Lemeshow chi2(8) =         9.31
              Prob > chi2 =         0.3168
```

```
. lroc

Logistic model for T0_Diu

number of observations =      319
area under ROC curve   =   0.8043
```

Appendix 4B: Comorbidity propensity score models for the association between FRIDs and Stride Time Variability (Stride Time CV)

1) SSRI

Estimation of the propensity score

```
Iteration 0:   log likelihood = -127.97957
Iteration 1:   log likelihood = -105.75859
Iteration 2:   log likelihood = -98.983307
Iteration 3:   log likelihood =  -98.92296
Iteration 4:   log likelihood = -98.922859

Logistic regression                             Number of obs   =        319
                                                LR chi2(5)      =      58.11
                                                Prob > chi2     =     0.0000
Log likelihood = -98.922859                     Pseudo R2       =     0.2270
```

T0_SSRI	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_oa	.8161337	.3715595	2.20	0.028	.0878904	1.544377
T0_depress	2.43967	.3823572	6.38	0.000	1.690264	3.189077
T0_dm	.3254476	.4782909	0.68	0.496	-.6119854	1.262881
T0_vision	-.2640163	.4165779	-0.63	0.526	-1.080494	.5524614
T0_Hear	.4991232	.3757007	1.33	0.184	-.2372366	1.235483
_cons	-3.458689	.4216554	-8.20	0.000	-4.285118	-2.63226

Logistic model for T0_SSRI, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)
(There are only 9 distinct quantiles because of ties)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
2	0.0305	2	2.6	88	87.4	90
3	0.0383	1	0.6	14	14.4	15
4	0.0493	1	1.7	36	35.3	37
5	0.0518	1	1.3	24	23.7	25
6	0.0664	3	1.9	26	27.1	29
7	0.1049	4	3.1	30	30.9	34
8	0.2652	5	6.0	22	21.0	27
9	0.4495	18	17.1	26	26.9	44
10	0.6506	9	9.7	9	8.3	18

```
      number of observations =       319
            number of groups =         9
  Hosmer-Lemeshow chi2(7) =         2.33
                  Prob > chi2 =         0.9395
```

```
. lroc

Logistic model for T0_SSRI

number of observations =      319
area under ROC curve   =   0.8242
```

2) Benzodiazepines

Estimation of the propensity score

```
Iteration 0:   log likelihood =  -69.22908
Iteration 1:   log likelihood = -67.054973
Iteration 2:   log likelihood = -66.670634
Iteration 3:   log likelihood = -66.667057
Iteration 4:   log likelihood = -66.667056

Logistic regression                             Number of obs   =        319
                                                LR chi2(4)      =       5.12
                                                Prob > chi2     =     0.2748
Log likelihood = -66.667056                     Pseudo R2       =     0.0370
```

T0_Benz	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_dm	.7822741	.5650485	1.38	0.166	-.3252006	1.889749
T0_vision	-.014796	.5328841	-0.03	0.978	-1.05923	1.029638
T0_Hear	.1672606	.5078056	0.33	0.742	-.8280202	1.162541
T0_depress	.8343479	.5038998	1.66	0.098	-.1532776	1.821973
_cons	-3.321141	.4210153	-7.89	0.000	-4.146316	-2.495966

Logistic model for T0_Benz, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)
(There are only 8 distinct quantiles because of ties)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0344	1	1.7	49	48.3	50
4	0.0349	4	3.1	86	86.9	90
5	0.0404	1	0.9	21	21.1	22
6	0.0409	1	1.8	42	41.2	43
7	0.0757	2	1.8	22	22.2	24
8	0.0768	2	2.5	30	29.5	32
9	0.0895	5	3.8	38	39.2	43
10	0.1769	2	2.5	13	12.5	15

```
      number of observations =       319
            number of groups =         8
  Hosmer-Lemeshow chi2(6) =      1.60
                  Prob > chi2 =      0.9525
```

```
. lroc

Logistic model for T0_Benz

number of observations =       319
area under ROC curve   =    0.6513
```

3) Alpha-blockers

Estimation of the propensity score

```
Iteration 0:   log likelihood = -80.054583
Iteration 1:   log likelihood = -76.389513
Iteration 2:   log likelihood = -76.048241
Iteration 3:   log likelihood =   -76.0465
Iteration 4:   log likelihood =   -76.0465

Logistic regression                             Number of obs     =        319
                                                LR chi2(4)        =       8.02
                                                Prob > chi2       =     0.0910
Log likelihood =   -76.0465                     Pseudo R2         =     0.0501
```

T0_Alpha	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_dm	.1896916	.5599783	0.34	0.735	-.9078458	1.287229
T0_vision	.4109478	.4563806	0.90	0.368	-.4835417	1.305437
T0_Hear	.6223448	.4553113	1.37	0.172	-.2700489	1.514739
T0_htn	.8548513	.4886706	1.75	0.080	-.1029254	1.812628
_cons	-3.557426	.4651458	-7.65	0.000	-4.469095	-2.645757

Logistic model for T0_Alpha, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)
(There are only 8 distinct quantiles because of ties)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
2	0.0277	2	2.2	76	75.8	78
3	0.0412	1	1.7	41	40.3	42
4	0.0504	3	1.7	31	32.3	34
6	0.0628	2	2.9	44	43.1	46
7	0.0750	2	1.9	23	23.1	25
8	0.1110	7	6.1	52	52.9	59
9	0.1312	1	0.9	6	6.1	7
10	0.1855	4	4.7	24	23.3	28

```
      number of observations =       319
            number of groups =         8
  Hosmer-Lemeshow chi2(6) =         1.91
                  Prob > chi2 =      0.9275
```

```
. lroc

Logistic model for T0_Alpha

number of observations =      319
area under ROC curve   =   0.6770
```

4) Beta-blockers

Estimation of the propensity score

```
Iteration 0:   log likelihood =  -141.8359
Iteration 1:   log likelihood = -123.13438
Iteration 2:   log likelihood = -121.01506
Iteration 3:   log likelihood = -119.66862
Iteration 4:   log likelihood = -119.66125
Iteration 5:   log likelihood = -119.66125

Logistic regression                             Number of obs   =        319
                                                LR chi2(5)      =      44.35
                                                Prob > chi2     =     0.0000
Log likelihood = -119.66125                     Pseudo R2       =     0.1563
```

T0_Beta	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_dm	.5734763	.4214119	1.36	0.174	-.2524759	1.399428
T0_vision	-.447395	.372341	-1.20	0.230	-1.17717	.28238
T0_Hear	-.0183083	.3479937	-0.05	0.958	-.7003634	.6637468
T0_htn	.9871234	.3555032	2.78	0.005	.2903499	1.683897
T0_mi	2.562018	.5542039	4.62	0.000	1.475798	3.648238
_cons	-2.406377	.3108808	-7.74	0.000	-3.015692	-1.797062

Logistic model for T0_Beta, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)
(There are only 9 distinct quantiles because of ties)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0545	4	2.5	43	44.5	47
2	0.0813	3	2.7	30	30.3	33
4	0.0827	4	6.4	73	70.6	77
5	0.0912	0	0.3	3	2.7	3
6	0.1339	3	4.7	32	30.3	35
7	0.1919	8	6.3	27	28.7	35
8	0.1948	9	8.2	33	33.8	42
9	0.2965	4	4.6	15	14.4	19
10	0.8476	17	16.4	11	11.6	28

```
      number of observations =       319
            number of groups =         9
  Hosmer-Lemeshow chi2(7) =      3.63
                  Prob > chi2 =      0.8214
```

```
. lroc

Logistic model for T0_Beta

number of observations =       319
area under ROC curve   =    0.7383
```

5) Vasodilators

Estimation of the propensity score

```
Iteration 0:   log likelihood = -165.28075
Iteration 1:   log likelihood = -140.02032
Iteration 2:   log likelihood = -138.02966
Iteration 3:   log likelihood =  -138.0002
Iteration 4:   log likelihood = -138.00017

Logistic regression                             Number of obs     =        319
                                                LR chi2(7)        =      54.56
                                                Prob > chi2       =     0.0000
Log likelihood = -138.00017                     Pseudo R2         =     0.1651
```

T0_Vaso	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_chf	1.489636	.8367167	1.78	0.075	-.1502981	3.129571
T0_dm	.4291406	.3837172	1.12	0.263	-.3229313	1.181213
T0_vision	.5015836	.3086849	1.62	0.104	-.1034278	1.106595
T0_Hear	.3569922	.3066299	1.16	0.244	-.2439913	.9579757
T0_htn	1.794857	.3468594	5.17	0.000	1.115025	2.474689
T0_Lung	.4249004	.5505183	0.77	0.440	-.6540957	1.503896
T0_mi	.5114883	.5376991	0.95	0.341	-.5423826	1.565359
_cons	-2.912223	.3402651	-8.56	0.000	-3.57913	-2.245315

Logistic model for T0_Vaso, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)
(There are only 9 distinct quantiles because of ties)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
2	0.0516	4	3.9	71	71.1	75
3	0.0721	2	2.2	29	28.8	31
4	0.0824	1	3.1	37	34.9	38
5	0.1147	2	1.8	14	14.2	16
6	0.2465	11	10.9	36	36.1	47
7	0.3186	7	7.8	18	17.2	25
8	0.3507	14	10.0	15	19.0	29
9	0.4357	15	12.2	14	16.8	29
10	0.7880	12	16.1	17	12.9	29

```
      number of observations =       319
            number of groups =         9
  Hosmer-Lemeshow chi2(7) =         7.58
                  Prob > chi2 =         0.3712
```

```
. lroc

Logistic model for T0_Vaso

number of observations =       319
area under ROC curve   =    0.7760
```

6) Statin

Estimation of the propensity score

```
Iteration 0:   log likelihood = -216.69065
Iteration 1:   log likelihood = -188.82834
Iteration 2:   log likelihood = -187.94783
Iteration 3:   log likelihood = -187.91892
Iteration 4:   log likelihood = -187.91883

Logistic regression                             Number of obs   =        319
                                                LR chi2(6)      =      57.54
                                                Prob > chi2     =     0.0000
Log likelihood = -187.91883                     Pseudo R2       =     0.1328
```

T0_Stat	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_dm	1.32326	.391023	3.38	0.001	.5568693	2.089651
T0_vision	-.0844945	.2691482	-0.31	0.754	-.6120154	.4430263
T0_angina	.103029	.6256997	0.16	0.869	-1.12332	1.329378
T0_Hear	.2502299	.2594105	0.96	0.335	-.2582054	.7586653
T0_htn	.9312035	.2550357	3.65	0.000	.4313427	1.431064
T0_mi	2.220269	.8129842	2.73	0.006	.6268497	3.813689
_cons	-1.143641	.2090855	-5.47	0.000	-1.553441	-.7338408

Logistic model for T0_Stat, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)
(There are only 9 distinct quantiles because of ties)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.2265	7	7.7	27	26.3	34
3	0.2417	17	18.4	59	57.6	76
4	0.2904	12	13.1	34	32.9	46
5	0.4263	10	7.5	8	10.5	18
6	0.4471	19	17.9	21	22.1	40
7	0.4883	8	8.7	10	9.3	18
8	0.5094	14	13.8	13	13.2	27
9	0.7557	19	19.1	10	9.9	29
10	0.9755	27	26.8	4	4.2	31

```
      number of observations =       319
            number of groups =         9
    Hosmer-Lemeshow chi2(7) =      1.98
                Prob > chi2 =    0.9608

. lroc

Logistic model for T0_Stat

number of observations =      319
area under ROC curve   =   0.7316
```

7) Aspirin

Estimation of the propensity score

```
Iteration 0:   log likelihood = -199.91101
Iteration 1:   log likelihood = -178.30642
Iteration 2:   log likelihood = -177.57651
Iteration 3:   log likelihood = -177.56967
Iteration 4:   log likelihood = -177.56967

Logistic regression                             Number of obs   =        319
                                                LR chi2(8)      =      44.68
                                                Prob > chi2     =     0.0000
Log likelihood = -177.56967                     Pseudo R2       =     0.1118
```

T0_Aspirin	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_chf	1.642657	.8288842	1.98	0.048	.0180737	3.26724
T0_angina	.4754107	.5539303	0.86	0.391	-.6102727	1.561094
T0_dm	.3636008	.3715883	0.98	0.328	-.3646989	1.091901
T0_vision	.4736277	.2668812	1.77	0.076	-.0494499	.9967053
T0_Hear	.303127	.2707272	1.12	0.263	-.2274886	.8337426
T0_htn	.8038146	.2704854	2.97	0.003	.2736729	1.333956
T0_depress	-1.303986	.361157	-3.61	0.000	-2.011841	-.5961311
T0_mi	.5157447	.5560413	0.93	0.354	-.5740762	1.605566
_cons	-1.341958	.2352431	-5.70	0.000	-1.803026	-.8808897

Logistic model for T0_Aspirin, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0876	4	2.4	28	29.6	32
2	0.1856	6	4.4	26	27.6	32
3	0.2072	7	12.0	51	46.0	58
4	0.2563	0	1.5	6	4.5	6
5	0.2956	17	14.1	33	35.9	50
6	0.3686	13	14.9	28	26.1	41
7	0.3805	2	1.9	3	3.1	5
8	0.4839	24	21.6	23	25.4	47
9	0.5594	9	10.2	10	8.8	19
10	0.9212	20	19.1	9	9.9	29

```
      number of observations =       319
            number of groups =        10
          Hosmer-Lemeshow chi2(8) =      8.66
                      Prob > chi2 =      0.3721
```

```
. lroc

Logistic model for T0_Aspirin

number of observations =      319
area under ROC curve   =   0.7255
```

8) Diuretics

Estimation of the propensity score

```
Iteration 0:   log likelihood = -154.21682
Iteration 1:   log likelihood = -127.41888
Iteration 2:   log likelihood = -124.02072
Iteration 3:   log likelihood =  -123.8808
Iteration 4:   log likelihood = -123.87984

Logistic regression                             Number of obs     =        319
                                                LR chi2(4)        =      60.67
                                                Prob > chi2       =     0.0000
Log likelihood = -123.87984                     Pseudo R2         =     0.1967
```

T0_Diu	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
T0_dm	.5543649	.3779611	1.47	0.142	-.1864253	1.295155
T0_vision	-.0217589	.333447	-0.07	0.948	-.675303	.6317851
T0_Hear	.037873	.324122	0.12	0.907	-.5973945	.6731404
T0_htn	2.509944	.4286344	5.86	0.000	1.669836	3.350052
_cons	-3.220326	.4103172	-7.85	0.000	-4.024533	-2.416119

Logistic model for T0_Diu, goodness-of-fit test

(Table collapsed on quantiles of estimated probabilities)
(There are only 8 distinct quantiles because of ties)

Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0376	3	1.4	33	34.6	36
3	0.0384	2	3.0	76	75.0	78
5	0.0398	1	1.9	46	45.1	47
6	0.3247	7	7.3	25	24.7	32
7	0.3295	16	14.5	28	29.5	44
8	0.3379	15	15.8	32	31.2	47
9	0.4557	3	2.7	3	3.3	6
10	0.4705	13	13.5	16	15.5	29

```
      number of observations =       319
            number of groups =         8
     Hosmer-Lemeshow chi2(6) =      3.22
                  Prob > chi2 =    0.7803
```

```
. lroc

Logistic model for T0_Diu

number of observations =       319
area under ROC curve   =    0.7748
```

Appendix 4C: Sensitivity analysis results.

1) The Associations between FRID Use and Gait Speed

Complete Case Analysis (n=319)			**MICE Imputed Data (n=345)**		
Drug class	**Regression coefficient***	**P-value**	**Drug class**	**Regression coefficient***	**P-value**
Antidepressants	-1.90	0.582	Antidepressants	-3.16	0.368
Benzodiazepines	-1.29	0.776	Benzodiazepines	1.26	0.776
Diuretics	**-7.97**	**0.009**	**Diuretics**	**-6.22**	**0.041**
Statin	-1.47	0.546	Statin	-2.56	0.293
Vasodilators	4.83	0.082	Vasodilator	4.84	0.084
Alpha-blockers	-6.20	0.147	Alpha-blockers	-3.90	0.348
Beta-blockers	-3.13	0.328	Beta-blockers	-3.54	0.276
Aspirin	-0.14	0.954	Aspirin	-0.44	0.858

2) The Associations between FRID Use and Stride Time Variability (Stride Time CV)

Complete Case Analysis (n=319)			**MICE Imputed Data (n=345)**		
Drug class	**Regression coefficient***	**P-value**	**Drug class**	**Regression coefficient***	**P-value**
Antidepressants	0.01	0.905	Antidepressants	0.05	0.570
Benzodiazepines	0.12	0.270	Benzodiazepines	0.02	0.825
Diuretics	-0.05	0.515	Diuretics	-0.04	0.606
Statin	**0.13**	**0.026**	**Statin**	**0.12**	**0.044**
Vasodilators	-0.05	0.491	Vasodilator	-0.05	0.438
Alpha-blockers	0.15	0.144	Alpha-blockers	0.13	0.178
Beta-blockers	0.09	0.209	Beta-blockers	0.07	0.364
Aspirin	-0.01	0.898	Aspirin	-0.03	0.959

* Regression coefficients after adjusting for covariates

Curriculum Vitae

Name: Abdelhady Osman

Post-secondary Education and Degrees:

The University of Western Ontario
London, Ontario, Canada
2019-2021 MSc Epidemiology and Biostatistics

The University of Western Ontario
London, Ontario, Canada
2014-2018 BMSc Honors Specialization in Physiology

Honours and Awards:

Ontario Graduate Scholarship (OGS)
2020-2021

Western Graduate Research Scholarship (WGRS)
2019-2021

Related Work Experience

Teaching Assistant
Master of Public Health (MPH) Program
The University of Western Ontario
September 2020 – December 2020

Research Assistant
Gait and Brain Lab - Parkwood Institute
2019 – Present

Publications

Schapira M, Calabro P, Montero-Odasso M, **Osman A** et al. A multifactorial intervention to lower potentially inappropriate medication use in older adults in Argentina.
Aging Clinical and Experimental Research (2020)

Oral presentations

Osman A, Speechley M, Ali S, Montero-Odasso M. Fall Risk-Increasing Drugs and Gait Performance in Community-Dwelling Older Adults: Results from the Gait and Brain Study.
Canadian Geriatrics Society 40th Annual Scientific Meeting. May 2021

Poster presentations

Osman A, Kamkar N, Speechley M, Ali S, Montero-Odasso M. Fall Risk-Increasing Drugs and Gait Performance in Community-Dwelling Older Adults: A Systematic Review.
London Health Research Day. May 2021