Incident Depression and Daily-life Mobility in Middle-aged and Older Adults

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Depression is among the most prevalent mental disorders in middle-aged and older adults, with a global prevalence of up to 11%. Effective preventive measures for depression are often costly and labour-intensive and therefore require risk screenings to be practical. Recent studies suggested that clinically measured walking speed is a risk factor for depression, while little is known about whether other aspects of mobility are also predictive. To explore the temporal association between mobility, in particular daily-life mobility, and incident depression in older adults, one systematic review, one study on method development and validation, and three large-scale cohort studies were conducted.

Significant findings include:

- The Timed Up and Go Test, which incorporates multiple aspects of mobility (i.e., gait initiation, turning, and sit-to-stand time), is more predictive of depressive trajectories than the Six-Metre Walk Test and Five Times Sit to Stand Test.
- Duration of the longest daily walking bout, measured with a waist-worn sensor, independently and significantly predicts incident depression over two years.
- Daily-life walking speed, quality, quantity, and distribution can be reliably and validly measured with a wrist-worn sensor.
- Daily-life gait quality and quantity, measured with a wrist-worn sensor, independently and significantly predict incident depression over nine years of follow-up.

These findings add to the understanding of the association between human locomotion and depression. Gait quality and daily-life gait performances are independent and potentially modifiable predictors of depression. These measures, therefore, may have value for upcoming screening program development. Future research should investigate whether interventions addressing daily-life gait can play a role in preventing depression in middle-aged and older adults.

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Incident Depression and Daily-life Mobility in Middle-aged and Older Adults

Lloyd Long Yu CHAN

A thesis in fulfilment of the requirements for the degree of

Doctor of Philosophy

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February 2023

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Details of publication #2:
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CO-AUTHORS' AGREEMENT TO SUBMISSION

The thesis includes five papers to which others contributed as co-authors, Professor Stephen Lord, Dr Matthew Brodie, Dr Yoshiro Okubo, Professor Kim Delbaere, Dr Katya Numbers, Dr Ben Lam, Dr Jasmine Menanta, Dr Daina Sturnieks, Professor Julian Trollor, Dr Kimberly van Schooten and Dr Tiffany Choi. On each paper the contribution of the PhD candidate on each paper was greater than 50% as stipulated by faculty requirements.

All authors agree to the inclusion of these papers as part of this Doctoral thesis.

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Abstract

Depression is among the most prevalent mental disorders in middle-aged and older adults, with a global prevalence of up to 11%. Effective preventive measures for depression are often costly and labour-intensive and therefore require risk screenings to be practical. Recent studies suggested that clinically measured walking speed is a risk factor for depression, while little is known about whether other aspects of mobility are also predictive. To explore the temporal association between mobility, in particular daily-life mobility, and incident depression in older adults, one systematic review, one study on method development and validation, and three large-scale cohort studies were conducted. Significant findings include:

- The Timed Up and Go Test, which incorporates multiple aspects of mobility (i.e., gait initiation, turning, and sit-to-stand time), is more predictive of depressive trajectories than the Six-Metre Walk Test and Five Times Sit to Stand Test.
- Duration of the longest daily walking bout, measured with a waist-worn sensor, independently and significantly predicts incident depression over two years.
- Daily-life walking speed, quality, quantity, and distribution can be reliably and validly measured with a wrist-worn sensor.
- Daily-life gait quality and quantity, measured with a wrist-worn sensor, independently and significantly predict incident depression over 9 years of follow-up.

These findings add to the understanding of the association between human locomotion and depression. Gait quality and daily-life gait performances are independent and potentially modifiable predictors of depression. These measures, therefore, may have value for upcoming screening program development. Future research should investigate whether interventions addressing daily-life gait can play a role in preventing depression in middle-aged and older adults.

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List of abbreviations

Abbreviation	Description
AIC	Akaike's Information Criterion
AUC	Area under Receiver Operator Characteristic Curves
AST	Aspartate aminotransferase
BDI	Beck's Depression Inventory
BMI	Body mass index
BIC	Bayesian Information Criterion
CES-D	Centre for Epidemiologic Studies Depressive symptoms Scale
COM	Center of mass
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
dB	Decibel
DGB	Digital gait biomarkers
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
EQuHR	Poorest quartile hazard ratio
EQ-VAS	EuroQol Visual Analog Scale
GDS	Geriatric Depression Scale
GBTM	Group-based trajectory modelling
HR	Hazard ratios
ICC	Intraclass correlation coefficient
ICD-10	International Classification of Disease 10th Revision
IPEQ	Incidental and planned exercise questionnaire
IMU	Inertial measurement unit
IL	Interleukin
IQR	Interquartile Range
IRR	Incidental rate ratio
MAPE	Mean absolute percentage error
MAS	Sydney Memory and Aging Study
ML	Mediolateral
MoCA	Montreal Cognitive Assessment
ms^{-1}	Meter per second
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NOS	Newcastle-Ottawa Scale
OR	Odds ratios
PCA	Principal component analysis
PHQ-9	Patient Health Questionnaire-9
PRISMA	Preferred Reporting Items for a Systematic Review and Meta-Analysis
PTOR	Poorest tertile odds ratio
SD	Standard deviation

ROC	Receiver operator characteristic curves
s	Second
SPPB	Short Physical Performance Battery
SOR	Standardised odds ratios
STS	Five Times Sit to Stand Test
SVM	Support Vector Machine
TUG	Timed Up and Go Test
WMH	White matter hyperintensities
WHODAS 2.0	World Health Organization Disability Assessment schedule 2.0
6MWD	Six-Minute Walk Distance
6mWT	Six-Metre Walk Test
γ-GTP	Gamma-glutamyl transpeptidase

List of manuscripts included in thesis

Chan, L. L. Y., Choi, T. C. M., Lord, S. R., & Brodie, M. A. (2022). Development and large-scale validation of the Watch Walk wrist-worn digital gait biomarkers. *Scientific Reports*, *12*(1), 16211. https://doi.org/10.1038/s41598-022-20327-z

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Chapter 1 Introduction and outline

1.1 Global population aging and late-life depression

With rapid developments in economic and healthcare sectors over the past century, life expectancy around the globe has been rising [1]. From 1950 to 2000, the average world life expectancy increased from below 50 to over 65 years. It has been projected to rise to over 75 years by 2050. With an increasing life expectancy comes a surge in the older population. In 2015, about 900 million people aged 60 years and over worldwide. That figure is expected to increase to 1.4 billion by 2030 and 2.1 billion by 2050 [2].

Depression is among the most common mental disorders in older people [3], with a global prevalence of 4% to 11% [4-6]. More commonly, the prevalence of clinically significant depressive symptoms has been estimated to be between 15 to 23% in older people [7, 8]. This disorder can lead to long-term disability and significantly reduced quality of life [9]. Late-life depression requires specific attention, as depression presenting in late life often has a different etiology from depression with an earlier onset [10]. It is less related to personality and social disorders and more associated with comorbidities and physical deterioration [10]. It has also been noted that depression may manifest differently between older and younger people. Late-life

depression is often presented without low mood and is marked with other somatic complaints, decreased activity level, and vague symptoms [11, 12]. It is not uncommon for older people to have the misconception that depressive symptoms are a normal aging phenomenon. Hence they are less likely to raise affective concerns [13]. Taken together, it is clear that late-life depression represents a pressing global public health issue.

1.2 Prevention and risk factors of late-life depression

Given the high prevalence and negative impacts associated with late-life depression, preventive measures are much required. These measures can be classified as universal and indicated [14]. Universal interventions are applied toward all individuals in the aging population, regardless of their risk of developing depression, as a general healthcare measure. Interventions that fall into this category are usually low-cost, easy to implement and have few side effects, such as dietary supplements (i.e. supplements of vitamin D, vitamin B12 and folic acid) and physical activity promotion [15, 16]. However, recent evidence suggested that these interventions are not effective in preventing the onset of depression [15, 16]. Psychosocial interventions which are tailored to an individual's abilities and preferences have been found to be more effective [17] but are more costly and labor-intensive. Therefore, these interventions

are often only feasible after a medical indication, i.e., prescribed to individuals with a high risk of developing depression. The higher effectiveness of indicated interventions over universal interventions for the prevention of depression is also evident in other age groups [14]. These observations emphasise the importance of identifying people at high risk of developing depressive symptoms using risk prediction tools, so that indicated preventions can be administered efficiently.

Several depression risk prediction models have been developed based on known risk factors. These risk factors include psychoactive medication use, psychiatric disorder history, demographics, blood test results (including hemoglobin, triglyceride, cholesterol, blood glucose, γ-GTP, AST, and creatinine levels), exercise levels, alcohol intake, sense of control, self-rated health, family history, childhood trauma, threatening life experiences and comorbidities collected thorough medical check-ups [18] or self-administered questionnaires [19]. However, in clinical practice, the prediction of late-life depression is yet to be routinely performed [20]. The extensive time required to collect a comprehensive list of risk factor information from patients is likely to have hindered the widespread use of these risk prediction tools. In contrast, risk prediction based on automatically measured information requires less commitment and effort from clinicians and patients and may therefore enable more

widespread depression risk screening.

1.3 Mobility and late-life depression

In the past decade, there has been a growing interest in whether mobility can help predict late-life depression. Mobility is defined as the ability to move oneself through a physical environment. It is often characterised by walking performances(gait), but also includes other abilities such as transferring, turning, and running. While psychomotor retardation, including slowness of walking, has long been identified as a significant feature of depression [21], particularly melancholic depression, little research has been conducted to identify affected gait parameters other than walking speed until recently. Shorter stride length [22] and higher swing time variability [22, 23] have been reported in individuals with depressive symptoms compared to a control group. Further, investigations on the temporal association between walking performance and depression are relatively recent and sparse. In the few studies conducted to date, it has been reported that changes in gait speed precede incident depressive symptom development by years [24, 25]. Older people with slower walking speeds or a shorter step length were found to have increased odds of developing depressive symptoms over four years [24]. However, little is known about whether other aspects of walking are also predictive of depression. Clinical mobility

tests, such as the Timed Up and Go test that captures more aspects of mobility, including rising from a chair, turning, and gait initiation, could be more predictive of depression. Further, daily walking performance has been found to be different from clinic/laboratory-based walking performance [26] and may better reflect an individual's usual performance. Other dimensions of gait, such as walking intensity, quality, quantity, and distribution, might also add additional information to the prediction of depression. However, few studies have examined whether these gait measures aid in predicting depression onset.

1.4 Daily-life mobility and wearable technology

Wearable devices incorporating inertial measurement units (IMU) may offer a feasible pathway to measure multiple aspects of daily walking performance. First used for aircraft navigation in the 1930s, IMUs have been miniaturised into highly portable, durable, low-cost, and low-processing power devices [27]. Such wearable devices were first used in the 1950s for measuring human movements and have gained increasing attention ever since. Conventionally, IMU contains two sensor types: linear accelerometers for measuring inertial acceleration and gyroscopes for measuring angular velocities. However, a range of wearable sensors are now available; some consist of linear accelerometers only [28], whereas others include

features such as magnetometers [29], flexible goniometers [29], force sensors [29], electromyography, or barometers [30].

Walking speed and other gait characteristics can be readily derived from wearable sensor data [31-33]. These sensors hold several advantages compared to self-reported physical activity and clinical gait/mobility tests. First, wearable sensors can reliably and validly measure parameters that reflect gait quantity and quality [34-36]. Second, it is feasible to conduct several days of continuous measurements, which capture gait performances and physical activity levels of daily living, with excellent test-retest reliability in field base settings [37]. As gait in daily life may reflect an individual's "usual" performance rather than a "laboratory-based" performance [31, 38], it may better predict the development of depressive symptoms. Third, wearable sensors, often incorporated into smartwatches or smartphones, are commercially available and increasingly ubiquitous, making sensor-based gait assessments and analysis easy to conduct remotely. This reduces commute time, disease transmission risks, and medical attention barriers. From a clinical perspective, activity monitoring enables screening programs of high-risk populations, classification of subtypes within disorders, effectiveness evaluation of exercise promotion programs, and behavior modification initiatives [39]. However, no studies to date have investigated the

association between incident depression and gait using wearable sensors.

1.5 Attachment sites of wearable sensors

Previous studies have used different sensor positions for movement measurements. Since most body movements occur in the lower extremities during locomotion, sensor attachments on the thigh, shank and foot have been commonly used [40]. Positioning sensors on these body locations accurately detect gait events (especially in toes-off) and lower extremity joint angles [41]. However, their application is often confined to laboratory measurements only [42]. This is mainly due to the inconvenience of attaching sensor devices to the lower limb in everyday life. Another widely used sensor placement position is near the center of mass (COM), such as the waist and pelvis [43]. Ergonomically, sensors placed proximal to COM require less energy to bear, and the attachment of a sensor to the belt provides a reasonably convenient means for a longer duration of data collection. However, some participants find wearing waist-worn sensors for a prolonged duration (eg. 24 hours) uncomfortable. In consequence, some previous studies have reported non-wear time has led to significantly distorted estimates of mobility and physical activities [44, 45].

In comparison, wrist-worn sensors usually result in higher compliance since they can

be worn continuously throughout the day and night. The wrist is also a well-accepted position for sensor positioning, as evidenced by the popularity of smart watches and activity bands. A high acceptance rate for wrist-worn sensors has also been found among older people [46, 47]. On the downside, the variability of arm position and movements lead to a considerable amount of noise in the measurement of whole-body movements, such as when rising from a chair and walking. The constantly changing orientation of wrist devices impedes the calculation of body segment acceleration as gravity, as a form of acceleration, cannot negate reliably. Also, the drift of the measurements limits the computation of velocity and displacement with integrations [48]. Consequently, there has been limited use of wrist devices to capture daily mobility performances hindering the understanding of how daily-life mobility predicts the risk of incident depression.

1.6 Thesis objectives

My thesis objectives were to:

1. Systematically and quantitatively synthesise previous findings on what aspects of mobility predict the onset of depression.

2. Identify sensorimotor, balance, mobility, and lifestyle factors most predictive of worsening depression trajectories over time.

3. Develop algorithms that extract daily life mobility performance measures from wrist-worn sensor data.

4. Investigate whether daily life mobility performance measures captured by wearable sensors predict the onset of depression.

1.7 Thesis format and structure

This thesis is submitted as a series of publications. Each results chapter includes a literature review, a description of methods, results, and a discussion of the findings and is presented in accordance with the format specified by the journal of publication. This has resulted in some repetitive information, particularly with respect to the description of methods. Copyright clearance and permission from co-authors have

been obtained for each published work included in this thesis.

1.8 Thesis Outline and Summary

Chapter 2 –is a systematic review of cohort studies evaluating whether mobility impairment can predict incident depression. It was published in *Experimental Gerontology.*

Chapter 3 –is a cohort study with a six-year follow-up of depressive symptoms in 553 individuals aged 70 to 90 years. It is currently under peer review by the journal *The Australasian Journal on Ageing*.

Chapter 4 –investigated whether waist sensor-measured daily-life walking quantity and quality predict depression onset. To the author's knowledge, this is the first study to predict depression with wearable technology. It was published in the *Journal of the American Medical Directors Association*.

Chapter 5 –reports the development and validation of an algorithm to remotely monitor daily walking speed, quantity, quality, and distribution with wrist-worn sensors. It was published in the journal *Scientific Reports.*

Chapter 6 – applies the WatchWalk method developed in Chapter 5 to a health record-linked large-scale database of 78,822 participants. It was accepted by *the journal of the American Medical Directors Association.*

Chapter 7 – presents the summary and general discussion of this thesis. Significant findings, limitations, clinical implications, new contributions to knowledge and directions for future research are discussed.

Chapter 2. Mobility performance predicts incident depression: a systematic review and meta-analysis

2.1 Abstract

Impaired mobility often co-occurs with depression. However, there is no systematic review evidence as to whether mobility impairments precede the onset of depression. The objective of this systematic review and meta-analysis was to evaluate whether mobility impairment could predict incident depression. A systematic search of cohort studies was performed in MEDLINE, EMBASE, CINAHL and PsycINFO. The target population was people with no depressive symptoms at baseline and follow-up for depression or depressive symptoms of at least three months. Of 1,061 identified abstracts, 13 studies met the review eligibility criteria. The majority of included studies (8 out of 13) were of high methodological quality. Follow-up periods ranged from 12 months to 16 years. Gait speed was the most consistently reported mobility measure. Participants with slow gait speed were at higher risk of developing depressive symptoms (pooled OR=1.93, 95%CI: 1.54 to 2.42, 11 studies). This review shows that slow gait speed is predictive of the onset of depressive symptoms.

Systematic review registration number: CRD42020153791

Keyword: Walking Speed; Mobility Limitation; Depression; Forecasting

2.2 Introduction

Depression is a prevailing ailment in older adults, with a reported prevalence ranging from 4% to 11% [4-6]. Depression is strongly associated with reduced quality of life [49] and increased mortality [50] but accurate and timely identification has been a major challenge. It has been suggested that primary care physicians can correctly recognise only 47% of cases and 79% of the non-cases [13]. Hence, it has been estimated that 80% of older adults with depression do not receive a diagnosis or intervention [51]. This suggests a need for better ways to predict depression, including using mobility assessments, which could be used to help inform interventions in people earlier in the disease progression.

It has been postulated that both mobility and depressive disorders are clinical presentations of neurobiological deficits and recent cross-sectional studies have reported high co-occurrences of depressive symptoms and mobility impairments [22, 52]. In addition, mobility limitations may result in depressive symptoms by restricting community participation, independence and performance of daily activities [53, 54]. However, the chronological sequence between the occurrence of mobility impairments and depressive symptoms has not been systematically reviewed.

Mobility assessments do not require invasive procedures, highly specialised personnel or laboratory investigations making them easy to implement in clinical practice. Mobility assessments may provide useful additional information that is independent of the existing diagnostic criteria for depression and, thus, increase precision of diagnostic tools. Further, a clearer understanding of the interaction between depressive symptoms and mobility impairment would help formulate preventive measures and interventions.

The objective of this review was to systematically and quantitatively synthesise the findings from longitudinal cohort studies that have examined whether mobility performance can predict the onset of depressive symptoms.

2.3 Methods

Our systematic review was registered with PROSPERO (registration number: CRD42020153791) and conducted in accordance with the guidelines of the preferred reporting items for a systematic review and meta-analysis (PRISMA).

2.3.1 Eligibility Criteria

Studies were included if they: 1) used a cohort design, 2) included adult participants without depression or without depressive symptoms at baseline, 3) objectively assessed mobility performances, 4) measured incident depression or incident depressive symptoms with at least three months of follow up and 5) were published in English. Exclusion criteria were: 1) lack of data to enable the assessment of associations between mobility performances and incident depression/depressive symptoms (e.g. odds ratio, relative risk, hazard ratio etc.), and 2) publication in non-peer-reviewed articles, theses or conference papers.

2.3.2 Search Strategy

Five electronic data bases: MEDLINE, EMBASE, CINAHL, PsycINFO and MEDLINE Epub Ahead of Print were searched from inception to 14th October, 2019. The following keywords and medical heading terms were used: [“inciden*” OR “develop*” OR “predict” OR “new” OR “traject” OR “later”], [“depressi*”] and [“gait*” or “walk*” or “mobility*” OR “frail*”]. The detailed search strategy is included in Appendix A1.

2.3.3 Study Selection

Titles and abstracts of the extracted articles were independently screened by two review teams (1: LC, 2: MB & YO) for eligibility. Subsequently, full texts of identified titles were retrieved and screened. Any discrepancies were resolved by discussion. The flow of the study screening process is outlined in Figure 2.1 and appendix A3.

2.3.4 Data extraction

The primary reviewer extracted data from the included studies. Data regarding author names, publication year, study name, sample size, target population, demographics, mobility performance measures, the definition of depression/ depressive symptoms, length of follow-up, the incidence of outcome, covariates and statistical procedures were extracted using a piloted form. Corresponding authors of the eligible studies were contacted if additional information was required.

2.3.5 Quality assessment

Two reviewers (YO and LC) independently assessed the methodological quality of the eligible studies using a modified version of the Newcastle-Ottawa Scale (NOS)

[55]. Discrepancies were solved by discussion.

2.3.6 Data synthesis and analysis

The study descriptions and primary findings are presented in tables and text summaries; i.e. information on participant characteristics, mobility performance measures, study methods, follow-up rates, outcome measures and methodological quality. The association between mobility performance and incident depressive symptoms was pooled using the adjusted odds ratio (OR) and corresponding 95% confidence interval. In studies that reported hazard ratios (HR) or mean differences, estimated odds ratios were calculated before inclusion in the meta-analyses. Random-effect meta-analyses were performed with results presented as forest plots. Heterogeneity between the studies was assessed with the chi-square test and the I^2 statistics. Two subgroup analyses were performed. The first examined whether gait assessments conducted at usual or maximal walking speed was more predictive of incident depressive symptoms. The second examined whether the association differed between population-based sampled older people and people diagnosed with medical conditions other than depression. A funnel plot was generated to assess publication bias. A sensitivity analysis including only studies that were graded as having good methodological quality were conducted. All analyses were performed with Review

Manager (RevMan) Version 5.3 (The Cochrane Collaboration, Copenhagen).

2.4 Results

2.4.1 Search and Selection

The search retrieved 1,061 records (Figure 2.1). A total of 614 titles remained after de-duplication, 550 were excluded at the title and abstract screening stage for the following reasons: Not published in English (n=3); not peer-reviewed (n=122); not a cohort design (n=110); did not include incident depression as an outcome (n=217); did not include any mobility measures as a predictor (n=76) and; measured mobility through self-reports (n=22). Of the 64 papers reviewed in full-text, 50 were excluded for the following reasons: published as a conference paper (n=3); conducted using a cross-sectional designs (n=2); provided only descriptive statistics (n=2); did not include incident depressive symptoms as an outcome (n=26) and lacked data to assess associations (n=17). Fourteen peer-reviewed articles from 13 studies published over the past nine years were eligible for this review and are summarised in Table 2.1. [24, 56-68] Gait speed was analysed as a categorical variable in eleven studies, while one study analysed it as a continuous variable. The combination of category-based odds ratios and continuous variable-based odds ratios rely on the assumption of normally

distributed variables [69], which could not be ascertained for the gait speed measurements. Hence, the meta-analyses were conducted using data from 11 studies.

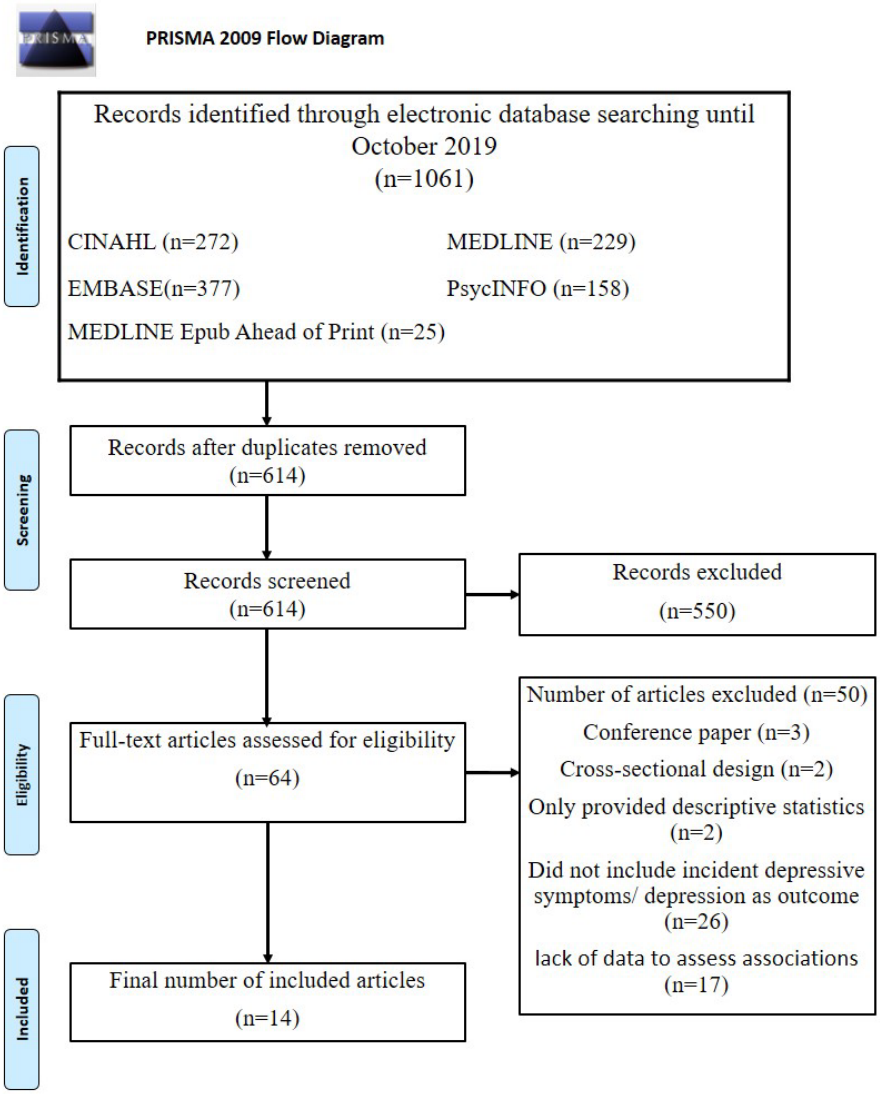

Figure 2.1. Flow diagram of the screening process

2.4.2 Study and participant characteristics

The eligible studies with a total of 25,572 participants were conducted in The Netherlands [56, 59], Singapore [57], Germany [58], Japan [60], the United States

[61, 62, 65, 67, 68], the United Kingdom [63], Italy [64] and Ireland [24, 66]. The study groups comprised community-dwelling older adults [24, 56, 57, 59, 60, 63, 64, 66], people with multiple sclerosis [58, 67], people with peripheral artery disease [61], people with chronic obstructive pulmonary disease [62], dialysis patients [68] and people with high risk of developing knee osteoarthritis [65]. The mean age of participants ranged from 44.3 to 73.6 years, and the proportion of female participants ranged from 30.2% to 72.0 % (Table 2.1). Follow-up periods were between 12 months to 16 years.

Twelve studies included gait speed as a predictor: two studies measured maximal gait speed [56, 58], three measured six-minute walk distances [61, 62, 64] and seven measured usual walking speed [24, 59, 60, 63-65, 67, 68]. One study used the Performance Oriented Mobility Assessment to grade gait performance [57] and one measured step length, step width and percentage time of double limb support with the GAITRite walkway [24]. Of the two studies that used other mobility measures, one assessed Five Times Sit to Stand Test performance [64], and two assessed standing balance, walking and chair-rise ability as combined Short Physical Performance Battery (SPPB) scores [60, 64]. Depressive symptoms were assessed with the Centre for Epidemiologic Studies Depressive symptoms Scale (CES-D) (seven studies) [24,

56, 59, 62, 63, 65, 66, 68], the Geriatric Depression Scale (GDS) (three studies) [57, 60, 61], the Beck's Depression Inventory (BDI) (one study) [58] and Patient Health Questionnaire-9 (PHQ-9) (one study) [67]. In the final study, depression was diagnosed by a psychogeriatrian [64].

Table 2.1. Characteristics of Included Studies

Reference/ Country/ Study Name Acronym (if applicable)	Sample size	Baseline Assessment			Follow up		Main Results [95%CI]	NOS score / 9)
		Target population	Percentage of women/ Mean age (SD)	Mobility performance measures	Length of Follow-up	Outcome definition/ Incidence		
Sanders 2012 [56] Netherlands LASA	1928	Community-dwelling older people	51.0% 69.9 (8.5)	Gait speed measured as time to walk 3 meters, make a 180° turn, and walk 3 metres back **as quickly as possible**	16 years	Fulfil both criteria: 1) ≥5 points increase in CES-D from baseline; 2) ≥16 points in CES-D in follow-up 24%	Men: EQuHR: 1.67 [1.08 to 2.57] [c,k] Women: EQuHR: 1.22 [0.87-1.72] [c,k]	6
Feng 2014 [57] Singapore SLAS-I	1618	Community-dwelling older people	Not given	Performance Oriented Mobility Assessment (POMA) gait subscale. Subjects walked 6 metres and returned the starting point **at a rapid pace**. Walk initiation ability, hesitancy, step height, symmetry, foot clearance, step continuity deviation and walking distance were assessed. The total score ranged from 0 to 12. <9 denotes slowness	Four years	≥ 5 points in the 15-item GDS. Not given	OR: 2.02 [0.93 to 4.36] [a, b, e, f] OR: 0.99 [0.42 to 6.35] [a, b, e, f, g, j, h, i, l]	6
Hildebrandt 2014 [58] Germany	40	Individuals with multiple sclerosis	Not given	Timed walk test: the time required to 25 feet (7.62 meters) **as quickly as possible**	One year	≥12 points in Beck's Depression Inventory (German), with items on tiredness and sleep disorders excluded	Participants with new onset of depressive mood: 5.7 seconds (SD:2.1) Participants without: 5.4 seconds (SD:2.0)	5

Makizako 2015 [60] Japan OSHPE	3025	Community-dwelling older people	50.3%, 71.4 (5.1)	**Usual gait speed** while walking through 2.4 meters of the middle section of a 6.4 meters walkway. Use of cane or walker permitted. A cutoff point of <1.0m/s determined slow speed. Physical performance was measured with SPPB which includes standing balance, walking and repeated chair-rise tests.	15 months	A score of ≥6 in the 15-item GDS 7.5%	Gait speed*: OR: 2.00 [1.41 to 2.84] SPPB compared to full score(12), score of 10-11: OR: 1.44 [1.00 to 2.06][a,b] OR: 1.10 [0.75 to 1.61][a,b,e,f,h,i,l,m,n,o] score of 9 or below: OR: 2.45 [1.36 to 4.43] [a,b] OR: 1.46 [0.77 to 2.77] [a,b,e,f,h,i,l,m,n,o]	8
Collard 2015 [59] Netherlands InCHIANTI	699	Community-dwelling older people	50.5%, 72.8 (6.1)	**Usual gait speed** measured in a 4-metre walking test Slowness defined as gait speed in the lowest quartile in stratified gender and height groups	Two years	Fulfil both criteria: 1) ≥4 points increase in CES-D from the prior measurement, 2) a CES-D score ≥20 in follow-up 30.6%	HR: 1.39 [0.95 to 2.03][a,b,e,g,h,i,l]	7
McDermott 2016 [61] USA WALCS	Without PAD: 765 With PAD: 415	Individuals with peripheral artery disease (PAD) and controls	with PAD: 38.2% 71.94 (8.93) without PAD: 54.7%, 69.61 (7.54)	6MWD: The **maximal distance** a participant covers in a 100-foot hallway for 6 minutes	Mean follow-up: 2.7±1.2 years,	A score of ≥6 in the 15-item GDS 12.7%	With PAD: HR per100 feet: 0.94 [0.89 to 1.00] [a,b,d,e,g,h,q,r] Without PAD: HR per100 feet: 0.86 [0.79 to 0.93] [a,b,d,e,g,h,q,r]	7
Yohannes 2016 [62] USA ECLIPSE	1095	Individuals with chronic obstructive pulmonary disease	30.2% 63.6 (10.3)	6MWD: The **maximal distance** a participant covers in a 100-foot hallway for 6 minutes	Three years	≥16 points in CES-D or reported antidepressant use 14.2%	Participants with new onset depression: 363metres (SD= 244) Participants without: 404metres (SD=139)	6
White 2017 [65] USA OAI	3939	Individuals between 45 to 79 year old who had os of age at high risk of	58% 61.4 (9.2),	Gait speed during a 20-meter walk at **usual pace**. Slow gait speed was defined as <1.2 m/s	Seven years	Trajectory group of worsening depressive symptoms (CES-D): on average a mean CES-D score	OR: 4.3 [3.2 to 6.0] OR: 3.1 [2.2 to 4.4][a,b,d,e,g,r,p]	7

		knee osteoarthritis				of 9.7 proceeded to 17.8. 7.69%		
Veronese 2017 [63] UK ELSA	4077	Community-dwelling older people	50.06% 70.8 (7.8),	Slow gait speed was defined using the mean walking speed of two 8 feet (2.43m) walks **at usual pace** with sex and height cut-off suggested by Fried et al. (2001). 70] Participants who could not perform the walking test owing to medical reasons were categorised as having low gait speed.	Two years	≥4 points in the eight-item version CES-D 8.83%	OR: 7.32 [4.51-11.94] OR: 1.82 [1.00 to 3.32][a,b,e,g,h,j,k,l,s]	8
Veronese 2017 [64] Italy the Progetto Vento Anziani Study	966	Community dwelling older people	54.5% 73.6(6.8)	Physical performance measured by SPPB 4- metre walking speed test: the best performance achieved in 2 walks at the participants' **usual pace** along a 4-metre corridor (m/s). Canes or walkers were permitted Five Times Sit to Stand Test 6-minute walk test	Mean follow-up:4.4 years	A geriatric psychiatrist diagnosed depression with the aid of 30-item GDS (cut-off at 10 points) and additional relevant information 21.01%	SPPB: PTOR: 2.07 [1.25 to 3.42] PTOR: 2.71 [1.57 to 4.68][a,d,j,k,l] AUC: 0.63 4-m gait speed: PTOR: 2.25 [1.54 to 3.31] PTOR: 1.79 [1.18 to 2.71] [a,d,j,k,l] AUC: 0.60 Chair stand time: PTOR: 2.37 [1.61 to 3.47] PTOR: 2.05 [1.36 to 3.07] [a,d,j,k,l] AUC: 0.61 6MWT: PTOR: 2.28 [1.54 to 3.36] PTOR: 1.89 [1.23 to 2.91] [a,d,j,k,l] AUC: 0.62	8
Briggs 2018 [66] & Briggs 2019 [24] Ireland TILDA	2459	Community-dwelling older people	51.5%, 69.9	TUG: Gait disturbance is defined by a score of 12 seconds or more	Two years	≥16 points in CES-D 9%	IRR: 2.11 [1.29 to 3.42] IRR: 2.25 [1.32 to 3.83][a,b,k] IRR: 2.00 [1.18 to 3.39][a,b,g,i,k,l,t,v,w]	6
	3615		50.8%, 63.6	Spatiotemporal gait analysis provided by the GAITRite system, a computerised mat with pressure sensors: **Usual gait speed**, step length,	Four years	≥16 points in CES-D 9.52%	Gait speed: PTOR:1.78 [1.30-2.44] PTOR: 1.54 [1.08 to 2.19][a,b,d,e,g,h,i,k,l,t,x] Step length: PTOR: 1.96 [1.42-2.70]	

				step width and double support phase duration			PTOR: 1.54 [1.01 to 2.35] [a,b,d,e,g,h,i,k,l,t,x] Step width: PTOR: 1.18 [0.83 to 1.68] PTOR: 1.19 [0.76 to 1.85] [a,b,d,e,g,h,i,k,l,t,x] Double support % : PTOR: 0.81 [0.59 to 1.11] PTOR: 0.92 [0.64 to 1.31] [a,b,d,e,g,h,i,k,l,t,x]	
Sy 2019 [68] USA ACTIVE/ADIPOSE	531	Individuals that attend haemodialysis	42.1%, 57.5(14.4)	Low gait speed was defined using the faster of two 15 feet (4.6 m) walking trials **at usual pace**, using standard cut-points based on sex and height	Two years	≥16 points in CES-D 16.4%	OR†: 1.53 [0.93-2.50] OR†: 1.62 [0.95-2.77] [a,b,r] OR†: 1.74 [1.01-3.01] [a,b,g,r] OR†: 1.52 [0.85-2.73] [a,b,g,n,r]	7
Briggs 2019 [67] USA MS	400	Individuals with relapsing-remitting multiple sclerosis	72.0%, 44.3(10.5)	Time needed to walk a distance of 25 feet (7.6 m) **at usual pace**. Upper and lower quartile cut-offs were 4.3 and 5.7 seconds respectively	Three years	≥5 points in PHQ-9 43.3%	PTOR†: 1.96 [1.14 to 3.41] PTOR†: 2.33 [1.26 to 4.40][a,b,r] PTOR†: 2.24 [1.15 to 4.41][a,b,r,s,y,z]	5

AUC, Area under Receiver Operator Curve; CES-D, Center for Epidemiologic Studies Depression Scale; COPD, Chronic Obstructive Pulmonary Disease; EQuHR, Poorest quartile hazard ratio; PTOR, Poorest tertile odds ratio; GDS, Geriatric Depression Scale; HR, hazard ratio; IRR, incidental rate ratio; NOS, Newcastle-Ottawa Scale; OR, odds ratio; PHQ-9: Patient Health Questionnaire-9; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go Test; 6MWD, six-minute walk distance.

Covariates adjusted for. a= Age; b= sex; c= height; d = BMI; e = education; f= living arrangements; g= medical comorbidity; h= smoking; i= alcohol use; j= ADL dependency/ score; k= baseline depression score; l= baseline cognition score; m= self-rated general health; n= frailty; o= fear of falling; p=pain; q=income; r= race; s= marital status; t= antidepressant use; v= loneliness; w= fall history; x= blood pressure; y=type of insurance (private, Medicare, Medicaid, Self-pay); z= median income by ZIP code.

*OR and the corresponding 95%CI were not provided in the article, but necessary information for the calculation was available. This OR and corresponding 95%CI were calculated with Review Manager (RevMan) version 5.3.

†OR and the corresponding 95%CI were not provided in the article, but the corresponding author provided additional information for this review.

2.4.3 Risk of bias within studies

The Newcastle-Ottawa Scale ratings of the included studies are presented in Table 2.2. Eight studies were considered to have high methodological quality [24, 59-61, 63-66, 68]. Five studies were considered of low quality [56-58, 62, 67] because outcomes were measured with self-reporting questionnaires [56-58, 62, 67], important confounders were not adjusted for [58, 68] and/or there were significant losses of follow up (>20%) [56, 57, 62, 68].

Table 2.2. Methodological quality of the included studies graded with Newcastle Ottawa Scale

First Author, Year	Selection	Comparability	Outcome	Total Score
Sanders 2012 [56]	****	*	*	6
Feng 2014 [57]	****	*	*	6
Hildebrandt 2014 [58]	***		**	5
Makizako 2015 [60]	****	**	**	8
Collard 2015 [59]	****	*	**	7
McDermott 2016 [61]	****	*	**	7
Yohannes 2016 [62]	****	*	*	6
White 2017 [65]	****	*	**	7
Veronese 2017 ELSA [63]	****	**	**	8
Veronese 2017 PVAS [64]	****	**	**	8
Briggs 2018 & 2019 TILDA [24, 66]	****	**	**	8
Sy 2019 [68]	****	*	**	7
Briggs 2019 MS [67]	****	*	*	6

2.4.4 Syntheses of results

Figure 2.2 and 2.3 present the results of individual studies and the pooled odds ratio for the association between walking speed and incident depressive symptoms. Participants with slow walking speed had twice the odds of developing depressive symptoms, when compared with participants with normal walking speed (pooled OR=1.93, 95%CI: 1.54 to 2.42, p<0.001). A moderate to high heterogeneity was observed among the studies (I^2= 70.0%; Chi^2= 36.09, df = 11; p <0.001). The subgroup difference for the analysis contrasting usual and maximal walking speed was not significant (I^2= 56.3%; Chi^2= 2.29, df = 1; p =0.13) (Figure 2.2). In the studies that measured maximal walking speed, the pooled OR was 1.56 (95%CI: 1.18 to 2.07, p=0.002), and a low level of heterogeneity was evident (I2= 38%; Chi2= 4.87, df = 3; p =0.18). In the studies that measured usual walking speed, the pooled OR was 2.11 (1.61 to 2.78, p<0.001), and a high level of heterogeneity was evident (I^2= 69%; Chi^2= 22.39, df = 7; p =0.002). The second subgroup analysis stratified community-dwelling older adults from other population groups (Figure 2.3). The subgroup difference was not significant (I^2=0%, Chi^2=0.19, df =1, p=0.66). Among studies that recruited community-dwelling older adults, the pooled OR was 1.81 (95%CI: 1.54 to 2.12, p<0.001), and very low heterogeneity was found (I^2=7%, Chi^2=6.45, df=6, p=0.37). In people with chronic medical conditions, the pooled OR was 2.06 (95%CI:1.17 to 3.64, p=0.01), and a high level of heterogeneity was observed (I^2=86%, Chi^2=28.28, df=4, p<0.001).

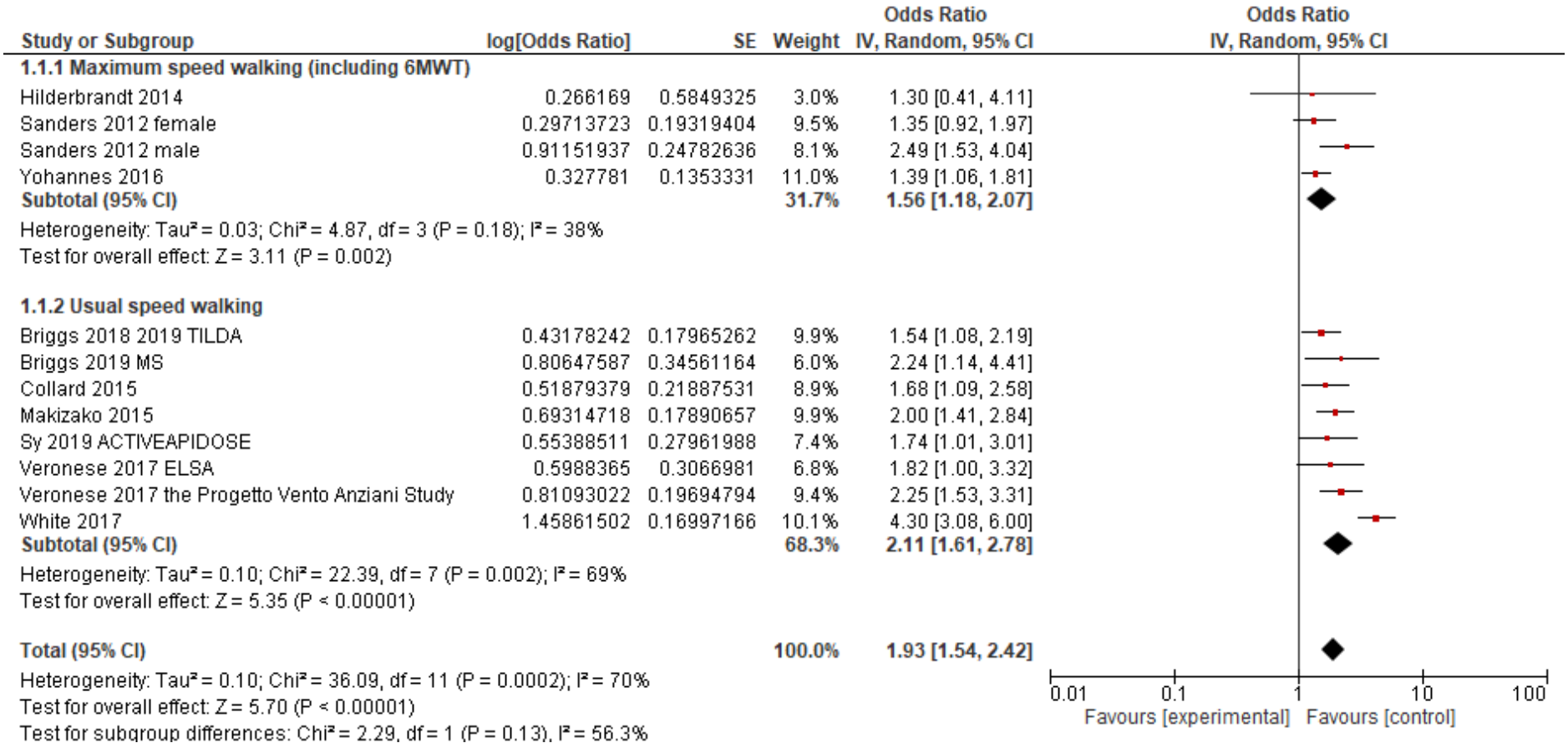

Figure 2.2 Meta-analyses for effect estimates of baseline gait speed on incident depressive symptoms stratified by instructions on walking speed.

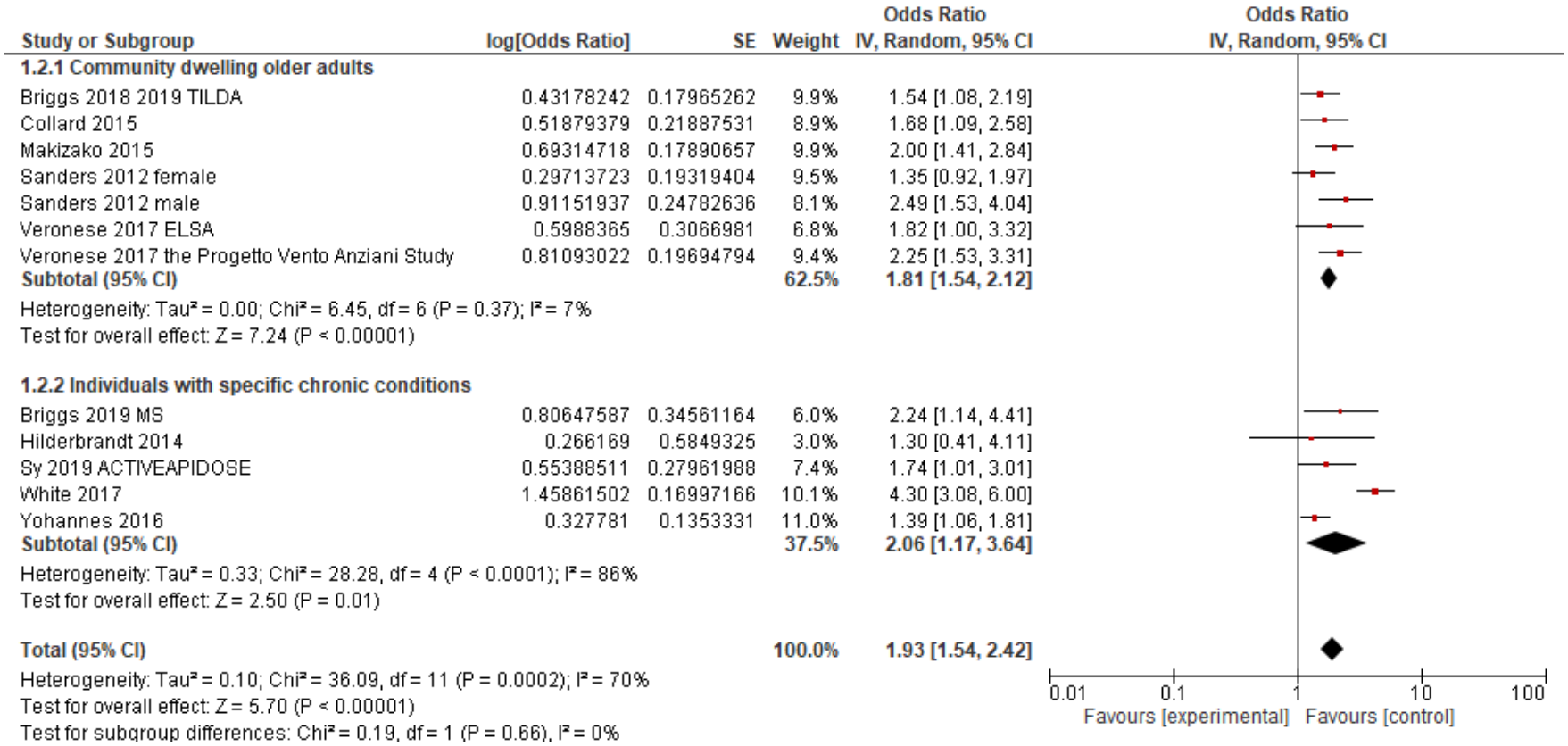

Figure 2.3 Meta-analyses for effect estimates of baseline gait speed on incident depressive symptoms stratified by population groups

The other mobility measures were included in only one or two studies, and as these studies used different measurement and analysis methods, we restricted our analysis to a narrative synthesis. Performance Oriented Mobility Assessment (POMA) gait sub-score was not significantly associated with the incidence of depressive symptoms (OR: 2.02, 95%CI: 0.93 to 4.36) [57]. Compared to participants who obtained high scores in the SPPB, those in the lowest tertile had significantly higher risks of developing depressive symptoms (Poorest tertile OR: 2.71, 95%CI: 1.57 to 4.68) [64]. Similarly, another study that compared participants with an SPPB score of 9 or below (considered to have poor to moderate mobility performance (3% of the sample) with those who had maximal SPPB scores (82% of the sample) reported an odds ratio of 1.44 (95%CI: 1.00 to 2.06) [60]. Those who had slow chair rise times (Lowest tertile) had a significantly higher risk of developing depressive symptoms (Lowest Tertile OR: 2.05, 95%CI: 1.36 to 3.07) [64]. Reduced step length was also significantly associated with the development of depressive symptoms (Lowest Tertile OR: 1.54, 95%CI: 1.01 to 2.35), but step width (Widest Tertile OR: 1.19, 95%CI 0.76 to 1.85) and double support time percentage (Longest Tertile OR: 0.92, 95%CI: 0.64 to 1.31) were not [24].

2.4.5 Publication bias

There was no significant publication bias evident by funnel plot asymmetry (Appendix A2).

2.4.6 Sensitivity analysis

A sensitivity analysis, pooling studies with high methodological quality only, showed no appreciable change in effect estimates (OR: 1.98, 95%CI: 1.51 to 2.58).

2.5 Discussion

2.5.1 Main findings

This systematic review and meta-analysis confirm that poor mobility is associated with a higher risk of developing incident depressive symptoms over 12 months to 16 years. Walking speed was the most consistently reported mobility measure and was a significant predictor of depressive symptoms. Poor sit-to-stand performance, low SPPB composite mobility scores and short step length were also found predictive of depressive symptoms in one or two studies.

Consistent findings were obtained across eight countries and five study populations. The findings for community-dwelling older adults had very low heterogeneity (I^2=7%, Chi^2=6.45, df=6, p=0.37) , demonstrating a consistent association between mobility impairment and incident depressive symptoms. In contrast, the effect sizes between individuals with specific medical conditions were more heterogeneous (I^2=86%, Chi^2=28.28, df=4, p<0.01), suggesting that chronic medical conditions may influence the mobility impairment-depression relationship differently.

2.5.2 Possible mechanisms

Mobility impairments limit one's ability to perform activities of daily living. This undermines self-esteem as well as perceived control, which leads to isolation and decreased social interactions. These may in turn result in depression via multiple pathways [53]. Reduced physical activity, as a direct consequence of mobility impairments, is known to be a predictor of incident depression [71]. Further, mobility impairment may pose a barrier to physical exercise participation with possible subsequent reduced levels of vitamin D, protective brain neurotransmitters (such as

endorphins, dopamine, serotonin and noradrenaline) [72], brain-derived neurotrophic factor (BDNF) [73] and adiponectin [73], which have been associated with the development of depressive symptoms [72-74].

It has also been proposed that depressive symptoms and impaired mobility can be consequences of the same underlying pathologies. For example, immune system dysregulation, characterised by chronic activation of pro-inflammatory mechanisms, is associated with both poor physical performance and depressive symptoms. Inflammatory cytokines, such as C-reactive protein (CRP) and interleukin (IL) are able to cross the blood-brain barrier and disrupt amygdala and anterior cingulate cortex function [75], and have been linked with subsequent depressive symptoms [76]. In addition, higher circulating levels of CRP and IL-6 have been shown to be related to poorer walking performance in a cross-sectional study [77]. These inflammatory cytokines may also stimulate proteolysis [78] and impair tissue repair in muscle fibers [79]. Finally, Anatomical changes of the brain, i.e. frontal region and global white matter hyperintensities (WMH), representing nerve tract damage, can lead to depressive symptoms [80-82]. Similarly, white matter lesions directly impact motor control, and thus impair gait [83, 84].

2.5.3 Implications for clinical practice and research

In clinical settings, mobility tests can be conducted with minimal time, cost and equipment, and based on our findings may help identify individuals at risk of developing depressive symptoms; an important issue given depression is often not diagnosed, particularly in older adults. Furthermore, current evidence suggests that impaired mobility and depression may be causally linked, which implies it is possible

that interventions improving walking performances could reduce the incidence of depressive symptoms as well. In terms of other future research priorities, more longitudinal studies are required to affirm that sit-to-stand performances predict incident depressive symptoms, and determine whether mobility screens have utility in identifying people with depression and/or add value to traditional diagnostic assessments. With the advances in motion-capturing technology and pressure-sensitive walkways, movement quality parameters can be captured and may provide a more comprehensive understanding of how impaired mobility is linked with depressive symptoms.

2.5.4 Strengths and limitations

To the authors' knowledge, this is the first systematic review and meta-analysis to examine the prospective association between mobility performances and incident depressive symptoms. Our eligibility criteria were restricted to studies with objectively measured mobility performance. This established baseline measurements and avoided recall and social desirability biases that typically exist in self-report mobility questionnaires. Further, data from a large number of participants were pooled in the meta-analysis. Hence, a more precise estimate of effect size could be achieved. All included studies were conducted in cohort designs with an extensive time of follow-up, which helps ascertain temporality between the predictor and outcome. Despite the length of follow-up, most studies (n=9/13) attained a follow-up rate beyond 80%. Further, most studies recruited large community-based samples, some drew participants based on nation-wide censuses [24, 64, 66], ensuring the representativeness of the sample. Taken together, our findings meet most of the criteria (strength of association; consistency; specificity; temporality; biological

gradient, plausibility; and coherence) for assessing causal links exists based on the Bradford Hill consideration of causality [85, 86] which is considered the textbook method in proving causation [87].

We also acknowledge certain limitations. First, all but one study recorded the outcome through self-reported depressive symptom scales. Although it is arguable that diagnoses by medical professionals would be more precise, these scales have been validated with excellent sensitivity and specificity. Second, various sets of confounders were adjusted for in the included studies, this limits the comparability and increases the methodological heterogeneity. Third, effect sizes were reported in a variety of formats, ranging from odds ratios to hazard ratios. Depending on the study, mobility performances were analysed as continuous variables, dichotomous variables and poorest quartile/ tertile variables (comparing participants in the lowest quartile/tertile to those in the highest). In order to pool most data in the meta-analysis, poorest-quartile/ tertile odds ratios and dichotomous odds ratios were taken as equal. Hazard ratios were interpreted as relative risks before being converted into odds ratios. These methods, while widely used in meta-analyses, may have introduced some biases.

2.6 Conclusions

This systematic review and meta-analysis provide evidence that slower gait speed predicts the onset of depressive symptoms. In addition, a limited number of studies supported that other mobility performances, such as sit-to-stand, step length and physical performance composite scores are associated with prospective depressive symptoms. Such findings support the inclusion of mobility measurements for

screening people at risk of developing depressive symptoms. It remains to be observed whether the combined use of mobility performance measures and other clinical markers of depressive symptoms can achieve higher diagnostic precision. Causality may exist between mobility performance and the development of depressive symptoms, which warrants clinical trials to examine whether mobility-oriented interventions might reduce the risk of developing depressive symptoms.

2.7 Funding and Conflict of interest

The authors have no conflict of Interest to declare. This study did not receive any grant from funding agencies in the public, commercial or not-for-profit sectors

Chapter 3. Poor mobility and lower limb weakness predict three distinct depressive symptom trajectories over six years in older people

3.1 Abstract

Objectives: Mobility impairment can be associated with the onset of depressive symptoms in later life. This study aimed to identify mobility and lifestyle predictors of depressive symptom trajectories in community-dwelling older adults.

Methods: Participants were 553 people aged 70 to 90 years who underwent baseline physical, psychological and lifestyle assessments. Group-based trajectory analysis was used to identify patterns of depressive symptom development over six years of follow-up. Strengths of associations between baseline functional test performances and depressive symptom trajectories were evaluated with univariable ordinal models. Subsequently, the adjusted cumulative odds ratios for the associations between identified predictors, demographic factors and baseline anti-depressant use were measured using multivariable ordinal logistic regression.

Results: Three distinct trajectories regarding depressive symptom were identified: a low-and-stable course (10% of participants), a low-and-increasing course (81%) and a moderate-and-increasing course (9%). Timed Up and Go Test time was the strongest predictor of worse depressive symptom trajectory, followed by Five Times Sit to Stand Test performance, planned physical activity levels, and knee extension strength (adjusted standardized ORs = 1.65 (95%CI:1.34to2.04), 1.44 (95%CI:1.16to1.77), 1.44(95%CI:1.17to1.76) and 1.41(95%CI:1.15to1.73) respectively). After adjusting for age, sex, body mass index, and baseline anti-depressant use, Timed Up and Go Test performance and knee extension strength were independently and significantly associated with worse depressive trajectories.

Conclusion: Timed Up and Go Test times, Five Times Sit to Stand Test performance, planned physical activity levels and knee extension strength predicted worse depressive symptom trajectories. These clinical tests may help identify older adults aged 70 to 90 years at risk of developing depressive symptoms and help guide subsequent strength and mobility interventions.

Keywords: Physical decline, Population-based, Longitudinal study, Prospective cohort Study, Clinical functional tests, Depression, Prediction

3.2 Introduction

Late-life depression is the most prevalent mental health disorder among older adults [88]. Persistent and debilitating, this public health issue is projected to grow in the coming decades with rapid population ageing [89]. While targeted interventions are efficacious and economically feasible [90, 91], recognizing late-life depression in primary care is a widely documented challenge [92, 93]. This can be partly due to older adults being less likely to report depression and often presenting with only somatic complaints [94].

Several physical impairments have been found to be significantly associated with the presence of depressive symptoms in older people in cross-sectional studies. These include abnormal walking patterns [95], characterized by slower speed [22, 96] and increased swing time variability [22], as well as hand-grip weakness [97], postural instability [98] and poor visual contrast sensitivity [99].

Over the past decade, new research has focused on analysing the trajectory of depressive symptoms, rather than depressive symptom occurrence at a single time-point. This work has found that the natural course of depressive symptoms is heterogenous [100-103], and that while most people experience little to no depressive symptoms throughout life, severe and persistent symptoms occur in 5 to 10% of the population [100, 101, 103]. Furthermore, it has been suggested that different trajectory patterns indicate underlying differences in etiology and that individuals with a long-term increasing trajectory of depressive symptoms may contribute disproportionately to the public health burden [100]. Risk factors associated with increasing depressive symptom trajectories include female gender [101, 103], older age [101], high body mass index [102], alcohol and tobacco use [102, 104], non-white race [105], functional limitations [104, 106] (e.g. self-reported inability to walk for three blocks, climb stairs, prepare meals, shop or do heavy house work) and low socio-economic status [102]. However, no studies have examined relationships between objectively measured physical performance measures (e.g. sensorimotor function, balance or mobility) and depressive symptom trajectories, which may help elucidate underlying pathophysiological pathways between physical decline and depression.

To address the above research gap, we conducted a prospective study in a large population –based sample of community living older adults incorporating a comprehensive range of baseline risk factors and a trajectory analysis over a six-year period. The primary objective was to identify sensorimotor, balance, mobility and lifestyle predictors of depressive symptom trajectories in older adults.

3.3 Materials and Methods

3.3.1 Participants

Participants were community-dwelling older adults who participated in the Balance and Falls component of the Sydney Memory and Aging Study (MAS) [107]. Initiated in 2005, 1037 individuals from Eastern Sydney were randomly recruited through the electoral roll registry. Participants were aged 70-90 years at baseline, had sufficient English proficiency to complete a psychometric assessment and give informed consent and did not have a previous or current diagnosis of dementia. Exclusion criteria included a previous or current diagnosis of schizophrenia, bipolar disorder, multiple sclerosis, motor neuron disease, developmental disability, progressive malignancy and psychotic symptoms, or a Mini-mental State Examination score of <24 (adjusted for age, education and non-English speaking background) [108]. Participants completed a comprehensive battery of assessments consisting of medical history, medical examination, neuropsychological testing, medication intake, disability and mood questionnaires (including the World Health Organization Disability Assessment schedule 2.0 (WHODAS 2.0) [109] every two years (Waves). In addition to their standard assessment, participants who completed the Balance and Falls Study component were assessed on their physical performance and physical activity levels at baseline. This study was approved by the corresponding institutional review board and informed written consents were obtained from all participants prior to participation.

The sample for this secondary analysis comprised participants who completed Balance and Falls Study baseline assessments and had GDS data for at least 3 MAS Waves (Appendix B1). All participants gave their informed consent prior to their

inclusion in the study. Data sharing for this analysis was approved by the University of New South Wales Human Research Ethics Committee (HC200671, 05037, 09382, 14327) and the study has been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. The research protocol, including the statistical analysis plan, dependent, independent, and adjusted variables for this secondary analysis, was registered on the OpenScience Framework prior to data access (https://osf.io/fe74h).

3.3.2 Depressive symptoms

Participants completed the 15-item Geriatric Depression Scale (GDS-15) [110], at baseline and 2-year, 4-year and 6-year follow-ups. Each item response indicating a depressive symptom scored one point, with a total score ranging from 0 to 15. The GDS-15 has demonstrated a high level of internal consistency (Cronbach's alpha=0.80), 2-week test-retest reliability (intraclass coefficient=0.83) and inter-rater reliability (Cohen's kappa=0.99) [110-112]. In its original design, a score of 5 or more was defined as an indication of probable depression, which has shown good sensitivity (78%) and specificity (82%) against psychiatric diagnosis [110].

3.3.3 Physical tests

All clinical tests were measured at baseline. Visual contrast sensitivity was assessed in decibels using the Melbourne Edge Test, which has a high two-week test-retest reliability in community-dwelling older people (intraclass correlation coefficient, ICC= 0.81, 95% confidence interval, 95%CI= 0.64 to 0.90) [113]. Proprioception was measured using a lower-limb–matching task (test-retest reliability: ICC= 0.50,

95%CI=0.15 to 0.74; Interrater reliability: ICC=0.70, 95%CI=0.17 to 0.92) [113]. Errors in degrees were recorded using a protractor inscribed on a vertical clear acrylic sheet (60 cm x 60 cm x 1 cm) placed between the legs. Handgrip strength in the dominant hand was assessed in kilogram-force with a hand-held digital dynamometer (Jamar, Lafayette Instrument Company, USA; test-retest reliability: 0.94; 95%CI: 0.91 to 0.96) [114]. Isometric knee extension strength in kilogram-force was measured in the dominant leg with the participants seated (test-retest reliability: ICC= 0.97, 95%CI=0.93 to 0.98) [113]. The angles of the hip and knee were 90 degrees [113]. For both hand grip and knee extension strength, the best of three trials were recorded. Simple reaction time was measured in milliseconds using a light as the stimulus and a finger-press as the response (test-retest reliability: ICC= 0.69, 95%CI=0.45 to 0.84). The average of 10 trials was taken as the test score. Postural sway was measured using a sway meter that measured displacements of the body at the level of the waist in centimeters and testing was performed with participants standing on a foam rubber mat (40 cm x 40 cm x 15 cm thick) with eyes open for 30s (test-retest reliability: ICC= 0.57, 95%CI=0.30 to 0.76).

Three mobility tests were also conducted: the Five Times Sit to Stand Test (STS) [115] which measured the time taken for participants to perform five consecutive sit-to-stand transitions (test-retest reliability: ICC= 0.89, 95%CI=0.79 to 0.95) [116]; the Timed Up and Go Test (TUG) [117] which assessed the time it took participants to stand up, walk 3 meters at a fast pace, turn around, walk back and sit down (test-retest reliability: ICC= 0.99) [117], and the 6MT [118], which measured the time required for participants to walk the middle 6-metre section of a 10-meter path at usual gait speed (test-retest reliability: ICC= 0.74, 95%CI=0.52 to 0.87) [116].

3.3.4 Physical activity

Average weekly physical activity over the past three months was assessed with the Incidental and Planned Exercise Questionnaire at baseline (test-retest reliability: ICC= 0.84) [119]. This provided estimates of the frequency and duration of planned exercise (exercise classes, home exercises, swimming, dancing, jogging, cycling, and planned walks) as well as incidental day-to-day activities. Weekly hours spent in planned, incidental and total physical activity were calculated as the total time spent in respective categories.

3.3.5 Statistical analysis

Initially, group-based trajectory modelling (GBTM) was used to differentiate individuals with discrete depressive symptom progressions [120]. GBTM makes no assumption on the number of underlying groups or distribution patterns [121] and identifies subgroups of individuals who have similar symptom progression over time. It has been previously utilized to differentiate normal from pathological development of depressive symptoms [121], which is in contrast to depression being determined by a clinical cut-point (e.g. GDS-15 score ≥6) at any follow-up [122]. GBTM captures more information from multiple time-points to inform the differentiation of discrete sub-groups within a population. The number of trajectory groups was determined by the Bayesian Information Criterion (BIC) with the minimum number of participants in each trajectory group set at 5% of the sample and the average posterior probability of group assignment > 0.7 [123]. The shape of each group's trajectory over time (e.g. linear, quadratic, etc.) was determined with a combination of substantive knowledge and the BIC [123].

Ordinal logistic regression analyses were then conducted to determine whether baseline physical tests and physical activity levels could predict depression trajectory grouping. In ordinal logistic regressions, sub-models are generated by re-grouping levels in dependent variables into dichotomous groups. Odds ratios were estimated in all sub-models simultaneously, assuming proportional odds between levels. Only one predictor was entered into each model with cumulative odds ratios presented (i) unadjusted and (ii) with standardized predictors to allow comparisons of the strength of associations among the predictor variables. Subsequently, all baseline clinical functional test performances, physical activity levels, demographics and baseline anti-depressant use were fitted into a multivariable ordinal logistic regression model with backward selection. The model's goodness-of-fit was accessed using an ordinal version of the Hosmer-Lemeshow statistic.

Analyses were performed using SAS (version 9.4). Expectation-maximization imputation was used to impute missing values for baseline clinical tests and physical activity levels. The alpha value for all analyses was set at $p < 0.05$.

3.4 Results

3.4.1 Included – excluded participant comparisons

A total of 815 participants underwent baseline Balance and Falls Study assessments at either Wave 1 or Wave 2 of the MAS study. Of these, 553 participants (67.9%) had GDS-15 data for three or more consecutive Waves and were included in this analysis. As shown in Appendix B2, compared to their included counterparts, participants excluded from the analysis due to missing GDS-15 data were older ($p < 0.001$), had

shorter body height ($p = 0.004$), lighter body weight ($p < 0.001$), lower BMI ($p = 0.001$), higher WHODAS 2.0 scores ($p < 0.001$), slower reaction times ($p = 0.043$), lower visual contrast sensitivity ($p = 0.018$), weaker knee extension strength ($p = 0.036$) and handgrip strength ($p = 0.002$), greater postural sway ($p < 0.001$), slower 6MT times ($p < 0.001$), slower TUG times ($p < 0.001$) and lower levels of planned activity ($p = 0.003$).

3.4.2 Identification of depressive symptom trajectory groups

The steps for fitting GBTM models are presented in Appendix B3. Three distinct depressive symptom trajectory groups were identified: (1) a low-and-stable group (10.1%, n = 56), (2) a low-and-increasing group (80.7%, n = 446), and (3) a moderate-and-increasing group (9.2%, n = 51), as presented in Figure 3.1. An intercept pattern (a horizontal straight line) was fitted to the low-and-stable group. At baseline, the mean (SD) GDS score for the group was 0.2 (0.4), and remained relatively stable over the follow-up period, increasing slightly to 0.4 (0.6) by the 6-year follow-up (Wave 4). A linear pattern (an inclined straight line) fitted the low-and-increasing group well. The baseline mean (SD) GDS-15 score of 1.9 (1.3) increased to 2.8 (1.7) by the 6-year follow-up. A quadratic pattern fitted the moderate-and-increasing group well, suggesting a non-linear increase in depressive symptoms in this group. At baseline, the group had a mean (SD) GDS-15 score of 5.4 (3.3), which increased to 8.1 (3.0) by the 6-year follow-up. The average posterior probabilities of the three groups were 0.96, 0.84, and 0.90 respectively, suggesting an excellent fit.

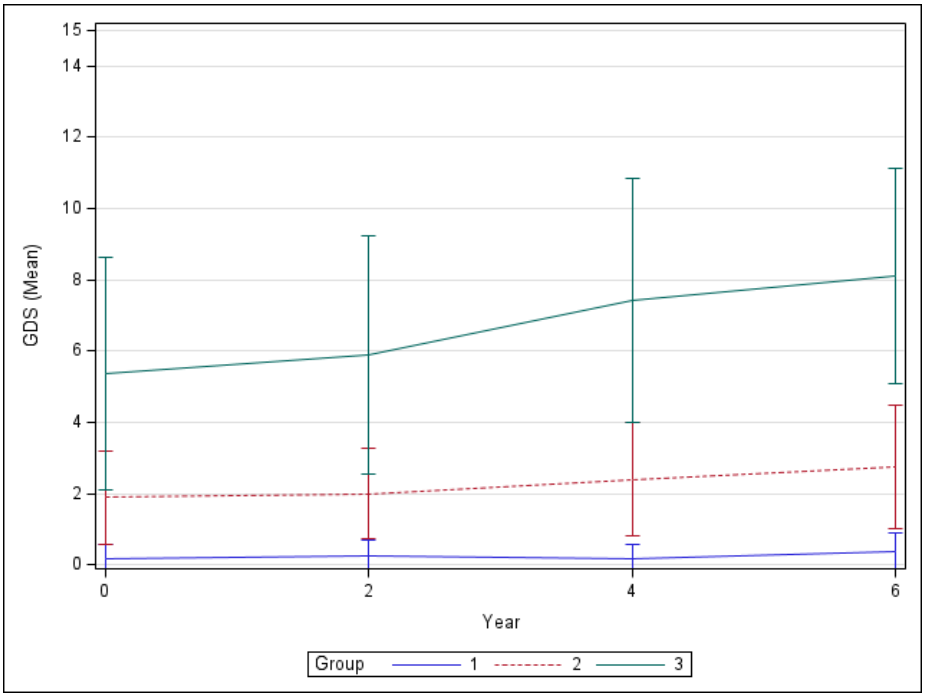

Figure 3.1 Depressive symptom trajectories, mean and standard error measured with the Geriatric Depression Scale (n=553).

Legend. Group 1: low-and-stable; Group 2: low-and-increasing; Group 3: moderate –and increasing. Error bar denotes standard deviation.

3.4.3 Predictors of depressive symptom trajectory group

Participant characteristics according to group assignment are presented in Table 3.1. Visual contrast sensitivity, knee extension strength, postural sway, handgrip strength, 6MT time, STS time, TUG time, and total and planned physical activity levels differed significantly between the trajectory groups in univariable analyses (Table 3.2). Comparing the cumulative odds ratios of the standardized predictors, slower TUG time was identified as the strongest predictor of depressive symptom trajectory, followed by longer STS times, lower levels of planned physical activity and lower knee extension strength (Table 2). After adjusting for age, sex, body mass index and baseline anti-depressant use, TUG performance and knee extension strength were

included in the final model as independent and significant predictors. The Hosmer-Lemeshow test indicated acceptable goodness-of-fit for each group (p=0.221).

Table 3.1 Participant characteristics by depressive symptom trajectories (data reported as mean (SD), unless otherwise indicated)

	Depressive symptom trajectories			
	Low-and -stable (N=56)	Low-and -increasing (N=446)	Moderate-and -increasing (N=51)	Total (N=553)
Age, yrs	76.3 (3.4)	78.4 (4.5)	80.5 (4.7)	78.4 (4.5)
Female, n (%)	29 (51.8%)	238 (53.4%)	24 (47.1%)	291 (52.6%)
Height, m	1.65 (0.1)	1.64 (0.1)	1.63 (0.1)	1.64 (0.1)
Weight, kg	71.4 (11.6)	74.7 (15.2)	73.2 (13.3)	74.2 (14.7)
Body mass index	26.0 (3.2)	27.7 (5.1)	27.6 (4.2)	27.5 (4.9)
Number of medications	4.5 (3.4)	5.0 (3.2)	5.4 (3.5)	5.0 (3.2)
WHODAS 2.0 score	13.9 (2.3)	17.7 (5.8)	23.5 (8.6)	17.9 (6.2)
Proprioception, deg	2.2 (1.5)	2.4 (1.6)	2.4 (1.4)	2.4 (1.6)
Simple reaction time, milliseconds	232.6 (42.4)	237.4 (44.2)	237.8 (45.6)	237.0 (44.1)
Visual contrast sensitivity, dB	21.3 (1.8)	20.7 (2.0)	20.3 (2.4)	20.7 (2.0)
Knee extension strength, kg	33.7 (12.0)	28.5 (11.9)	26.5 (12.2)	28.8 (12.0)
Postural Sway, mm	160.3 (63.9)	186.4 (99.8)	222.9 (134.8)	187.1 (101.4)
Handgrip strength, kg	29.7 (11.3)	27.5 (11.1)	25.2 (9.2)	27.5 (11.0)
Six-Metre Walk Test, s	8.2 (3.6)	9.0 (2.6)	9.7 (3.7)	9.0 (2.8)
Five Times Sit to Stand Test, s	13.8 (3.6)	16.1 (4.9)	17.1 (5.1)	16.0 (4.9)
Timed Up and Go Test time, s	7.7 (1.4)	9.5 (3.0)	10.7 (4.1)	9.4 (3.1)
Total physical activity, hr/wk	34.7 (16.1)	31.1 (16.0)	28.2 (17.8)	31.2 (16.2)
Planned physical activity, hr/wk	5.9 (7.8)	3.2 (4.0)	3.0 (8.2)	3.5 (5.1)
Incidental physical activity, hr/wk	28.8 (14.5)	27.9 (16.1)	25.2 (15.8)	27.7 (15.9)

WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0

Table 3.2 Relationships between sensorimotor, balance, mobility and physical measures and depressive symptom trajectory, expressed as cumulative odds ratios. (n=553)

Functional test, unit	**Crude cumulative odds ratio (95%Confidence Interval)**	**Standardized cumulative odds ratio (95%Confidence Interval)**	**Adjusted cumulative odds ratio~ (95% Confidence Interval)**
Proprioception, deg	1.05 (0.91 to 1.20)	1.07 (0.87 to 1.32)	—
Simple reaction time, milliseconds	1.00 (1.00 to 1.01)	1.06 (0.87 to 1.32)	—
Contrast sensitivity, dB	0.87 (0.79 to 0.97)*	1.32 (1.07 to 1.62)*†	—
Knee extension strength, kg	0.97 (0.96 to 0.99)*	1.41 (1.15 to 1.73)*†	0.97 (0.94 to 0.99)*
Postural Sway, mm	1.00 (1.00 to 1.01)*	1.38 (1.13 to 1.69)*	—
Handgrip strength, kg	0.98 (0.96 to 1.00)*	1.24 (1.01 to 3.53)*†	—
Six-Metre Walk Test, s	1.12 (1.04 to 1.19)*	1.36 (1.12 to 1.65)*	—
Five Times Sit to Stand Test, s	1.44 (1.17 to 1.77)*	1.44 (1.16 to 1.77)*	—
Timed Up and Go Test, s	1.18 (1.10 to 1.26)*	1.65 (1.34 to 2.04)*	1.10 (1.02 to 1.18)*
Total physical activity, hours/week	0.99 (0.97 to 1.00)*	1.26 (1.02 to 1.55)*†	—
Planned physical activity, hours/week	0.93 (0.89 to 0.97)*	1.44 (1.17 to 1.76)*†	—
Incidental physical activity, hours/week	0.99 (0.98 to 1.01)	1.13 (0.92 to 1.40)†	—
Demographics, unit (if applicable)			
Age, yrs	—	—	1.11 (1.06 to 1.17)*
Female	—	—	0.53 (0.31 to 0.91)*
Body mass index	—	—	1.05 (1.01 to 1.10)*
Baseline anti-depressant use	—	—	3.80 (1.78 to 8.13)*

*p<.05

~ Adjusted for age, sex, BMI and baseline antidepressant use.

† Adjusted standardized ORs are expressed as SD change and inverted to allow comparison of the strengths of the Odds Ratios among the predictor variables.

3.5 Discussion

We examined the trajectory of depressive symptom progression in a sample of community-dwelling older adults over 70 years old. Our analyses identified three distinct groups: people who had low depressive symptoms which remained stable over time; people with low depressive symptoms at baseline which increased steadily over the six-year follow-up; and people who had moderate baseline depressive symptoms

which increased more markedly (non-linearly) over time.

We found that in order of strength of association, slower TUG time, slower STS time, lower planned physical activity levels, weaker knee extension strength, increased postural sway, slower walking speed in 6MT, poorer visual contrast sensitivity, lower total physical activity levels, and handgrip strength at baseline were predictive of worse depressive symptom trajectory over six years. After adjusting for age, sex, body mass index and baseline anti-depressant use, TUG times and knee extension strength remained significant and independent predictors of depression trajectory over six-years.

Nine percent of our sample had a moderate and increasing trajectory of depressive symptoms, a finding compatible with previous cohort studies that have reported depression incidence rates between 8% to 21% in older adults [124]. The mean GDS-15 score for this group at baseline was 5.4, which falls below the conventional clinical cut-off for further psychiatric assessments of 6 [122]. Further, the overlap of error (standard deviation) with the stable group indicates baseline GDS-15 scores alone are not sufficient to discriminate depressive symptom trajectories. Over the 6-year follow-up, depressive symptoms increased substantially (i.e., from 5.4 to 8.1) in the moderate-and-increasing group, which highlights the importance of early identification and treatment of depression.

Once a trajectory of increasing depressive symptoms is identified, it may be intervened through early targeted treatments [90, 91]. Our findings support a multi-factorial approach towards identifying approximately 9% of older adults aged 70 to 90

at risk of an increasing trajectory of depressive symptoms. Our findings suggest that depression risk assessment might benefit from combing self-reported assessment such as the GDS-15 (that inquires about depressed mood in the past week) with simple tests of strength and mobility (e.g. knee extensor strength and TUG time). The use of these tests in older adults at risk of depression may help guide subsequent multi-factorial interventions that include some strength and mobility components.

Out of a comprehensive range of mobility, sensorimotor and physical activity measures, TUG performance was found to be the most predictive variable of increasing depressive symptom trajectories, followed by planned physical activity levels, STS times and knee extension strength. TUG was relatively more important in predicting depressive symptom trajectories than the 6-metre walk, which may be attributed to the multifaceted nature of TUG in that it comprises sit-stand transitions, turning, and gait initiation in addition to walking speed. Planned physical activity levels, and not incidental physical activity, independently predicted depressive symptom trajectories. This may be due to planned physical activities (e.g., exercise classes, etc.) being more vigorous than incidental physical activities. It is also possible that planned physical activities are more structured and robust against recall bias, and therefore are more reliable indicators of physical activity levels [125]. In addition, planned physical activities may be more related to one's self-efficacy [126], planning ability [127], and social participation [128], which are known correlates of depression.

Slow walking speed is a prominent feature of psychomotor retardation frequently observed in people with a major depressive disorder, particularly in more severe subtypes including melancholic depression and endogenous depression [129]. Some

findings suggested that dopaminergic dysregulation [130] and structural changes of the basal ganglia circuits [131] following major depressive episodes may lead to psychomotor retardation. The association between poorer baseline mobility and depressive symptom progression in the present study may be linked to impairments in these brain regions. It is possible that psychomotor retardation is a manifestation of not only depression, but also vulnerability to more severe depressive disorders.

In multivariable analysis, knee extension strength and TUG performance were predictive of depressive trajectories, after adjusting for potential confounders such as age, gender, body mass index and baseline anti-depressant use. This may be explained via several theoretical pathophysiological pathways. Skeletal muscle contractions produce brain-derived neuro-trophic factor (BDNF) [132], which drives neurogenesis in the hippocampus [133], a brain region that has a key role in the development of depressive disorders [134]. Alternatively, skeletal muscle weakness may be linked to depression through curtailing mobility [135] and physical activity levels [136]. Poor mobility, as reflected by slow TUG times, may restrict activities of daily living, and impair perceived control and self-esteem [137], thus leading to depression. Further, poor mobility may limit physical activity levels, which reduces levels of vitamin D and protective brain neurotransmitters and lead to depressive symptoms [138]. Identification of muscle strength and mobility impairment as predictors of depressive trajectories in this study has provided support for these three theories. However, while these theories have strong pathophysiological plausibility, they require validation with multivariate statistical modelling studies (e.g., structural equation modelling) in future studies.

Strengths of this study include the large, well-characterized sample of older adults, the inclusion of a comprehensive battery of objective sensorimotor, mobility and lifestyle baseline measures and the relatively long (6-year) follow-up period of depressive symptomology. We also acknowledge certain limitations should be considered when interpreting our results. First, although the six-years of follow-up provided an appropriate temporal sequence, we did not collect self-reported pre-baseline measures of depression and physical activity. Thus, we cannot rule out that individuals with worse health at baseline may have had worse health for several years prior which contributed to accelerated depressive symptoms. Further, the development of the physical measures across the six-year follow-up were not analysed. It is not known whether the trajectories of physical performance followed those of depressive symptoms. Second, as depression is also a major deterrent to physical activity and a healthy lifestyle, further research including clinical trials is required to elucidate causal relationships between these inter-related conditions. Third, participants of this study were relatively healthy, which restricts the generalization of our findings to frailer older adults. Fourth, 262 participants had missing GDS-15 data which prohibited their inclusion in the GBTA and subsequent analyses. Comparison of their characteristics revealed they were generally older and performed worse in a series of physical performances. As such, selection bias due to missing data could have influenced our results.

To summarise, we studied the associations between three discrete trajectories of depressive symptoms and a range of sensorimotor, balance, mobility and physical performance measures in community dwelling older adults. Longer TUG time was the best predictor of an increasing depressive trajectory, followed by lower planned

physical activity level, poorer STS performance and reduced knee extension strength. After adjusting for age, sex, body mass index and baseline anti-depressant use, TUG time and knee extension strength predicted depressive symptoms trajectories. These findings could further inform the understanding of the pathophysiological pathway between physical decline and increasing depressive symptom trajectories in older adults. The combined use of self-reported mood, strength and mobility tests may help identify older adults at risk of increasing depressive symptoms and guide subsequent multi-factorial intervention. Future studies could conduct multivariate analyses or clinical trials to delineate interactions between declines in physical performance and depressive symptomatology and causal pathways between them.

Chapter 4. Short daily-life walking bouts and poor self-reported health predict the onset of depression in community-dwelling older people: a two-year longitudinal cohort study

4.1 Abstract

Objectives: This study aimed to assess whether the amount and quality of daily-life walking obtained using wearable technology can predict depression onset over a two-year period, independently of self-reported health status.

Design: Longitudinal Cohort Study

Setting and Participants: Three-hundred and twenty-two community-dwelling older people recruited in Sydney, Australia

Methods: Participants were assessed at baseline on: (i) depressive symptoms using the Patient Health Questionnaire-9; (ii) average weekly physical activity levels over the past month using the Incidental and Planned Activity Questionnaire, (iii) clinical mobility tests (i.e. Short Physical Performance Battery, Timed Up and Go Test, Six-Metre Walk Test); and (iv) amount and quality of daily-life walking assessed with a trunk accelerometer (MoveMonitor, McRoberts) for one-week. Participants were followed-up for the onset of depressive symptoms for 2 years at 6-monthly intervals.

Results: Daily-life walking (i.e. gait intensity in the mediolateral axis, daily step counts, duration of longest walk) and self-rated health predicted the new onset of depressive symptoms at two years in univariable logistic regression models. In multivariable models containing a self-rated health measure, clinical mobility tests were not predictive of the onset of depressive symptoms. In contrast, a measure of daily-life walking (duration of the longest walking bout) was identified as a

significant predictor of depressive symptom onset (Standardized Odds Ratio: 2.44, 95%CI: 1.62 to 3.76) independent of self-rated health (Standardized Odds Ratio: 1.51, 95%CI: 1.16 to 1.96), with these two measures achieving a satisfactory prediction accuracy (AUC=0.67, Sensitivity: 0.78, Specificity: 0.52).

Conclusions and implications: A risk algorithm based on daily-life walking bouts and self-reported health demonstrated good accuracy for the prediction of depression onset in older people over two years. Wearable sensor data compared favourably with clinical mobility screens and may add important independent information for screening for depression among older people.

4.2 Introduction

Late-life depressive symptoms are common in people aged 65 and over with a prevalence ranging from 15 to 23% [7, 8]. Depressive symptoms are associated with poor quality of life [139], restricted daily function [140], elevated risk of chronic diseases [141] and mortality [140]. Depression also places a major burden on caregivers and health care systems [142].

Recent studies have found that poor gait is significantly associated with the occurrence of depressive symptoms [24, 25, 65]. It has been reported that individuals with depressive symptoms exhibit slower walking speed [22], shorter stride lengths [22] and higher swing time variability in laboratory settings when compared to control groups [22, 23]. Further, it has been reported that older people with slower walking speed and/or a shorter step length have increased odds of developing depressive symptoms over the next four years [24]. Systematic review evidence from 13 cohort studies indicates individuals with slow walking speed are at twice the odds of

developing depressive symptoms compared with controls in follow-up periods of 1 to 16 years [25].

Walking speed and amount of physical activity can be assessed remotely using wearable sensors (often incorporating accelerometers and gyroscopes) [31-33], and have certain advantages compared to self-reported physical activity and clinical mobility tests. These include: ecological validity as several days of continuous gait data can be obtained to capture an individual's "usual" performance, rather than a "clinical" performance [31, 38]; and the measurement of both gait quantity (e.g. the number of walks and the longest walking bout per day) and quality (e.g. through harmonic ratios and the distributions of walking bouts [36, 143, 144]). However, despite such advantages of wearable technology, the associations between incident depression and daily-life walking assessed with wearable sensors have yet to be reported.

This study investigated the associations between daily-life and clinical gait tests and the onset of depressive symptoms in a large sample of community-living older people over two years. We hypothesised that baseline daily-life gait performance is an important and independent predictor of depressive symptoms over the follow-up period.

4.3 Methods

4.3.1 Participants

Participants included 322 out of 503 community-living older people with valid accelerometry data, recruited for the StandingTall randomised controlled trial, which investigated the effectiveness of the eHealth balance exercise program to reduce falls in older people [145], Data collection took place between February 2015 and October 2017. Participants were recruited in the Sydney metropolitan area through advertisements in newsletters, newspapers, social media, retirement villages and community centres. Eligibility criteria were: aged 70 or over, living in the community, independent in activities of daily living, able to walk household distances without the use of a walking aid, no unstable or acute medical condition that precluded exercise participation, no progressive neurological condition (such as Parkinson's disease and Multiple Sclerosis), not cognitively impaired as defined by a Pfeiffer Short Portable Mental Status Questionnaire score exceeding 7 [146], and not already participating in a fall prevention program [147]. Appendix C1 presents the number of participants in recruitment and analysis.

Written informed consent was obtained and the study was approved by the Ethics Committee in December 2014 (HC#14/266). The research protocol, including the statistical analysis plan and selection of predictor and outcome variables, for this analysis was registered on OpenScience Framework prior to data access (osf.io/XZY9M).

4.3.2 Incident depressive symptoms

The presence of depressive symptoms was assessed using the Patient Health Questionnaire-9 (PHQ-9) [148]. This questionnaire comprises nine items based on the DSM-IV criteria of major depression scored from "0" (not at all) to "3" (nearly every day), providing a total score between 0 (no depressive symptoms) and 27 (major depressive symptoms). The PHQ-9 scale has a sensitivity and specificity of 88% for major depression [148]. Scores of 5, 10, 15 and 20 represent mild, moderate, moderately severe and severe depression respectively [148]. We used the cut point of 5 to be inclusive of all severity levels of depression. Participants were asked to complete the PHQ-9 every six months for two years. Incident depression was defined as the transition of a participant from no depression (PHQ-9 < 5) at baseline to having a PHQ-9 score of ≥5 at any of the follow-up measurements.

4.3.3 Demographic, health and activity measures

Participant information, including age, gender, body mass index (BMI), years of education and anti-depressant usage, was assessed at baseline. Participants were also asked to rate their physical health using the EuroQol Visual Analog Scale (EQ-VAS) [149]. The scale is numbered from 0 (worst health imaginable) to 100 (best health imaginable). Physical activity levels were measured with the incidental and planned exercise questionnaire (IPEQ) [119]. Cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) [150]. Participants reported the frequency and duration of their weekly incidental and planned physical activities over the past three months. The scores correspond to the estimated hours of planned, incidental and total physical activity per week.

4.3.4 Clinical mobility tests

Participants completed the Timed Up and Go and Six-Metre Walk Tests and Short Physical Performance Battery in one session at our offices at Neuroscience Research Australia. For the Timed Up and Go Test [117], participants were instructed to stand up from a chair, walk for three metres, turn around, return to the chair and sit down at a comfortable pace. In the Six-Metre Walk Test [151], the time taken for participants to walk six metres at a self-selected walking pace was recorded. The Short Physical Performance Battery [152] provides a composite mobility score comprising three timed items: standing balance, walking speed and sit-to-stand tests. Performance on each test is scored from 0 to 4 using standardised criteria, with a total score range from 0 (worst) to 12 (best).

4.3.5 Daily-life gait assessment

Daily-life gait was assessed using the McRoberts MoveMonitor (McRoberts, the Netherlands). Participants wore a MoveMonitor for a week on the lower back, held in place by an elastic belt worn around the waist. The MoveMonitor registered 3D accelerations with a range of three gravity units and sampled at 100 Hz. Periods of locomotion were recognised using the manufacturer's algorithm. Daily-life activity data were collected over a median of 6 (IQR 1) days. The raw data of locomotion episodes were extracted, divided into 10-second epochs and realigned with anatomical axes using left-right symmetry and the sensor’s orientation with respect to gravity [36, 38]. Gait quantity parameters comprised: averages of total daily walking duration, and median and longest walking bouts per day. A walking bout is a period of continuous walking without breaks exceeding 1 second [36]. Gait quality parameters comprised: walking speed, stride frequency, root mean square, range, power at step frequency,

index of harmonicity, harmonic ratio, logarithmic rate of divergence and sample entropy [36, 38]. The median values over all epochs were used in the analyses.

4.3.6 Statistical analysis

The baseline characteristics of participants are presented with descriptive statistics. Differences between participants who developed depressive symptoms and those who did not were identified using independent t-tests for normally distributed continuous data, Wilcoxon rank-sum tests for non-normally distributed continuous data and chi-square tests for categorical data. The normality of data was tested with the Shapiro-Wilk test. Considering that many daily-life gait quality parameters could be extracted, a principal component analysis (PCA) was initially used to reduce the number of parameters and the likelihood of type I statistical errors. A Varimax rotation with Kaiser Normalization was applied. The number of principal components was determined based on eigenvalues >1. The extracted principal components were labelled according to the composite variables that contributed the most.

Univariable binary logistic regression models were fitted to determine the associations between clinical mobility test performances, self-reported questionnaire scores, principal components of daily-life gait quality, daily-life gait quantity variables and incident depressive symptoms. Analyses were adjusted for age, gender and intervention group allocation in the StandingTall trial, as it has been reported that these demographic factors are associated with gait performances [153] and depressive symptoms [154]. The odds ratios for the predictor variables are presented in crude form as well as in standardized (z) score form with inverse scales as appropriate to allow comparison of the strengths of the independent variables in predicting

depressive symptom onset. Subsequently, a multivariable logistic regression model with backward selection was performed to identify significant predictors of new depressive symptom onset. The accuracy of the prediction models was expressed as area under curve (AUC) for receiver operator characteristic curves (ROC) with leave-one-out cross-validation, with the optimum cut point for sensitivity and specificity based on Youden's index. To restrict multi-collinearity, only predictors correlated with a Pearson's correlation coefficient, R, of lower than 0.7 were included. As cognitive function has been found to be associated with both gait performance [155] and the development of depressive symptoms [156], we conducted a sensitivity analysis additionally adjusting for MoCA scores. Statistical analyses were conducted using SAS® Enterprise 8.3 software. A two-tailed alpha level of 0.05 was set to denote significance.

4.4 Results

Table 4.1 presents the baseline characteristics of the 322 participants analysed (62% female), stratified by the presence of incident depressive symptoms. The median age of the sample was 75.5 (IQR: 72.3, 80.1) years. The mean body mass index was 27.3 (SD 4.7) kg/m^2 and the mean score for the MoCA was 26.5 (SD 2.4) indicating little to no cognitive impairment. Forty-two percent (n=136) of participants reported incident depressive symptoms in the follow up period of 2 years (Appendix C2).

Table 4.1 Baseline characteristics for participants who did and did not report depressive symptoms over the two-year follow-up and for the total sample

Baseline Characteristics	Total Sample (N = 322)	Incident depressive symptoms		*p*
		No (N=186)	Yes (N=136)	
Demographics				
Age, yr[2]	75.5 (72.3, 80.1)	75.0 (72.0, 80.4)	75.5 (72.3, 80.1)	0.40†
Female, *n* (%)	200 (62.1)	10 (58.6)	91 (66.9)	0.13§
BMI [1]	27.3±4.7	27.0±4.6	27.6±4.8	0.33‡
Years of education [1]	14.6 4.1	14.4±3.9	14.9±4.3	0.32‡
Allocated to exercise group, n (%)	159(49.4)	89(47.8)	70 (51.5)	0.52§
MoCA [1]	26.5±2.40	26.6±2.40	26.3±2.40	0.28†
Clinical tests of mobility				
TUG, seconds [2]	7.3 (6.4, 8.8)	7.2 (6.4, 8.6)	7.5 (6.4, 9.4)	0.45†
6mWT, seconds [2]	7.6 (6.8, 9.0)	7.6 (6.9, 9.1)	7.6 (6.5, 9.0)	0.20†
SPPB, out of 12 [2]	11.0 (10.0, 12.0)	11.0 (10.0, 12.0)	11.0 (10.0, 12.0)	0.40†
Daily-life gait quantity(averaged daily value from 1 week's data;McRoberts waist-mounted device)				
Step count[2]	7485 ±3308	7861±3575	6970±2835	**0.02‡**
Total walking duration, min [1]	82.4 ±31.9	85.4±33.7	78.3±29.0	**0.05‡**
Longest walking bout, s [1]	276.9 ±254.4	332.6±310.0	200.6±110.1	**<0.001†**
Median walking duration, s [1]	6.3±0.8	6.3±0.8	6.2±0.8	0.28‡
‖Daily-life gait quality (averaged daily value from 1 week's data; McRoberts waist-mounted device)				
Overall gait quality	0.0±1.00	0.1±1.01	-0.1±0.98	0.12‡
ML intensity	0.0±1.00	0.1±1.07	-0.2±0.88	**0.02‡**
AP intensity	0.0±1.00	0.1±1.00	-0.1±1.00	0.06‡
ML rhythmicity	0.0±1.00	0.1±1.03	-0.1±0.95	0.14‡
Complexity	0.0±1.00	0.0±1.06	-0.0±0.92	0.83‡
Self-reported questionnaires				
Self-rated health, 0 to 100 [2]	90.0 (80.0, 95.0)	85.0 (80.0, 90.0)	90.0 (80.0, 95.0)	**<0.001†**
Incidental activity, hrs [1]	35.2±20.6	34. 9±20.6	35.5±20.7	0.72†
Planned activity, hrs [1]	8.0±6.6	8.6±7.2	7.03±5.6	0.24†

[1] Mean ± SD with ANOVA F-test p-value; [2] Median, Interquartile range with Kruskal-Wallis p-value; BMI, Body Mass Index; hr, hours; IQR: inter-quartile range; min, minutes; MoCA , Montreal Cognitive Assessment; s, second; SD, standard deviation; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go Test; 6mWT, Six-Metre Walk Test. ‡Independent t-test; †Wilcoxon rank-sum test; §Chi-square test. p-value relate to incident depressive symptom – no incident depressive symptom group comparisons, bolded indicates a $p<0.05$. ‖ Parameters generated from Principal Component Analysis with a mean of zero and standard deviation of one. Variables are labelled according to the composite factors that contributed the most. The underlying composite factors of each principal component are presented in Appendix C3.

Five principal components were identified in the principal component analysis for the 24 daily-life gait quality parameters, which explained 81.2% of the variance. The five resulting factors were labelled gait quality, gait intensity in the mediolateral axis, gait intensity in the anteroposterior axis, gait rhythmicity in the mediolateral axis and gait complexity. Appendix C3 presents the varimax-rotated factors of each principal component.

Across all independent variables, five were found to be significantly associated with incident depressive symptoms in univariable models (adjusting for age, gender and intervention group allocation) (Table 2). Individuals with poorer self-rated health (Standardized odds ratios, SOR: 1.64, 95%CI: 1.26 to 2.13), lower gait intensity in the mediolateral axis (SOR: 1.28, 95%CI: 1.00 to 1.64), lower ML rhythmicity (SOR: 1.41, 95%CI: 1.08 to 1.84), lower total steps per day (SOR: 1.31, 95%CI: 1.03 to 1.68) and shorter longest walking bouts per day (SOR: 2.52, 95%CI: 1.67 to 3.81) had higher odds of developing incident depressive symptoms in two years.

The multivariable model identified self-rated health (SOR: 1.51, 95%CI: 1.16 to 1.96) and the duration of the longest walking bout per day (SOR: 2.44, 95%CI: 1.62 to 3.76) as statistically significant and independent risk factors for depressive symptom onset, adjusting for intervention group allocation. The prediction model yielded an area under the curve (AUC) of 0.67, a sensitivity of 0.78 and a specificity of 0.52 in the leave-one-out analysis (Table 4.2 and Figure 4.1).

Table 4.2 Odds ratios for incident depressive symptoms associated with various risk factors

	OR (95% CI)			
Variables	Univariable†	Univariable, standardized† §	Multivariable†	Multivariable, standardized† §
Clinical tests of mobility				
TUG, seconds	1.02 (0.94 to 1.12)	1.07 (0.84 to 1.35)	—	—
6mWT, seconds	1.00 (0.89 to 1.12)	1.00 (0.79 to 1.27)	—	—
SPPB, score out of 12	0.94 (0.80 to 1.11)	1.08 (0.86 to 1.37) ‡	—	—
Daily-life gait quality				
Overall gait quality, per SD	0.84 (0.67 to 1.05)	1.20 (0.95 to 1.50) ‡	—	—
ML intensity, per SD	0.78 (0.61 to 1.00)*	1.28 (1.00 to 1.64) ‡*	—	—
AP intensity, per SD	0.82 (0.65 to 1.03)	1.23 (0.97 to 1.55) ‡	—	—
ML rhythmicity, per SD	0.71 (0.54 to 0.93)*	1.41 (1.08 to 1.84) ‡*	—	—
Complexity, per SD	0.95 (0.75 to 1.19)	1.06 (0.84 to 1.32) ‡	—	—
Self-reported questionnaire				
Planned activity, hours	0.97 (0.94 to 1.01)	1.21 (0.95 to 1.54) ‡	—	—
Incidental activity, hours	1.00 (0.99 to 1.01)	1.00 (0.80 to 1.26) ‡	—	—
Overall health, 0 to 100	0.96 (0.94 to 0.98)*	1.64 (1.26 to 2.13) ‡*	0.97 (0.95 to 0.99)*	1.51 (1.16 to 1.96) ‡*
Cognitive function				
MoCA score, 0 to 30			—	—
Daily-life gait quantity				
Daily step count, 1000 steps	0.92 (0.86 to 0.99)*	1.31 (1.03 to 1.68) ‡*		
Daily total walking duration, hours	0.65 (0.42 to 1.00)	1.23 (0.97 to 1.56) ‡	—	—
Median walking bout duration, seconds	0.90 (0.68 to 1.20)	1.09 (0.86 to 1.38) ‡	—	—
Longest walking bout duration, minutes	0.80 (0.73 to 0.89)*	2.52 (1.67 to 3.81) ‡*	0.81 (0.73 to 0.89)*	2.44 (1.62 to 3.76) ‡*
Predictive performance				
AUC (with leave-one-out cross-validation)		—		0.67
Sensitivity		—		0.78
Specificity		—		0.52

OR, odds ratio; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go Test; 6mWT, Six-Metre Walk Test; 95%CI, 95% confidence interval. * **p<0.05**;

†Adjusted for intervention group allocation, age and gender; § Adjusted standardised ORs are expressed as SD change; ‡ Inverted to allow comparison of the strengths of the odds ratios among the predictor variables.

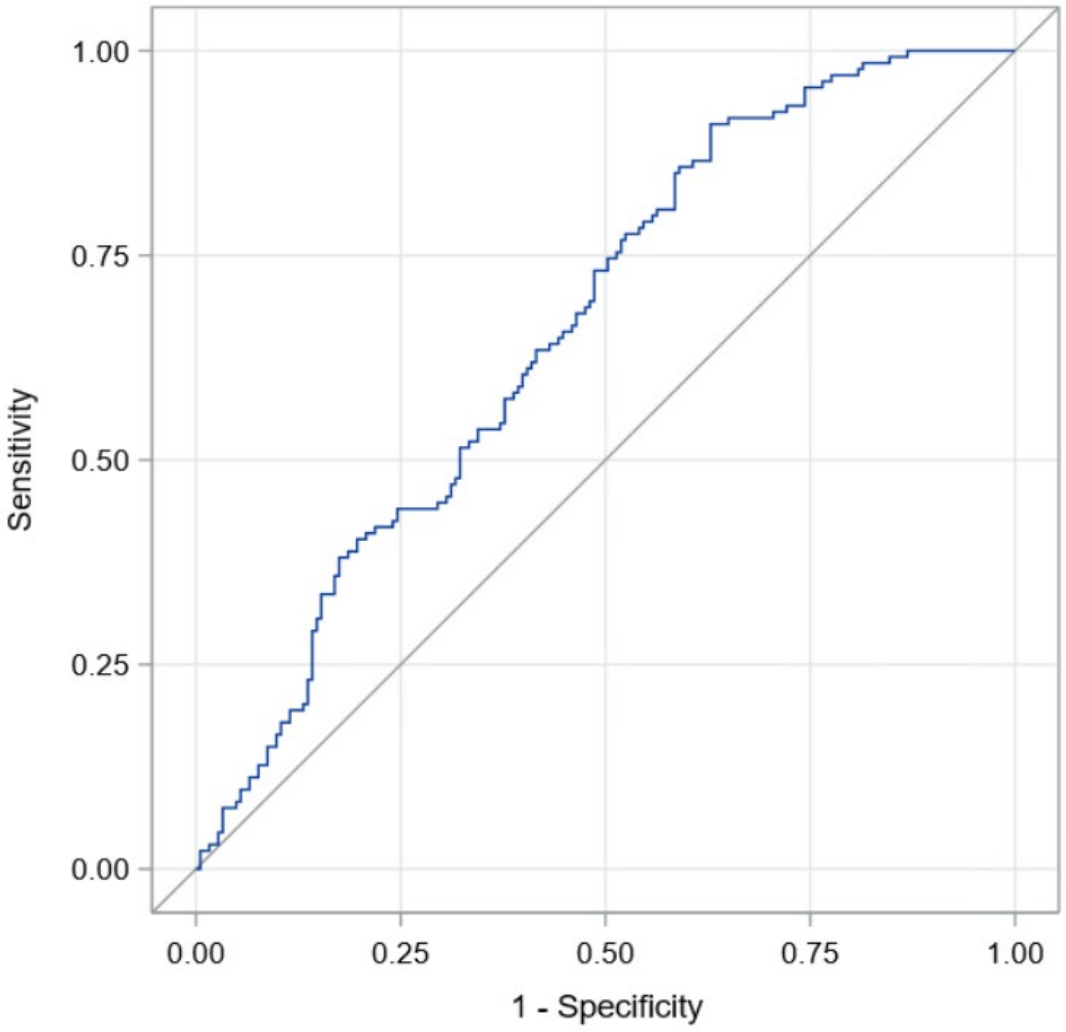

Figure 4.1 ROC curve of incident depressive symptoms prediction

Receiver operator characteristics (ROC) curve for predicting incident depressive symptoms with leave-one-out cross-validation. AUC: 0.67, maximum Youden index: 0.29, sensitivity: 0.78, specificity: 0.51

The inclusion of MoCA scores as a covariate did not change the primary findings; the standardized odds ratios for the self-rated health and the longest walking bout per day were 1.49 (95%CI: 1.15 to 1.93) and 2.45 (95%CI: 1.61 to 3.76) respectively. The AUC of the sensitivity analysis model remained 0.67.

4.5 Discussion

This study investigated the associations between daily-life gait assessed with wearable sensors, in addition to clinical mobility and health measures, and the onset of depressive symptoms in older people. Gait intensity in the mediolateral axis of daily-life gait, gait rhythmicity in the mediolateral axis of daily-life gait, daily step count, duration of the longest walking bout and self-rated health scores were associated with incident depressive symptoms in univariable analyses. Of these five measures, poor self-rated health scores and duration of the longest walking bout in daily life were found to be independent predictors of depressive symptom onset in a multivariable model with satisfactory accuracy after leave-one-out cross-validation.

Cross-sectional associations between measures of poor self-rated health and depressive symptoms in older people have been frequently reported [157, 158], and a recent study found that self-rated health is a mediator between physical health conditions (i.e. presence of chronic diseases and functional disability) and depressive symptoms [157]. Self-rated health has also been shown to be influenced by health behaviour [159], individual and neighbourhood social economic status [160] and social support [161]. These findings imply that self-rated health may be amenable to change, and if so, such changes may also attenuate the risk of developing depressive symptoms.

Self-rated health and frailty (assessed using the Fried criteria of mobility, strength, endurance, physical activity and weight loss) have previously been found to be independent predictors of depressive symptoms over 15 months [162]. These findings concur with ours in that both a subjective perception of general health and an objective measurement of physical performance contribute to the prediction of depressive symptoms. However, a mobility measure obtained with a wearable sensor has advantages over assessing frailty for a screening program, as it does not require physical contact, reduces clinician-involved assessment time and minimises recall and social desirability biases related to self-report.

Wearable sensors can extract a plethora of parameters, which could be considered both a strength and a limitation. Using principal component analysis to reduce the number of daily-life gait parameters, we identified factors that represented overall gait quality, gait intensity in the mediolateral axis (ML intensity), gait intensity in the anteroposterior axis (AP intensity), gait rhythmicity in mediolateral axis (ML rhythmicity) and gait complexity. These factors were comparable to those extracted using a similar methodology by van Schooten and colleagues [163] highlighting the robustness of this approach. Among the identified daily life gait factors, lower ML intensity (heavily informed by the root mean square and range of acceleration in the mediolateral axis) and ML rhythmicity (heavily informed by the harmonic ratio in the mediolateral axis) was found to be predictive of incident depression. Such reduced intensity and rhythmicity in the ML plane are indicative of a more rigid, less energetic and less rhythmic walking pattern, which has also been associated with an increased risk of falls [163].

However, in our multivariable regression, the daily-life gait quality principal components did not meet the model entry criteria when the median duration of the longest walking bout was also included. It is plausible that people with poor gait quality cannot perform long walks without rests, as supported by the correlation between the duration of the longest walking bout and overall daily gait quality found in this study (Pearson's $R= 0.39$, $p<0.001$; Appendix C4). Longer walks without pauses may also indicate more regular outdoor walking and exercise routines, which have been shown to maintain positive affect and alleviate depressive mood [164]. Moreover, an inability to walk long distances has been found to be associated with lower perceived coping, helplessness [165], and mobility-related fatigue [166] – all factors closely related to depression.

Interestingly, while daily-life gait performance was significantly associated with the onset of depressive symptoms, both the Six-Metre Walk Test and Timed Up and Go Test performances were not. This may reflect that a one-dimensional measurement (time required to cover a distance) restricts their predictive capabilities. Further, these clinical tests do not measure gait in daily life, which might be more affected by depression. In contrast, wearable sensors are capable of capturing other aspects of gait performance (e.g. intensity in ML axis) and daily walking behaviour (i.e. the duration of the longest walking bout per day). Finally, the sensor-measured longest walking bout was found to be a better predictor of depressive symptom onset than the questionnaire items of planned, incidental and total activity captured by the IPEQ. This may reflect not only the sensor measure being a more direct activity measurement, but that it also captures participants' physical capacity and behaviour in daily life.

Among our participants, the MOCA scores were 26.6 (no symptoms) versus 26.3 (depressive symptoms). Both groups' averages were well above the cut-off for mild cognitive impairment of 25. This likely reflects that the study cohort comprised relatively healthy and independent living older people. Understanding the effect of cognitive impairment on the development of depressive symptoms and deterioration of daily life gait in cognitively impaired cohorts would require further research.

Limitations of this study should be acknowledged. While our sample size (n=322) was not particularly restrictive for cohort studies, it limited the full utilization of the daily-life gait parameter set. To maintain a reasonable subject-to-variable ratio and avoid over-fitting, a dimension reduction technique (i.e., PCA) was used which inevitably led to information loss. Similarly, instead of more flexible machine learning techniques, logistic regression was used to avoid overfeeding. This may lead to an under-estimation in the predictive precision of daily-life gait parameters. Future studies should consider replicating the current study with a much larger sample size, which would enable external validation and inclusion of a full set of daily-life gait variables.

4.6 Conclusions and ¡mplications

Our findings showed that a risk algorithm based on daily-life walking bouts and self-reported health has good accuracy for the prediction of depression onset in older people over two years. Wearable sensor data compared favourably with clinical mobility screens and may add important independent information for screening for depression among older people.

Chapter 5. Development and large-scale validation of the Watch Walk wrist-worn digital gait biomarkers

5.1 Abstract

Digital gait biomarkers (including walking speed) indicate functional decline and predict hospitalization and mortality. However, waist or lower-limb devices often used are not designed for continuous life-long use. While wrist devices are ubiquitous and many large research repositories include wrist-sensor data, widely accepted and validated digital gait biomarkers derived from wrist-worn accelerometers are not available yet. Here we describe the development of advanced signal processing algorithms that extract digital gait biomarkers from wrist-worn devices and validation using 1-week data from 78,822 UK Biobank participants. Our gait biomarkers demonstrate good test-retest-reliability, strong agreement with electronic walkway measurements of gait speed and self-reported pace and significantly discriminate individuals with poor self-reported health. With the almost universal uptake of smart-watches, our algorithms offer a new approach to remotely monitor life-long population-level walking speed, quality, quantity and distribution, evaluate disease progression, predict the risk of adverse events and provide digital gait endpoints for clinical trials.

Keywords: wrist sensor, inertial unit, validation, mobility, walk, remote monitoring

5.2 Introduction

The use of technology to quantify daily walking activity can provide important indicators of individual and population health [167]. Digital gait biomarkers are quantitative measures of gait derived from wearable device data. As a gait-focused subset of digital biomarkers and mobility outcomes [168, 169], they can be remotely acquired and may provide complementary information to clinical gait assessments [31]. Digital gait biomarkers may be associated with functional status [170] and general health [171]; and are predictive of functional decline, hospitalization [172] and mortality [173].

Previous studies have demonstrated that wearable devices positioned on the lower back or lower limbs can provide valid and reliable digital gait biomarkers. However, their placement on these body regions is awkward which limits user acceptability and compliance [174, 175]. In contrast, wrist-worn devices, including smart watches, have superior acceptance and are approaching almost universal uptake. Wrist-worn acceleration data have been acquired in large longitudinal studies, including the UK Biobank [28], NHANES [176] and Newcastle85+ studies [177]. For example, the UK Biobank includes 1-week activity data acquired from the AX3 wrist-worn tri-axial accelerometer in 103,578 people in its repository of health data [28]. While measures of physical activity levels [28] and activity types [178] have been obtained, the extraction of digital gait biomarkers from these studies has not yet been undertaken.

This omission is likely due to several technical challenges in extracting digital gait biomarkers using a wrist-worn device. Wrist-worn devices are located far from the wearer's centre of mass and subject to arm movements which increase measurement

noise with resultant lower precision and reliability [179, 180]. In consequence, conventional digital gait biomarker extraction techniques, such as signal peak detection and integration of acceleration with zero-velocity updates, can be hampered by large changes in orientation and independent movement of the arms. In fact, the research conducted to date aimed at extracting digital gait biomarkers from wrist-worn devices has mostly been restricted to constrained walks on treadmills and set-length walkways; with resultant algorithms likely inappropriate for more complex walking activities in real-world environments [181, 182]. Two studies have used wrist-worn sensors (including barometers and accelerometers) to estimate walking speed and cadence [183, 184]. While both studies reported promising results, their inclusion of only healthy volunteers and moderate sample sizes ($n \leq 30$ participants) may limit the generalizability of their findings to broader populations. Unsurprisingly, a consensus on which digital gait biomarkers are best for remote assessments has yet to be reached [168].

Clearly, valid and reliable digital gait biomarkers that can be extracted from a wrist-worn device would be valuable for a range of health objectives. We, therefore, aimed to meet this need by conducting a two-stage development and validation study.

In the first stage, 101 participants (19 to 81 years of age) wore the UK Biobank wrist sensor and were recorded while performing a structured mobility routine in free-living settings and then walking and running across an instrumented electronic walkway in our laboratories. We developed (a) the activity classification models using the synchronised video recordings, and subsequently (b) the digital gait biomarker extraction algorithms (including walking speed and cadence) using the instrumented

walkway measurements of the instructed walks and runs as ground truth.

In stage two, the convergent validity of the digital gait biomarkers in relation to self-reported walking speed and self-rated health and their test-retest reliability were determined in 78,822 participants from the UK Biobank cohort.

5.3 Methods

5.3.1 Stage 1: Development and initial evaluation of an activity classification schema and Watch Walk digital gait biomarker algorithms

5.3.1.1 Participants

One hundred and one participants aged 19 to 81 years (mean 47± 18(SD)) (67% female) were recruited from two study sites through volunteer databases (HC190949) and online advertisements from 2020 to 2021: 51 in Sydney, Australia and 50 in Hong Kong, China. The participants' mean height was 1.67m (±0.1m) and their mean weight was 66kg (±14kg). The methods were performed in accordance with relevant guidelines and regulations and approved by the Human Research Ethics Committees at the University of New South Wales (HC200839) and Caritas Institute of Higher Education (HRE210124).

All participants gave written informed consent prior to inclusion.

5.3.1.2 Assessments

Participants wore an AX3 data logger (Axtivity Limited, Newcastle upon Tyne, UK) on their dominant wrist, configured according to UK Biobank's data collection protocol and were video-recorded while they undertook a series of mobility tasks. The AX3 data logger is a compact device (23 x 33x 8 mm) weighing 11 grams that contains a tri-axial logging accelerometer. Acceleration data were sampled at 100 Hz with a range of ± 8 gravitational acceleration units (g).

Participants first walked and ran on a 5.7-meter electronic walkway (GAITRite, CIR Systems Inc. Franklin NJ, USA) at three paces (usual, slower than usual and faster than usual) for seven conditions (walking with arm swing, walking with hands in pockets, walking while texting, walking with a mobile phone held to the ear, walking while carrying a bag over the shoulder, walking while carrying a briefcase and jogging). Gait speed (metre per second), step time (second), step length (metre) and the standard deviation (SD) of step times were extracted using the GAITrite software.

Participants then performed a series of semi-structured daily-life activities in a set order in areas where they frequently encountered other people. No specific instructions were given as to how to perform the tasks, which included: sitting down and standing up from a chair; lying down and getting up from a mattress; walking along a corridor; taking an elevator; walking up and down stairs; writing, typing, reading a book and tying shoelaces while seated; and washing hands and rinsing a cup in the sink while standing. Wearable sensor data were synchronised with the video

data and manually annotated (e.g. marking the start and end-points of a walk with arm swing) by a trained exercise physiologist.

5.3.1.3 Pre-processing of Data

A sample level Euclidean norm from the x/y/z axes acceleration vectors was obtained [185]. Static noise was subsequently removed by subtracting the average signal amplitude over 60 s from the resulting Euclidean norm [185]. A fifth-order Butterworth low pass filter with a cut-off frequency of 20Hz was applied to remove machine noise. A low pass filter with a frequency passband of 0.25 and 2.5 Hz was also applied to the Euclidean norm to facilitate acceleration signal peak detection [186]. Subsequently, non-wear episodes and sleep period time windows were removed. Non-wear episodes were defined as consecutive stationary episodes that exceeded 50 minutes with a standard deviation of 13 milli-gravity units or less [28]. Sleep period time windows were identified using the method proposed by van Hees and colleagues [187]. Acceleration vectors were separated into non-overlapping 4-second windows (rationale for this window size provided in Appendix D7). A vector of 54-dimensional features was extracted from 99 features through backward selection of feature importance (**Appendices D1 and D5**). This included the mean, standard deviation, 25^{th}, 50^{th}, 75^{th} percentile of the static-block-removed and crude Euclidean norms of the acceleration signal, respectively. It also included the correlation coefficients between the local x, y, and z accelerations and the normalized autocorrelation coefficient, the ratio between the 1^{st}-2^{nd} and 1^{st}-3^{rd} autocorrelation values and time-lag.

5.3.1.4 Activity Classification

The activity classification algorithms were trained and validated using Matlab Statistics and Machine Learning Toolbox version 11.6. Support vector machines (SVMs) were used for multi-class classification of activities, as it has been demonstrated to be highly accurate and robust in activity recognition [188]. Initially, six activity categories were trained: 1) Walking with arm-swing; 2) Other complex walking; 3) Running; 4) Stationary (which includes windows that captured travelling in vehicles); 5) unspecified arm activities while standing/ sitting; and 6) unspecified arm activities while walking. The second refined classification separated windows under "Other complex walking" into the five annotated sub-categories: a) Walking with hands in pockets; b) Walking while texting; c) Walking with a mobile phone held to the ear; d) Walking while carrying a bag over the shoulder; and e) walking while carrying a briefcase/grocery bag. Activity classification was trained with ten-fold cross-validation with data partitioning at the individual level. This is arranged to avoid over-estimation of prediction accuracy from intra-class correlation. The activity categories are described in **Appendix D2**.

5.3.1.5 Extraction of the Watch Walk Digital Gait Biomarkers

Gait quantity and its distribution

In periods classified as walking, steps were detected with bandpass-filtered acceleration local maxima and local minima. Local maxima and local minima were checked to ensure they were alternating, aligned with autocorrelation-estimated step time and were higher/lower than the adaptive thresholds, respectively [185]. Details of the step-detection process are summarised in **Figure 1**. Total step count was defined

as the total number of steps detected per day and the longest walking bout was defined as the duration of the largest number of consecutive walking windows. The proportion of duration in walking with arm-swing to the total duration of all forms of walking was extracted. The distribution between the number of walks and the steps per walk was obtained by fitting a linear model to the log-log transformed data. A steeper slope (β1) represents that more short walks and fewer longer walks were performed. Gait quantity was also quantified through the cumulative exposure of walking durations (Equation below) [189].

$$X_i = \frac{\sum d \quad for \quad d \le d_i}{\sum d} * 100\%$$

The percentage of walks of less than (1) 7 seconds and (2) 60 seconds were extracted. Total minutes of running per day was obtained through the activity classification process.

Gait Speed

Average walking speed in each 4-second window was estimated by fitting a Medium Gaussian SVM regression model (10 k-fold validation) with (1) height of the participant [190], (2) interquartile range and (3) median of the Static-block-removed Euclidean norm of acceleration signal, (4) mean of crude Euclidean norm of acceleration signal, (5) mean step time within the window and correlation coefficients between acceleration signal in (6) x- /y- axes and (7) x- /z- axes. The median, 95th percentile and interquartile range of walking speed in a 24-hour period were extracted. Median walking speed represents the usual walking speed in daily life. The 95th percentile of walking speed represents the maximal walking speed in daily life with outliers excluded, which reflects an individual's optimal gait performance better than

medium values [38].

Gait Quality

Walks were further regrouped into 8-step episodes. Walks longer than the cut-off were separated into smaller parts. For example, a walk with 18 steps was separated into the first to 8th steps, 9th to 16th steps and with the 17th and 18th steps truncated. Cadence was obtained by measuring the time required for an 8-step episode. The standard deviation of step times was used to quantify step-time variability. A log-normal model was fitted to the distribution to extract the mode (equation below).

$$Mode = e^{\mu - \sigma^2}$$

Eight-step harmonic ratios were defined as the repeating patterns in the Euclidean norm acceleration (stabilising peaks) over the incomplete patterns (destabilising troughs) implemented with a fast Fourier transform [191]. The 8-step harmonic ratio has demonstrated good test-retest reliability (ICC =0.72) and performed better in identifying fall risk when compared to the traditional (2-step) harmonic ratio. Step and strike regularity were extracted through autocorrelation. The first and second peaks of autocorrelation values indicate correlation between steps and between strides, respectively and were subsequently normalized through dividing by auto-correlation value at zero time-lag. Hence the resulting parameters vary only from -1 to +1.Further details of the gait quality biomarkers have been reported by Brodie et al. [189] in their study on remote monitoring with pendent devices.

5.3.1.6 Statistical analysis

Pre-processing, algorithm development and parameter extraction were completed in MATLAB, version R2019b. The hierarchical framework of the extraction process is presented in **Figure 5.1**. The accuracy of the activity classification algorithms was examined with 10-fold validation, using the annotated class of the walking and running trials on the electronic walkway, the semi-structured daily-life activity routine and vehicle passenger episodes as the ground truth activities. The sensitivity and precision of each class were presented along with confusion matrixes. The criterion validity of the Walk Watch step time and walking speed biomarkers were tested against the corresponding measurements from the electronic walkway and reported as mean absolute percentage error (MAPE).

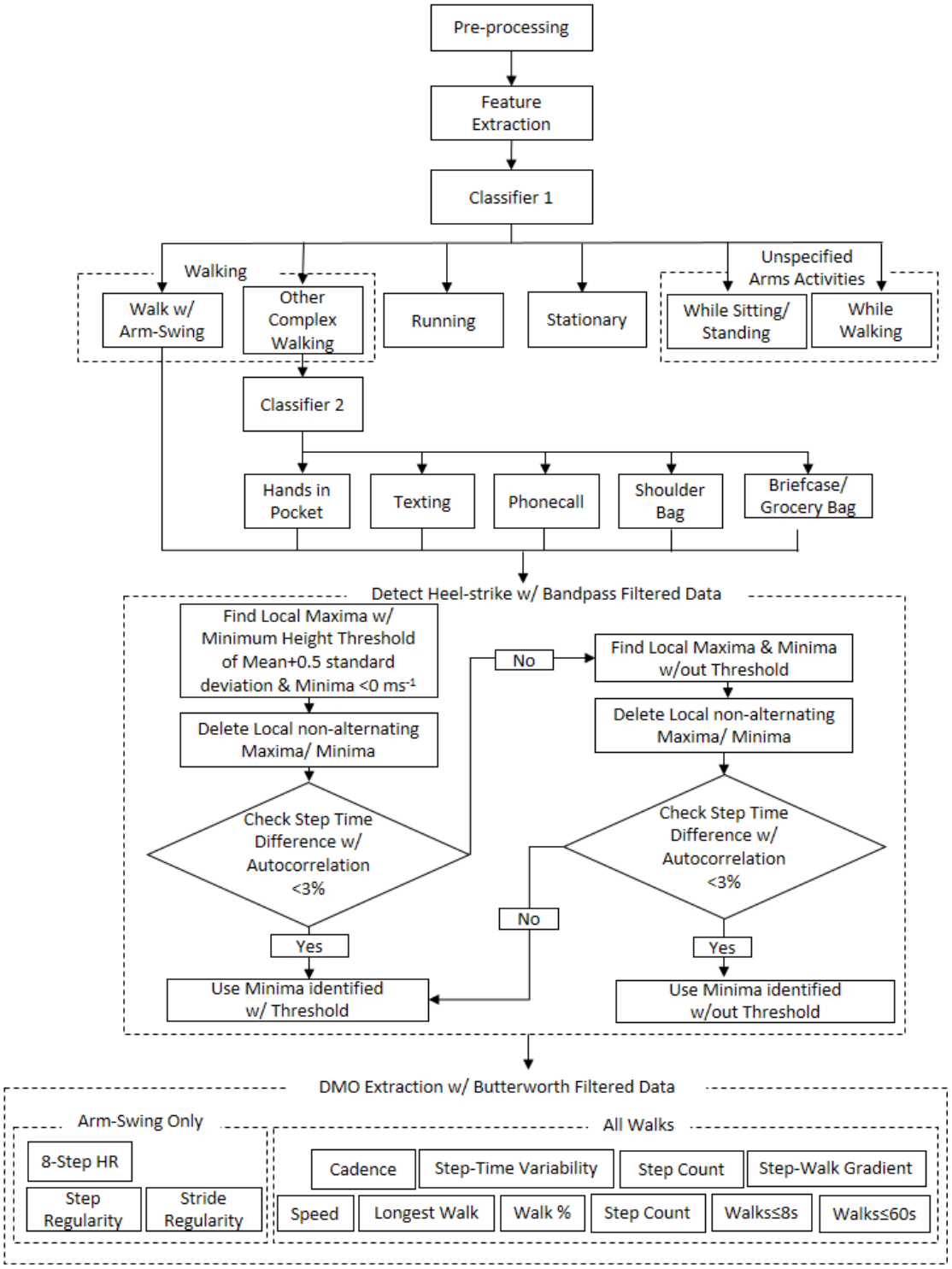

Figure 5.1 Hierarchical framework of digital gait biomarker extraction (Stage 1)

5.3.2 Stage 2: Test-retest reliability and convergent validity of the digital gait biomarkers with respect to self-reported walking pace and health

5.3.2.1 Participants

Participants for stage 2 comprised 78,822 participants from the UK biobank. Participants were instructed to wear an AX3 data logger over their dominant wrist for seven days in 2013. They were aged 46 to 77 years (Median 64, IQR 57 to 69) (56% female). Ethical approval for UKBiobank data transfer and analysis was obtained from the NHS National Research Ethics Service (Ref 11/NW/0382). Participant flow is presented in **Appendix D4**.

5.3.2.2 Data quality and exclusions

Accelerometry data were excluded if considered to be of low quality by the UK Biobank accelerometer working group due to: 1) the data were collected with accelerometers that were poorly calibrated; 2) the accelerometry data were of an abnormal size; and/or 3) the data collection period contained a daylight savings transition. In addition, we used only participant data with 24-hour sensor wear-time for five or more days with at least one walking bout and complete self-reported walking pace and self-rated health data.

5.3.2.3 Statistical analysis

Test-retest reliability of the Watch Walk digital gait biomarkers was examined with intraclass correlation coefficients (2-way random effects, absolute agreement, mean of multiple measurements) for seven consecutive days. The Watch Walk digital gait biomarkers were contrasted between participants self-rated health status using the

Kruskal-Wallis test and Dunn post-hoc test for non-parametric continuously scaled data; ANOVA and Tukey post-hoc test for parametric continuously scaled data; and chi-square test for contingency tables for categorical data. The maximal walking speed was compared among participants who reported slow, average and brisk walking paces with the Kruskal-Wallis test, with post hoc comparisons performed with the Dunn post-hoc test.

5.4 Results

A Support Vector Machine (SVM) classification algorithm was trained for identifying walking bouts from all daily-life activities. A total of 11,646 4-second windows (660 minutes of free-living recording, 1487 structured walks and 249 structured runs from 101 test participants) were included in the training and validation sets and were classified into Walking, Running, Stationary or Unspecified Arm activities. The performance of the classifier was evaluated using a confusion matrix (**Figure 5.2** and **Appendix D6**).

The walking activity class had a sensitivity of 92% and a precision of 93%; the running activity class had a sensitivity of 97% and a precision of 98%; the stationary activity class had a sensitivity of 91% and a precision of 86%; and the unspecified arm activities class had a sensitivity of 71% and precision of 74%.

Examples of the time-series and autocorrelation function for walking with arm-swing at slow, average and fast paces are presented in **Figure 5.3. Table 5.1** presents the accuracy of sensor-based step time and walking speed when compared with the electronic walkway measures. The mean absolute percentage error (MAPE) of step time for the walking conditions ranged between 1.2% and 4.8%, and the MAPE of sensor-based walking speed for the walking conditions ranged between 3.0% and 4.4%. **Figure 5.4** presents the scatterplot for the relationship between walking speed measured by the wrist sensor and the electronic walkway.

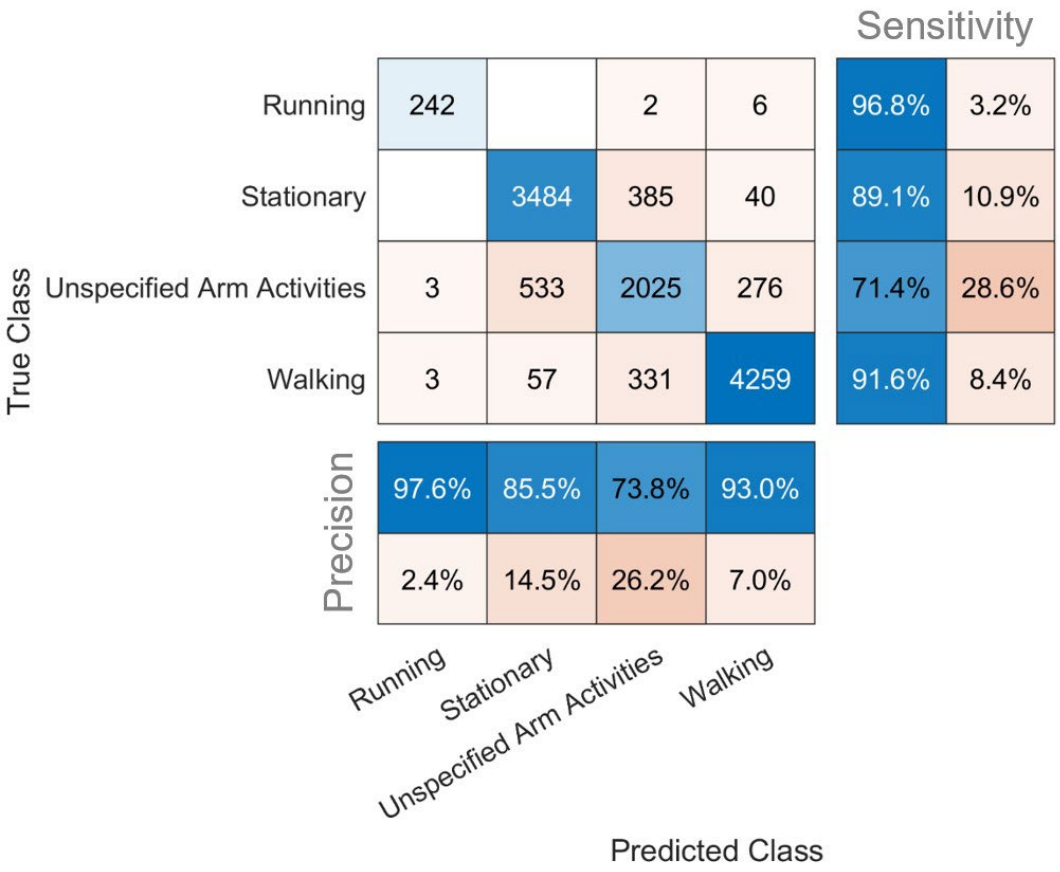

Figure 5.2 Confusion Matrix of Stage 1 classification. N=101 with 11,646 4-second windows. The blue column on the far right of these matrices displays the percentage of correctly identified windows over all the windows that actually belong to that category (i.e. sensitivity). The blue column at the bottom of the matrices represents the percentage of correctly identified windows over all windows that were predicted to be of that category (i.e. precision).

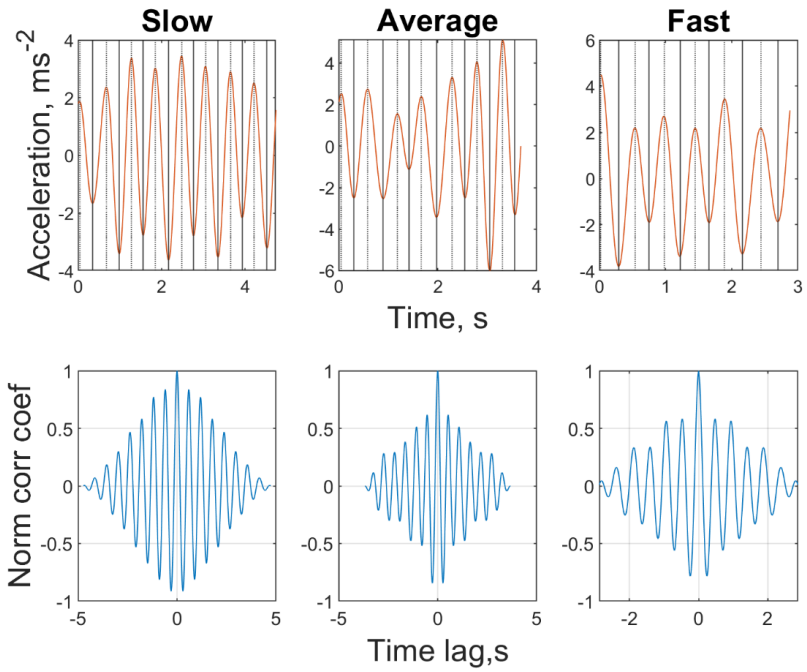

Figure 5.3 An example of the time-series of the static noise-removed bandpass-filtered Euclidean norm of the acceleration vectors and autocorrelation functions for walking with arm-swing at slow, usual and fast paces

Table 5.1 Comparison of spatiotemporal gait parameters assessed by the wrist-worn sensors and the electronic walkway (n=101 with 1487 walks)

Arm movement pattern while walking	**GAITRite Steptime(s)**	**Sensor-measured step time**	**GAITRite walking speed (ms^{-1})**	**Sensor-measured walking speed**
	Mean±SD	Mean absolute percentage error ±SD(%)	Mean±SD	Mean absolute percentage error ± SD(%)
Arm-Swing	0.54 ± 0.07	4.8 ± 12.4	1.32 ± 0.29	4.4 ± 6.4
Hands in pocket	0.55 ± 0.07	1.4 ± 2.8	1.31 ± 0.26	3.1 ± 3.8
Texting	0.56 ± 0.08	1.2 ± 2.2	1.20 ± 0.27	3.4 ± 3.8
Phonecall	0.55 ± 0.13	1.7 ± 5.5	1.31 ± 0.26	3.4 ± 5.7
Shoulder bag	0.54 ± 0.06	1.4 ± 3.5	1.34 ± 0.25	3.0 ± 4.9
Briefcase	0.53 ± 0.07	2.4 ± 8.1	1.37 ± 0.27	3.8 ± 8.4

ms^{-1}: metre per second; s: second; SD: standard deviation.

Figure 5.4 Relationship between wrist sensor and electronic walkway measured walking speed. N=101 with 1487 walks. Each individual dot represents an individual data point. Combined data from six walking conditions.

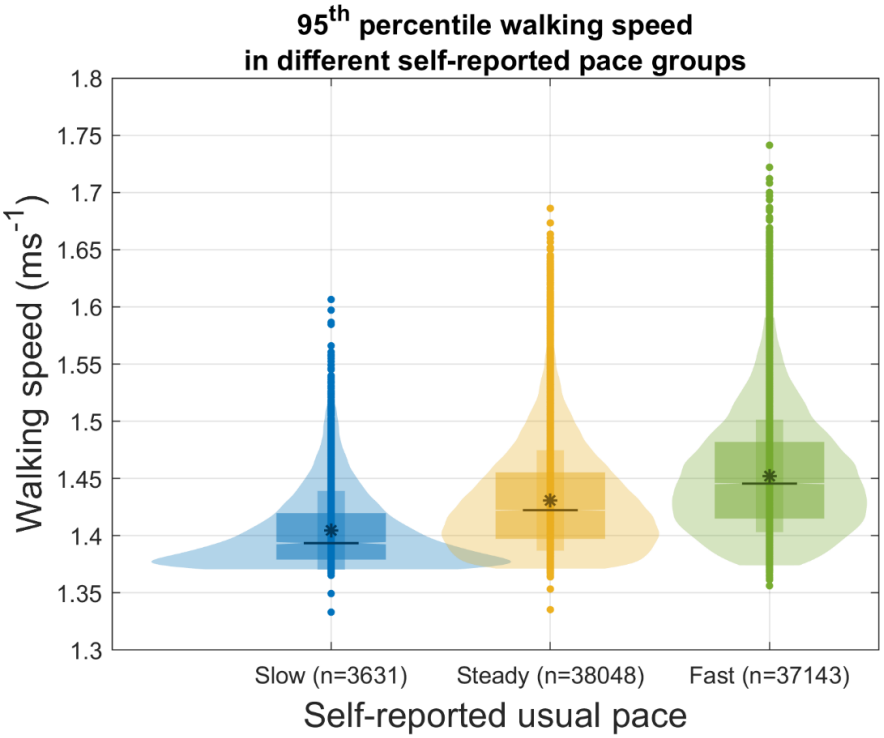

Figure 5.5 Maximal walking speed for people who reported slow, steady and brisk walking paces (N=78822)

Table 5.2 presents the comparison of maximal walking speed between UK Biobank participants who reported routinely walking at a slow, steady or brisk walking pace. The maximal walking speed differed significantly between participants who usually walked at a slow pace (Median: 1.39 ms^{1}, Inter-quartile range: 1.38 to 1.42 ms^{1}), steady pace (Median: 1.42 ms^{1}, Inter-quartile range: 1.40 to 1.46 ms^{1}), and brisk pace (Median: 1.45 ms^{1}, Inter-quartile range: 1.42 to 1.48 ms^{1}), **(Figure 5.5)**. All extracted digital gait biomarkers also differed significantly between individuals with different self-reported health levels (**Table 5.3**, **Figure 5.6**) Post-hoc comparisons between groups are presented in **Appendix D 3**. Finally, most extracted Digital gait biomarkers, except longest walk duration and stride regularity (ICC 0.66 and 0.68, respectively), demonstrated good test-retest reliability (ICCs ranging from 0.71 to 0.89).

Table 5.2 Maximal walking speed stratified by self-reported walking pace and self-rated health (n=78,822)

	Maximal walking speed (arm-swing), ms^{-1}		**Kruskal-Wallis Test**		
	Median	**IQR**	**df**	**Chi-square**	**P-value**
Pace			78821	6643.7	<0.001
Slow	1.39	1.38 to 1.42			
Steady	1.42	1.40 to 1.46			
Brisk	1.45	1.42 to 1.48			
Self-reported health			78821	2380.7	<0.001
Excellent	1.44	1.41 to 1.48			
Good	1.43	1.40 to 1.47			
Fair	1.42	1.39 to 1.45			
Poor	1.40	1.38 to 1.43			

P-values of the Dunn post-hoc test between each group are all <0.001. IQR: Inter-quartile range; ms^{-1}: metre per second.

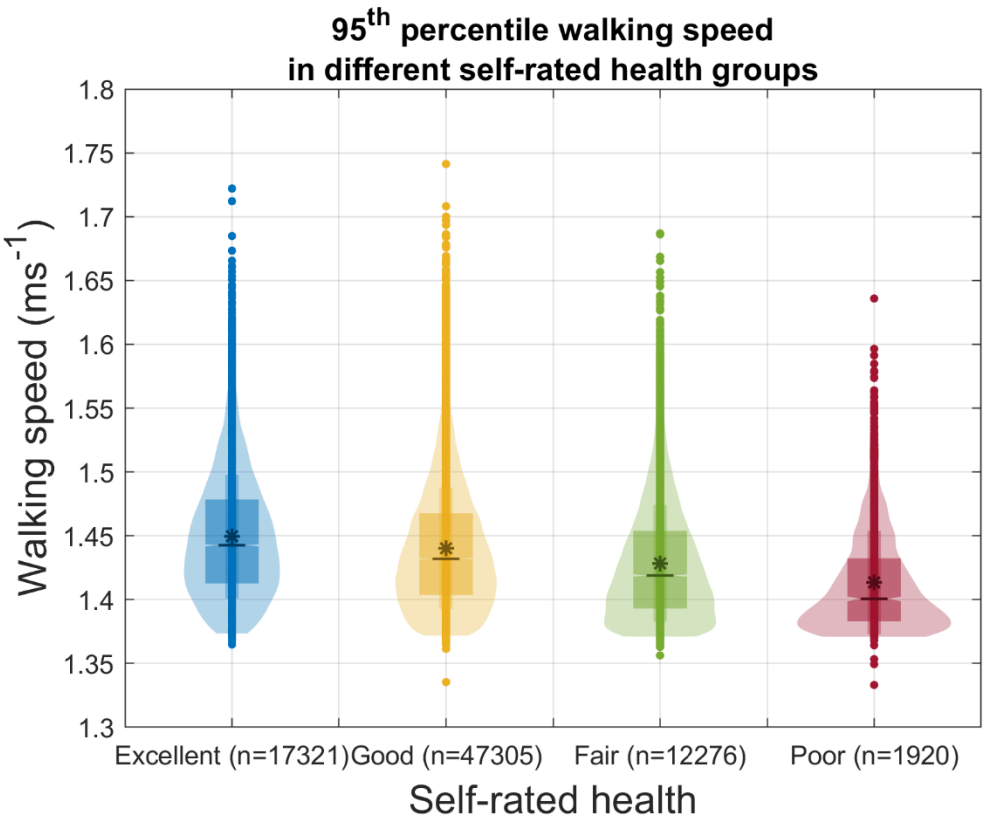

Figure 5.6 Maximal walking speed for people who reported poor, fair and good and excellent health. (N=78822)

Individual dots at the upper and lower extreme, raw data outliers. Widths of the violin plots, kernel densities; Top and bottom of the violin plots, 1st and 99th percentiles; Top and bottom of the narrower boxes, mean ± standard deviation; Top and bottom of the wider box, 1st and 3rd Quartile; Notches of the wider box, 95% confidence intervals of the population median; Black lines in the middle of the boxes, group medians; The asterisks in the middle of the boxes, group means. ms^{-1}: metre per second.

Table 5.3 Summary statistics and test-retest reliability of digital gait biomarkers (n=78,822)

Self-rated Health	Excellent (N=17321)	Good (N=47305)	Fair (N=12276)	Poor (N=1920)	Total (N=78822)	p-value	ICC
Demographics							
Female, n (%)	9778 (56.5%)	26051 (55.1%)	5988 (48.8%)	943 (49.1%)	42760 (54.2%)	<.0001[1]	
Age	57.0 (49.0, 62.0)	58.0 (50.0, 63.0)	57.0 (50.0, 62.0)	56.0 (50.0, 61.0)	57.0 (50.0, 62.0)	<.0001[2]	
Gait quantity and its distribution							
Steps per day	8671.4 (3273.21)	8111.6 (3261.81)	7089.0 (3275.40)	5666.1 (3209.29)	8015.7 (3321.01)	<.0001[3]	0.83
Longest walk duration [s]	266.9 (172.6, 399.2)	244.0 (152.0, 373.7)	202.7 (121.6, 324.6)	140.7 (77.3, 249.3)	240.6 (148.0, 370.7)	<.0001[2]	0.66
Arm-swing proportion [%]	79.3 (71.6, 86.1)	80.1 (72.5, 87.0)	81.4 (73.6, 88.2)	83.0 (75.3, 89.1)	80.2 (72.5, 87.1)	<.0001[2]	0.89
Hands in pocket proportion [%]	4.2 (3.0, 5.9)	4.0 (2.8, 5.6)	3.7 (2.6, 5.3)	3.4 (2.3, 4.8)	4.0 (2.8, 5.6)	<.0001[2]	0.78
Texting proportion [%]	8.3 (5.5, 11.6)	8.2 (5.4, 11.5)	8.0 (5.2, 11.4)	8.3 (5.2, 11.8)	8.2 (5.4, 11.5)	<.0001[2]	0.88
Phone-call proportion [%]	0.6 (0.2, 1.3)	0.5 (0.2, 1.3)	0.5 (0.2, 1.3)	0.5 (0.2, 1.3)	0.5 (0.2, 1.3)	<.0001[2]	0.78
Shoulder-bag proportion [%]	2.5 (1.1, 5.0)	2.2 (1.0, 4.5)	1.8 (0.8, 3.9)	1.3 (0.6, 2.9)	2.2 (1.0, 4.5)	<.0001[2]	0.82
Briefcase proportion [%]	2.2 (1.0, 4.2)	2.0 (0.9, 3.9)	1.6 (0.7, 3.4)	1.1 (0.4, 2.7)	2.0 (0.9, 3.8)	<.0001[2]	0.81
Step-walk Gradient*100	-111.6 (23.13)	-113.9 (23.99)	-116.6 (25.94)	-122.3 (28.59)	-114.0 (24.33)	<.0001[3]	0.76
Walks≤8s [%]	54.3 (10.16)	55.3 (10.47)	56.7 (11.22)	60.5 (12.38)	55.4 (10.63)	<.0001[3]	0.80
Walks≤60s [%]	94.9 (89.7, 98.0)	95.4 (90.3, 98.2)	96.0 (91.3, 98.6)	97.1 (92.8, 99.4)	95.4 (90.4, 98.3)	<.0001[2]	0.75

Self-rated Health	Excellent (N=17321)	Good (N=47305)	Fair (N=12276)	Poor (N=1920)	Total (N=78822)	p-value	ICC
Gait Speed							
Median (usual) [ms-1]	1.33 (1.32, 135)	1.33 (1.31, 1.35)	1.32 (1.30, 1.34)	1.32 (1.30, 1.34)	1.33 (1.31, 1.35)	<.0001[2]	0.86
95th percentile(maximal) [ms-1]	1.44 (1.41, 1.48)	1.43 (1.40, 1.47)	1.42 (1.39, 1.45)	1.40 (1.38, 1.43)	1.43 (1.40, 1.47)	<.0001[2]	0.85
Gait Quality							
Cadence Median [spm]	105.9 (5.91)	105.0 (5.76)	103.8 (5.67)	102.4 (5.53)	105.0 (5.82)	<.0001[3]	0.85
Cadence IQR [spm]	22.0 (4.42)	21.7 (4.43)	21.6 (4.59)	22.4 (5.15)	21.8 (4.48)	<.0001[3]	0.77
Mode of step-time variability	2.8 (1.8, 4.1)	3.1 (2.0, 4.5)	3.6 (2.2, 5.1)	4.4 (2.8, 6.1)	3.1 (2.0, 4.5)	<.0001[2]	0.77
8-step HR (arm-swing)	13.9 (4.07)	13.6 (4.23)	13.1 (4.51)	11.7 (4.91)	13.6 (4.27)	<.0001[3]	0.77
Step regularity (arm-swing) [%]	66.4 (55.3, 76.0)	64.6 (53.2, 74.9)	61.5 (49.3, 72.8)	55.5 (43.1, 69.1)	64.4 (52.8, 74.8)	<.0001[2]	0.71
Stride regularity (arm-swing) [%]	54.7 (42.6, 65.3)	53.1 (40.5, 64.6)	50.8 (37.5, 63.6)	44.3 (31.1, 59.4)	53.0 (40.2, 64.5)	<.0001[2]	0.68

HR: Harmonic Ratio; ICC: intraclass correlation; IQR: Interquartile range; ms^{-1}: metre per second; s: second; spm: steps per minute.[1] Count and proportion with Chi-Square p-value; [2] Median and Inter-quartile range with Kruskal-Wallis p-value; [3] Mean and standard deviation with ANOVA F-test p-value;

5.5 Discussion

The main aims of this study were to develop and validate digital gait biomarkers derived from a wrist-worn device using both laboratory-assessed and real-world data. We found our digital gait biomarkers demonstrated good test-retest reliability, strongly agreed with electronic walkway measurements of gait speed and self-reported pace and significantly discriminated between individuals with poor and good self-reported health. The algorithms were readily applied in the large UK Biobank database that collected 7-day wrist-sensor data indicating the good utility of these measures.

The Watch Walk method presented in this paper enables the retrieval of digital gait biomarkers that summarise walking speed, gait quality, walking patterns and the statistical distributions of gait measures in daily life. These digital gait biomarkers, commonly assessed through sensors located at inconvenient attachment sites (i.e. ankle and lower back), have been proven to accurately predict adverse health events [192, 193] and used as surrogate endpoints in pharmaceutical trials [194]. Watch Walk advances the range and depth of measures obtained from wrist-worn accelerometer measures, which have predominantly featured step-count [195], vector magnitude as a proxy of physical activity intensity [28] and time spent in sleep, physical activity and sedentary behaviours [178]. Watch walk builds on previous advances using wrist-worn sensors to estimate walking speed and cadence [183, 184] through enhanced generalizability and new applications in large-scale activity monitoring. Considering that wrist-worn accelerometers are widely available, either incorporated in commercially-available smart-watches or measurement tools in large longitudinal studies, our new method offers a practical tool to remotely monitor

multiple aspects of mobility, which has been considered as the sixth vital sign [171], in a reliable, valid and cost-effective way.

Our study findings build on previous work undertaken in this field in several ways. First, despite daily-life gait parameters varying from day-to-day [196], our results showed that most of the digital gait biomarkers computed as daily averages over seven-days have good test-retest reliability. This supports the continued use of seven-day wrist-worn accelerometry measures that have high compliance in older adults [174] and are commonly used in physical activity research [197]. The ICCs for the longest daily walk duration and stride regularity were found to be 0.66 and 0.68, respectively, which represent moderate reliability [198]. Both week and weekend days were included in the test-retest reliability analysis as the collection period comprised continuous seven-day data. Therefore, different routines between week and weekend days and throughout the week may have resulted in lower ICCs. Second, our classification accuracy for walking activities was above 91% which compares favourably with a previous activity classification algorithm proposed for the UK Biobank dataset (70% in the CAPTURE24 study). It is likely our higher accuracy was due to the use of 4-second window frames that better reflect the short walking bouts undertaken in daily life [199]. Third, compared to previous studies that estimated walking speed/distance with wrist-worn accelerometers [181, 182], our development and technical validation study involved a substantially larger sample (101 participants), a wider age range of participants (19 to 81 years of age) and included more diverse walking activities and different hand positions while walking; all factors that provide greater external generalizability and reduce over-feeding bias. Finally, The Watch Walk method was developed with a hardware-agnostic approach and the

data format required (seven-day 100 Hz tri-axial wrist acceleration) has been widely utilized. Hence, it is applicable not only to the UK Biobank dataset, but also to other healthcare databases such as NHANES, as well as future studies using commercially available smartwatches.

We also acknowledge certain limitations. First, our measure of sensor-based walking speed was validated with an electronic walkway in a laboratory setting and daily-life activity classification was based on simulated, as opposed to real life, day-to-day activities. Second, it was not practical to use body-camera recordings to validate our activity classification schema in real-life due to the short timeframes and wide dispersion of the activity capture windows. Third, the digital gait biomarkers were not validated in participants who use walking aids, so such walks may have been missed. Finally, walking speed accuracy was lower for walks slower than $0.7ms^{-1}$ and faster than $1.8ms^{-1}$, i.e. beyond 2 standard deviations of mean gait-speed of older adults [200]. Further studies are required to refine walking speed estimations at these extremes. Future studies should investigate the clinical validity of these new digital gait biomarkers by: (1) developing normative values to provide a reference base to identify mobility impairments in clinical populations; (2) assessing their predictive capabilities with regard to important clinical outcomes such as falls and fall-related injuries, frailty, cognitive impairment, depression and mortality; and (3) using them to monitor the progression of chronic conditions and evaluate the effectiveness of interventions. The use of these practical and objective measurements of daily-life mobility performance may also assist in the early detection of mobility decline to enable early interventions to maximise health and wellbeing.

Chapter 6. Prediction of incident depression in middle-aged and older adults using digital gait biomarkers extracted from large-scale wrist sensor data

6.1 Abstract

Objectives: To determine if digital gait biomarkers captured by a wrist-worn device can predict the incidence of depressive episodes in middle-age and older people.

Design: Longitudinal Cohort Study

Setting and Participants: A total of 72,359 participants were recruited in the United Kingdom

Methods: Participants were assessed at baseline on gait quantity, speed, intensity, quality, walk length distribution and walk-related arm movement proportions using wrist-worn accelerometers for up to seven days. Univariable and multivariable Cox proportional hazard regression models were used to analyze the associations between these parameters and diagnosed incident depressive episodes for up to 9 years.

Results: A total of 1,332 participants (1.8%) had incident depressive episodes over a mean of 7.4 ± 1.1 years. All gait variables, except some walk-related arm movement proportions, were significantly associated with the incidence of depressive episodes ($p<0.05$). After adjusting for socio-demographic, lifestyle and comorbidity covariates; running duration, step count and step regularity were identified as independent and significant predictors ($p<0.001$). These associations were consistent in the subgroup analysis of older people and individuals with serious medical conditions.

Conclusions and implications: The study findings indicate digital gait quality and quantity biomarkers derived from wrist-worn sensors are important predictors of

incident depression in middle-aged and older people. These gait biomarkers may facilitate screening programs for at-risk individuals and the early implementation of preventive measures.

Keywords: wearable sensors, depression, gait, middle-aged, aged, UK Biobank

6.2 Introduction

Clinical depression affects 280 million people worldwide [201], with reported incidence rates of 18 and 12 per 1000 person-years in middle-aged and older people, respectively [202]. Depression significantly increases the risk of self-neglect, comorbidity and suicide [9], and therefore poses a serious public health problem world-wide. It is crucial, therefore, to identify risk factors for depression to enable early identification of at-risk individuals and the implementation of indicated preventive measures.

Over the last decade, there has been a growing interest in the association between mobility performance and incident depression in middle-aged and older adults. Poor performances in commonly used clinical mobility tests, such as the Six-Metre Walk Test, Timed Up and Go Test and Short Physical Performance Battery have been shown to predict the occurrence of depressive episodes. However, these studies have focused on “optimal” mobility performance assessed in clinical settings, and have not incorporated other aspects of daily walking behaviours; a knowledge gap attributed to the lack of sensor-acquired physiological data [203].

In the few cohort studies on depression using wearable sensors assessing every-day

activities conducted to date [25], low acceptability of lower-body mounted sensors and poor long-term compliance have been identified as barriers to use [204]. In contrast, wrist-worn devices such as smart watches have near-universal acceptance [205], and have been used successfully in large-scale studies such as the UK Biobank project that collected wrist-worn sensor data along with matching health records from over 100,000 individuals [206]. However, technical challenges due to arm movements that increase measurement noise and their placement far from the wearer's centre of mass have until recently, hampered the extraction of digital gait biomarkers from wrist-worn devices [207, 208]. Fortunately, digital gait biomarkers from wrist-worn sensor data such as walking speed, daily step counts and gait quality measures have recently been comprehensively validated, enabling their use in large population studies and clinical settings [209].

Identification of digital gait biomarkers predictive of depression would further the understanding of how daily walking behaviours and affective disorders interact and build on previous studies that have primarily focussed on self-reports of daily mobility [210, 211]. The availability of validated gait biomarkers may also facilitate screening programs for at-risk individuals [212] and would require minimal financial resources if incorporated with smart watches.

The aim of the current study, therefore, was to determine whether validated digital gait biomarkers derived from wrist-worn sensor data could predict incident depression in a large sample of middle-aged and older people (over 70,000 participants from the UK Biobank database). Subgroup analyses were also undertaken to determine whether

the digital gait biomarkers also predicted incident depression in people of different ages and individuals with serious medical conditions. We hypothesized that digital biomarkers assessing both gait quality and quantity would predict the onset of depression and provide additional value to established risk factors in predicting depression.

6.3 Methods

6.3.1 Participants

Data were obtained from the UK Biobank Resource (Application Number 56109). The UK Biobank prospective cohort study commenced in 2006 and collected biological and medical data from over half a million people aged 40 to 69 years at the time [206]. Postal invitations were sent to National Health Service (NHS) registrants who lived within a 40 km radius of one of 22 assessment sites in the United Kingdom. About six percent of invitees participated in the baseline assessment [213], and between 2013 and 2015, 7-day accelerometry data were collected from a randomly selected sub-sample of 103,712 individuals (response rate: 44.8% of the invitees). Of these, 72,359 participants (70%) provided valid accelerometry data and sufficient wear-time for digital gait biomarker extraction. Participant data were linked to the National Health Service (NHS) electronic health records with entries last updated in January 2022. Participants gave informed consent prior to their participation, and ethical approval for the UK Biobank study (which also covers this current work) was obtained from the NHS National Research Ethics Service (Ref 11/NW/0385). Further details of the scientific rationale, research questions and methods of the UK Biobank study are provided on the UK Biobank website (https://www.ukbiobank.ac.uk/).

6.3.2 Depression outcome

Our depression outcome was derived from the date of the first reported occurrence of a depressive episode (Code F32) according to the International Classification of Diseases tenth revision (ICD-10; Data-field #130894). To ensure the analyses pertained to depressive symptom onset, participants with a reported depressive episode in their lifetime prior to the collection of accelerometry data (Data-field #90003) were excluded from this study. The number of days between the accelerometry data collection and the first report of a depressive episode was extracted as time-to-event data (Appendix E1). Death (Data-field #40000) and Lost-to-follow-up (Data-field #191) were set as censoring events.

6.3.3 Digital Gait Biomarkers

The Digital Gait Biomarkers were extracted using the Watch Walk algorithms which were derived in a two-stage development and validation study [209]. This development and validation process showed these measures have: good test-retest reliability; strong agreement with gold standard electronic walkway measures from over 100 individuals aged between 18 to 71; and significantly discriminate between groups with slow, medium and fast self-reported walking pace in over 70,000 UK Biobank participants.

In this study, tri-axial accelerometry data from the median wear time of the wrist sensor (AX3 by Axivity Ltd, UK) was six days (IQR: 6 to 7). These data were compressed into vector magnitude series, low-pass filtered and separated into 4-

second non-overlapping windows. For each data window, 54 features were extracted for subsequent Support Vector Machine (SVM) classification, which categorised each window into one of four activity classes (walking, running, stationary/in vehicle, or unspecified arm activities). Windows identified as walking were further classified according to six walking-related hand positions (wearing a shoulder-bag, having hands in pockets, carrying a briefcase, walking with swinging the arms, making a call with a mobile phone, or texting). The digital gait biomarkers were then extracted from the acceleration signals of the walking windows.

Twenty-one digital gait biomarkers representing five aspects of walking were extracted:

(1) Gait Quantity: assessed by step counts (steps per day); and daily running duration (seconds).

(2) Gait Speed and Intensity: assessed by usual walking speed defined as median daily walking speed (centimetres per second); maximal walking speed defined as the 95th percentile of daily walking speed (centimetres per second); cadence median (steps per minute); and cadence interquartile range (steps per minute).

(3) Gait Quality: assessed by step time variability defined as the standard deviation of step times (milliseconds); 8-step harmonic ratio; step and stride regularity defined as the normalized autocorrelation coefficient of the filtered acceleration vector magnitude between each step or stride.

(4) Walk Length Distribution: assessed by the daily median walk duration (seconds) and longest walk duration (minutes), the cumulative proportion of walks

under 8 seconds (%) and under 60 seconds (%), and the step-walk gradient, which describes the distribution of walks according to a power law.

(5) Walk Hand Positions: assessed by the percentage of walking performed with different hand positions (comprising carrying a shoulder bag defined as wrist over the shoulder, hands in pocket, carrying a briefcase or grocery bag, with arm-swing, texting while walking, or making a phone call defined as holding the wrist next to the ear).

6.3.4 Covariates

Data for many established risk factors for depression were extracted from the UK Biobank for inclusion in the statistical analyses. These covariates included: sex (Data-field #31); age-group (38-50 years, 50-60 years, or 60-73 years) derived from the date of birth (#33) and date of wrist sensor data collection (#90003); marital status derived from the number of individuals in household (#709) and their relationship with the participants (#6141); household income (#738); highest educational qualification (#6138); Townsend deprivation index (#189); weekly working hours (#767); mode of transportation to work (#6143b); body mass index (BMI; #21001); smoking status (#20116); alcohol consumption status (#20117); and presence of serious medical conditions including stroke (#2443); dementia (#2453); cardiovascular disease (#2463); diabetes (#2473); cancer (#4056); recent fracture (#6150); pulmonary embolism (#6152); deep venous thrombosis (#42018); and emphysema (#6152).

Sleeping periods were also extracted from the wrist sensor data using van Hees' method [187]. Participants who had total sleep durations less than 6 hours or more than 9 hours per day were categorised as having deficient and excessive sleep respectively [214]. Bedtimes before 9 pm and after 1 pm are considered advanced and

delayed bedtimes, respectively [215].

6.3.5 Statistical Analysis

The statistical analysis plan outlining the included variables and proposed statistical methods for this study were registered on the Open Science Framework Registry (http://osf.io/6yg3x/) prior to data analysis.

Sociodemographic, health and gait characteristic differences between participants who did and did not have depressive episodes in the follow-up period were assessed with independent t-tests for continuous parametric data, Mann-Whitney U tests for non-parametric continuous data and Chi-square tests for categorical data.

Separate univariable Cox proportional-hazard regression models for time to the first depressive episode were run with individual digital gait biomarkers as predictors. Multivariable Cox proportional-hazard regression models were then run with established risk factors for depression (covariates) entered at step 1, and then with digital gait biomarkers included using backward selection. Changes in Akaike's Information Criterion (AIC) between the base model comprising the known risk factors only and the new model which also included the digital gait biomarkers was used to assess the additional predictive value [216]. AIC assesses how much information is explained by the model and penalises overfitting with the number of included parameters. Additionally, subgroup analyses were performed according to age-group and presence/absence of other medical conditions.

For the multivariable models, multi-collinearity was assessed with Pearson's correlations, and if two variables had a coefficient of ≥0.8, one was removed before the multivariable analyses to ensure a parsimonious fit. The proportional hazards assumption was checked with weighted Schoenfeld residuals vs time plots [217]. Functional forms of covariates were assessed with the Martingale Residual plot [218]. Non-fitting covariates were log-transformed. Hazard ratios (HR) and two-tailed 95% confidence intervals (95%CI) are reported, and standardized HRs and 95%CIs of the z-transformed biomarkers are reported to facilitate interpretation. Statistical inference was set at 0.05 and analyses were performed in SAS Enterprise 8.3 software.

6.4 Results

In total, 1,332 participants reported a depressive episode over an average of 7.4 years (SD: 1.1, range 0.1 to 9 years) of follow-up; with an overall incidence of 1.8%. Most of the objectively assessed wrist-sensor gait measurements were significantly associated with incident depressive episodes (Table 6.1). People were more likely to report a depressive episode if they were less active (7282 vs. 8086 steps/day), walked slower (1.42 ms vs. 1.43 -1), had fewer regular arm swings while walking (61.5 vs. 64.3%), completed shorter uninterrupted walks (209.0 vs. 244.0 s) and used fewer arm movement patterns while walking. Only two variables (proportion of walking while texting or making phone calls) were not significantly associated with depressive episodes.

Table 6.1 Digital gait biomarkers for participants who did and did not have a depressive episode in the follow-up period

	Incident Depression			
	No (n=71027)	Yes (n=1332)	Total (N=72359)	P-value
1. Gait Quantity				
Steps per day	8086.7 (3307.76)	7281.9 (3255.12)	8071.9 (3308.55)	<.0001[2]
Running duration [min/day]	0.2 (0.1, 0.7)	0.1 (0.0, 0.5)	0.2 (0.1, 0.7)	<.0001[1]
2. Gait Speed and Intensity				
Max walking speed [ms-1]	1.43 (1.40, 1.47)	1.42 (1.40, 1.46)	1.43 (1.40, 1.47)	<.0001[1]
Usual walking speed [ms-1]	1.32 (1.31, 1.35)	1.33 (1.30, 1.34)	1.33 (1.31, 1.35)	<.0001[1]
Cadence Median [spm]	105.0 (5.83)	104.3 (5.90)	105.0 (5.83)	<.0001[2]
Cadence IQR [spm]	21.8 (4.47)	22.2 (4.77)	21.8 (4.47)	0.0003[2]
3. Gait Quality				
Step-time variability [ms]	3388 (1944, 4506)	3396 (2167, 5114)	3092 (1949, 4517)	<.0001[1]
8-step Harmonic ratio	1.4 (0.43)	1.3 (0.46)	1.3 (0.43)	<.0001[2]
Step regularity [%]	64.6 (53.1, 74.9)	61.5 (48.2, 73.0)	64.6 (53.0, 74.9)	<.0001[1]
Stride regularity [%]	52.1 (15.05)	49.2 (16.02)	52.0 (15.07)	<.0001[1]
4. Walk Length Distribution				
Median walk duration [min]	0.2 (0.1, 0.2)	0.1 (0.1, 0.2)	0.2 (0.1, 0.2)	<.0001[1]
Longest walk duration [min]	4.1 (2.5, 6.2)	3.5 (2.1, 5.5)	4.0 (2.5, 6.2)	<.0001[1]
Walks ≤ 8s [%]	55.3 (10.56)	57.2 (11.33)	55.3 (10.57)	<.0001[2]
Step-walk Gradient	-1.14 (0.24)	-1.18 (0.26)	-1.14 (0.24)	<.0001[2]
Walks ≤ 60s [%]	95.4 (90.3, 98.3)	96.1 (91.4, 98.7)	95.4 (90.3, 98.3)	<.0001[1]
5. Walk Hand Positions				
Shoulder bag [%]	2.2 (1.0, 4.5)	1.9 (0.7, 4.0)	2.2 (1.0, 4.5)	<.0001[1]
Hands in pocket [%]	4.0 (2.8, 5.7)	3.6 (2.6, 5.0)	4.0 (2.8, 5.6)	<.0001[1]
Briefcase [%]	2.0 (0.9, 3.9)	1.7 (0.6, 3.6)	2.0 (0.9, 3.9)	<.0001[1]
Arm swing [%]	80.1 (72.4, 87.0)	81.3 (73.5, 88.5)	80.2 (72.5, 87.0)	<.0001[1]
Phone call [%]	0.5 (0.2, 1.3)	0.5 (0.2, 1.3)	0.5 (0.2, 1.3)	0.2417[1]
Texting [%]	8.2 (5.4, 11.5)	8.2 (5.1, 11.4)	8.2 (5.4, 11.5)	0.3641[1]

[1]Kruskal-Wallis p-value; [2]ANOVA F-test p-value; [3]Chi-Square p-value; Seconds (s); centimetres per second (cms-1); minutes (m); steps per minute (spm)

Of the above digital gait biomarkers, median walk duration demonstrated the strongest univariable association with time to first depressive episode (Table 6.2); each standard deviation (SD) decrement was associated with a 51% decrease in depressive episode hazard. This was followed by total steps per day (24% decrease in hazard per SD), step time variability (23% increase in hazard per SD) and longest walking duration (22% decrease in hazard per SD).

Table 6.2 Univariable associations between the digital gait biomarkers and incident depression (n=72359)

	Hazard Ratio	Confidence Interval	Standardized Hazard Ratio	Confidence interval
1. Gait Quantity				
Steps per day [per 1000]	0.92*	(0.90 to 0.94)	0.76*	(0.71 to 0.80)
Log of daily running duration	0.87	(0.84 to 0.90)	0.80*	(0.76 to 0.85)
2. Gait Speed and Intensity				
Maximal walking speed [cms-1]	0.96*	(0.95 to 0.97)	0.82*	(0.77 to 0.87)
Usual walking speed [cms-1]	0.95*	(0.93 to 0.97)	0.86*	(0.82 to 0.91)
Cadence Median [spm]	0.98*	(0.97 to 0.99)	0.87*	(0.83 to 0.92)
Cadence IQR [spm]	1.02*	(1.01 to 1.03)	1.10*	(1.04 to 1.16)
3. Gait Quality				
Step-time variability*100 [s]	1.11*	(1.09 to 1.14)	1.23*	(1.17 to 1.29)
8-step Harmonic ratio	0.59*	(0.52 to 0.67)	0.80*	(0.76 to 0.85)
Step regularity [%]	0.99*	(0.98 to 0.99)	0.82*	(0.77 to 0.86)
Stride regularity [%]	0.99*	(0.98 to 0.99)	0.83*	(0.78 to 0.87)
4. Walk Length Distribution				
Median walk duration [min]	0.54*	(0.33 to 0.91)	0.49*	(0.27 to 0.89)
Longest walk duration [min]	0.93*	(0.91 to 0.95)	0.78*	(0.73 to 0.84)
Walks ≤ 8s [%]	1.02*	(1.01 to 1.02)	1.21*	(1.15 to 1.28)
Step-walk Gradient [per 100]	0.54*	(0.43 to 0.67)	0.86*	(0.82 to 0.91)
Walks ≤ 60s [%]	1.01*	(1.01 to 1.02)	1.11*	(1.04 to 1.17)
5. Walk Hand Positions				
Shoulder bag [%]	0.97*	(0.95 to 0.98)	0.87*	(0.82 to 0.93)
Hands in pocket [%]	0.96*	(0.94 to 0.98)	0.89*	(0.84 to 0.95)
Briefcase [%]	0.97*	(0.95 to 0.99)	0.90*	(0.85 to 0.96)
Arm swing [%]	1.01*	(1.00 to 1.01)	1.10*	(1.04 to 1.17)
Phone call [%]	1.02	(0.99 to 1.05)	1.03	(0.98 to 1.08)
Texting [%]	1.00	(0.99 to 1.01)	0.99	(0.94 to 1.05)

Seconds (s); milliseconds (ms); centimetres per second (cms^{-1}); minutes (m); steps per minute (spm); hours (h). * indicates a statistically significant result ($p<0.05$).

Correlations among the digital gait biomarkers are presented in Appendix E2. After considering multi-collinearity, eight digital gait biomarkers were included in the multivariable analyses: (1) daily step count, (2) log of running duration, (3) maximal walking speed, (4) usual walking speed, (5) median cadence, (6) step regularity, (7) longest walk duration, and (8) proportion of walks with durations of seven seconds or less. Daily running duration was log-transformed to fulfil functional form requirements.

As anticipated, numerous demographic, health and lifestyle factors were also significantly associated with incident depressive episodes (Table 6.3). After adjusting for these covariates (Table 6.4), our analyses revealed people were more likely to become depressed if: they did no running (10% increase in hazard per SD of log-transformed daily running duration), took fewer steps per day (12% increase in hazard per SD), had a less regular walking pattern (10% increase in hazard per SD). The adjusted model including digital gait biomarkers had a significantly better fit compared to the model with known risk factors only, as demonstrated by a decrease in AIC of 80.6. For reference, an AIC decrease >10 provides strong evidence that the new model has a better fit [216].

Table 6.3. Participant Characteristics stratified by incident depression in the follow-up period

	Incident Depression			
	No(n=71027)	Yes(n=1332)	Total(N=72359)	P-value
Female, n (%)	37708 (53.1%)	825 (61.9%)	38533 (53.3%)	<.0001[3]
Age	62.0 (7.84)	61.7 (8.26)	62.0 (7.85)	0.4936[1]
Married, n (%)	55310 (77.9%)	930 (69.8%)	56240 (77.7%)	<.0001[3]
Total household income, n (%)				<.0001[3]
Less than 18,000	9880 (13.9%)	293 (22.0%)	10173 (14.1%)	
18,000 to 30,999	17134 (24.1%)	367 (27.6%)	17501 (24.2%)	
31,000 to 51,999	20538 (28.9%)	391 (29.4%)	20929 (28.9%)	
52,000 to 100,000	18177 (25.6%)	232 (17.4%)	18409 (25.4%)	
Greater than 100,000	5298 (7.5%)	49 (3.7%)	5347 (7.4%)	
Highest Educational Qualifications, n (%)				<.0001[3]
College or University degree	31089 (43.8%)	477 (35.8%)	31566 (43.6%)	
A levels/AS levels or equivalent	9275 (13.1%)	180 (13.5%)	9455 (13.1%)	
O levels/GCSEs or equivalent	14431 (20.3%)	283 (21.2%)	14714 (20.3%)	
CSEs or equivalent	2805 (3.9%)	69 (5.2%)	2874 (4.0%)	
NVQ or HND or HNC or equivalent	3923 (5.5%)	95 (7.1%)	4018 (5.6%)	
Other professional qualifications	3578 (5.0%)	77 (5.8%)	3655 (5.1%)	
None of the above	5926 (8.3%)	151 (11.3%)	6077 (8.4%)	
Townsend deprivation index	-1.8 (2.78)	-1.3 (3.01)	-1.8 (2.78)	<.0001[2]
Hours of work per week	33.0 (12.87)	31.6 (12.85)	32.9 (12.87)	0.0002[2]
Transport type for work commute, n (%)				0.0022[3]
None of the above	270 (0.4%)	7 (0.5%)	277 (0.4%)	
Car/motor vehicle	55861 (78.6%)	1013 (76.1%)	56874 (78.6%)	
Walk	6801 (9.6%)	144 (10.8%)	6945 (9.6%)	
Public transport	6188 (8.7%)	146 (11.0%)	6334 (8.8%)	
Cycle	1907 (2.7%)	22 (1.7%)	1929 (2.7%)	
Body mass index (BMI)	26.6 (4.41)	27.7 (5.27)	26.6 (4.43)	<.0001[2]
Smoking status, n (%)				<.0001[3]
Never	41047 (57.8%)	682 (51.2%)	41729 (57.7%)	
Previous	25518 (35.9%)	519 (39.0%)	26037 (36.0%)	
Current	4462 (6.3%)	131 (9.8%)	4593 (6.3%)	
Alcohol drinker status, n (%)				<.0001[3]
Never	1963 (2.8%)	46 (3.5%)	2009 (2.8%)	
Previous	1723 (2.4%)	64 (4.8%)	1787 (2.5%)	
Current	67341 (94.8%)	1222 (91.7%)	68563 (94.8%)	
Stroke, n (%)	535 (0.8%)	20 (1.5%)	555 (0.8%)	<.0001[3]
Cardiovascular diseases, n (%)	1103 (1.6%)	26 (2.0%)	1129 (1.6%)	<.0001[3]
Diabetes, n (%)	2353 (3.3%)	76 (5.7%)	2429 (3.4%)	<.0001[3]
Cancer, n (%)	5078 (7.1%)	120 (9.0%)	5198 (7.2%)	0.0092[3]
Bone fracture in last 5 years,n (%)	6124 (8.6%)	146 (11.0%)	6270 (8.7%)	0.0026[3]
Pulmonary embolism, n (%)	282 (0.4%)	8 (0.6%)	290 (0.4%)	<.0001[3]
Deep vein thrombosis, n (%)	1063 (1.5%)	37 (2.8%)	1100 (1.5%)	<.0001[3]
Emphysema, n(%)	609 (0.9%)	34 (2.6%)	643 (0.9%)	<.0001[3]
Other serious medical condition, n (%)	12928 (18.2%)	393 (29.5%)	13321 (18.4%)	<.0001[3]
Abnormal sleep duration, n (%)				<.0001[1]
Normal (6-9hours)	50399 (71.0%)	821 (61.6%)	51220 (70.8%)	
Deprived (<6hours)	1235 (1.7%)	26 (2.0%)	1261 (1.7%)	
Excess (>9hours)	19393 (27.3%)	485 (36.4%)	19878 (27.5%)	
Sleep phase, n (%)				<.0001[1]
Normal	55101 (77.6%)	922 (69.2%)	56023 (77.4%)	
Delayed (bedtime after 1 am)	1026 (1.4%)	25 (1.9%)	1051 (1.5%)	
Advanced (bedtime before 9 pm)	14900 (21.0%)	385 (28.9%)	15285 (21.1%)	

[1]Kruskal-Wallis p-value; [2]ANOVA F-test p-value; [3]Chi-Square p-value;

Table 6.4 Multivariable association between digital gait biomarkers and incident depression.

Parameter	Hazard Ratio	95%CI	Standardized Hazard Ratio	95%CI
Main Analysis* (n=72359)				
Log of daily running duration	0.94	0.91 to 0.98	0.90	0.85 to 0.96
Steps per day [per 1000]	0.96	0.94 to 0.98	0.88	0.82 to 0.93
Step regularity [%]	0.99	0.99 to 1.00	0.90	0.85 to 0.96
Subgroup analysis by age group*				
40 to 50 years (n=6,007)				
None				
50 to 60 years (n=20,241)				
Longest walk duration [min]	0.94	0.90 to 0.97	0.80	0.70 to 0.91
Log of daily running duration	0.89	0.84 to 0.95	0.83	0.74 to 0.92
60 to 70 years (n=46,111)				
Log of daily running duration	0.94	0.90 to 0.99	0.91	0.84 to 0.98
Steps per day [per 1000]	0.97	0.95 to 1.00	0.91	0.84 to 1.00
Step regularity [%]	0.99	0.98 to 1.00	0.86	0.80 to 0.92
Usual walking speed [cms^{-1}]	0.97	0.95 to 1.00	0.93	0.87 to 0.99
Subgroup analysis by other medical conditions*				
Absent (n=49264)				
Log of daily running duration	0.94	0.90 to 0.98	0.90	0.83 to 0.97
Walks ≤ 8s [%]	1.01	1.00 to 1.02	1.12	1.04 to 1.21
Usual walking speed [cms^{-1}]	0.97	0.94 to 1.00	0.92	0.85 to 0.99
Present (n=23095)				
Log of daily running duration	0.90	0.85 to 0.95	0.84	0.77 to 0.93
Steps per day [per 1000]	0.96	0.94 to 0.99	0.89	0.80 to 0.98
Step regularity [%]	0.99	0.98 to 1.00	0.87	0.80 to 0.94

*Adjusted for age range, body mass index, sex, marital status, average total household income, education level, main mode of transportation, smoking status, drinking status, presence of abnormal sleeping duration, alternated sleep phase and diagnoses of other severe medical conditions

In the subgroup analyses, running duration, step regularity and step count remained significantly associated with depressive episodes and participants with other medical conditions. In addition to these biomarkers, usual walking speed is also predictive of depressive episodes in participants older than 60 years. Usual walking speed, the proportion of walks of 8 seconds or less and running duration were associated with incident depressive episodes in participants without other severe medical conditions. The longest walk duration and running duration were independently predictive of depressive episodes in participants aged 50 to 60 years. No digital gait biomarkers

were associated with the hazard of developing depressive episodes in participants aged 40 to 50 years, after adjusting for known risk factors.

6.5 Discussion

6.5.1 Main findings

This study comprising 72,359 older adults is one of the largest community-based cohort studies to investigate the association between mobility and incident depressive episodes and provides evidence that digital gait biomarkers are useful in predicting the onset of depression. In univariable models, all aspects of gait measured with the wrist sensor over seven days were associated with incident depressive episodes including: (1) Gait Quantity; (2) Gait Speed and Intensity; (3) Gait Quality; (4) Walk Length Distribution; and (5) Walk Hand Positions. We found people were more likely to become depressed if they were less active, walked slower, had more variable and less regular gait, completed shorter uninterrupted walks, and used fewer arm movement patterns while walking. After adjusting for established risk factors, we found that daily running duration, number of steps per day, and step regularity were predictive of depressive episode onsets in up to 9 years.

A low level of daily walking has previously been identified in people with depression [203, 212, 219]. However, few studies have investigated associations with the initial onset of depression [203]. Using a well-accepted wrist-sensor, our findings corroborate that continuous monitoring of daily walking assists in the early identification of at-risk older adults at the population level [212].

The sub-group analysis by age demonstrated that gait quantity and gait quality measures were independently predictive of depressive episodes in adults over 60 years of age, but only gait quantity was predictive in individuals aged 50-60 years, and no gait measures were predictive in those aged 40-50 years. This finding agrees with previous reports that the aetiology and presentation of late-onset depression differ from early-onset depression [10]. While personality disorders, a family history of psychiatric conditions and dysfunctional maternal relationships are more common in early-onset depression [220], less leisure activity and subjective mobility limitations are more predictive of late-life depression [221]. A similar pattern was observed in the other sub-group analysis. While low gait quantity and speed predisposed depression in healthy individuals, measures of gait quality, as well as quantity, predicted depression in their counterparts with serious medical conditions. This interaction is consistent with previous findings that have shown gait unsteadiness (e.g. gait quality) mediated the association between diabetes and depressive symptoms [222] and functional limitations mediated the chronic condition-depressive symptoms association in older adults [223].

6.5.2 Possible mechanisms underlying the associations between digital gait biomarkers and incident depressive episodes

Three possible mechanisms for the prospective association between mobility and depression have been proposed. First, deterioration in physical activity, may lead to decreases in vitamin D [224], brain-derived neurotropic factors [225], dopamine, endorphin, serotonin and noradrenaline levels [72]. These biochemical changes may subsequently increase the risk of depression. Second, mobility impairment may lead

to socio-psychological distress, with a resulting loss of independence and functional status that leads to an increased risk of depression [53, 226]. Third, depression and mobility impairments may result from similar underlying pathophysiological changes. Cardiovascular diseases, deep venous thrombosis and diabetes may cause both mobility impairment and depression [227-230]. Gait [231] and affective disorders [232] may involve similar prefrontal cortex and basal ganglia circuitry. Gait disturbances may also be an indicator of cerebrovascular diseases [233], and lesions in these brain regions may increase the risk of depression [234]. Finally, chronic systemic inflammation may lead to both mobility decline [235, 236] and incident depression [237].

6.5.3 Strengths and limitations

This study has several strengths. First, the Walk Watch digital gait biomarkers used in this study demonstrated validity and reliability. Second, the depressive episode outcome was based on ICD-10 diagnostic criteria, which provided higher validity than self-administered questionnaires. Third, the data were extracted from a large medical database with detailed socio-demographic data and reliable public health record linkage. Finally, we restricted the study population to individuals without a history of clinical depression at baseline, which provides a temporal association between day-to-day mobility and depression. We also acknowledge some study limitations. We included only participants who wore a wrist sensor continuously for at least five days to preserve data quality which may have limited the generalizability of the study findings to the more able, motivated participants. Second, although we found both gait quantity and gait quality independently predicted the onset of depression, the casualty between these factors requires further validation through randomised controlled trials.

6.6 Conclusions and Implications

The study findings indicate digital gait biomarkers derived from wrist-worn sensors are important predictors of incident depression in middle-aged and older people. In univariable models, we found people were more likely to become depressed if they were less active, walked slower, had more variable gait, completed shorter uninterrupted walks and had fewer arm movement patterns while walking. After adjusting for previously established risk factors, measures of both gait quantity and gait quality remained independent and significant predictors of incident depression, particularly in older adults and those with comorbidities. These gait biomarkers, therefore, may facilitate screening programs for at-risk individuals and the early implementation of preventive measures.

Chapter 7. General Discussion and Conclusion

Through clinical assessments and wearable technologies, this body of work has comprehensively explored the association between quantitative walking performance and incident depression. The preceding chapters have examined and discussed how specific aspects of mobility predict depression episodes and onset. This chapter summarizes these findings in the context of the thesis objectives and describes its limitations, clinical implications, real-world applications, and directions for future research.

7.1 Summary of findings

Chapter 2 comprised a systematic review that summarised previous studies and affirmed the predictive value of slow gait speed for depressive symptoms. Individuals with slower walking speed have twice the odds of developing depressive symptoms over 1 to 16 years. The strength of this correlation is more consistent in community-dwelling older adults than in individuals with specific medical conditions. Through a systematic review of existing literature, this chapter identifies gaps in the body of knowledge, in that the research scope has been focused on clinic-based straight-line walking speed only, and that other aspects of gait may be scientifically and clinically relevant to elucidating depression risk. These include: (1) **Other locomotor tasks such as performances in gait initiation, turning and sit-to-stand**; as these transition movements require complex physiological and cognitive integration [238]. (2) **Gait quality;** as a number of neurological and mental disorders are characterised by aberrant abnormal walking patterns [239, 240]. These deviations may be reflected more precisely through measurements such as harmonic ratios and step time/length regularity. (3) **Daily-life gait;** it has been found that clinically assessed gait differs

from that in daily life because people tend to give their best performances in clinics. An individual's "usual" performance has higher ecological validity and may, therefore, better reflect their risk of developing depression [30]. The subsequent chapters were designed to address these knowledge gaps.

Chapter 3 aimed at identifying locomotor tasks predictive of depression trajectory in a large cohort of community-living older people. A total of 553 individuals, aged 70 to 90 years, were followed up on their depressive symptoms for six years. Baseline locomotion was assessed with three clinical tests, including the Six-Metre Walk Test (6mWT), the Five times Sit to Stand Test (5-STS) and the Timed Up and Got Test (TUT). Three trajectories of depressive symptom development were identified: a low-and-stable course (10% of participants), a low-and-increasing course (81%) and a moderate-and-increasing course (9%). All three clinical locomotion tests were found to be predictive of the worst depression trajectory. Timed Up and Go Test (TUG) performance had the largest effect size and the association remained significantly associated with depressive trajectories after adjusting for age, sex, body mass index, and baseline anti-depressant use. This finding suggests that incorporating multiple aspects of walking (i.e. gait initiation, turning and sit-to-stand time) may be more predictive of depressive episodes than walking speed alone.

Chapter 4 investigated whether digital gait biomarkers (DGBs), such as daily-life walking quantity and quality, predict the onset of depression. Baseline walking data were collected with an accelerometer and a gyroscope positioned at the lower back in a sample of 322 community-dwelling older people. They were subsequently followed up for depressive symptoms for two years. To the author's knowledge, this is the first

study to predict depression with daily-life walking using wearable technology. I found that gait intensity and rhythmicity were associated with new depression episodes. The duration of the longest daily walking bout was identified as an independent and significant predictor of depression. While analysing the data of this study, I observed that the sample size (n=322) limits the full utilisation of the daily-life gait parameter set. To maintain a reasonable subject-to-predictor ratio, a principal component analysis was conducted to reduce the number of predictors. More flexible classification techniques, such as machine learning, were also unsuitable for the same reason. Practically, it is difficult to scale up the study population while using sensors located at the lower back, as this attachment site is inconvenient and uncomfortable [174, 241]. This warranted the development of DGB extraction algorithms for sensors located at body regions with better acceptance.

Chapter 5 reported the development of algorithms that extract DGBs with wrist-worn sensors, including daily-life gait speed, quantity, quality and distribution, and their validation in more than 78,000 individuals. I found that DGBs derived from wrist sensors can achieve good test-retest-reliability, strong agreement with electronic walkway measurements and self-reports of walking speed. These DGBs also significantly identified individuals with self-rated poor physical health.

Chapter 6 applied the DGBs developed in Chapter 5 to a health record-linked large-scale database of more than 75,000. Over follow-up periods up to 9 years follow-ups, 1332 participants (1.8%) developed incident depressive episodes. After adjusting for known risk factors, running duration, step count and step regularity were found to be independent and significant predictors of incident depression. Further analyses

revealed that running duration, step count and step regularity, and usual walking speed were predictive of depressive episodes in participants older than 60 years. However, no DGBs were associated with the hazard of developing depressive episodes in participants aged 40 to 50 years, after adjusting for known risk factors. This phenomenon agrees with previous studies that the aetiology and presentation of late-onset depression differ from early-onset depression [10]. While personality disorders, a family history of psychiatric conditions and dysfunctional maternal relationships are more common in early-onset depression [220], less leisure activity and subjective mobility limitations are more predictive of late-life depression [221]. This finding suggests different screening strategies for depression should be used in different age groups.

Several DGBs have been extracted from accelerometric data, which can be correlated to one another and reflect the same underlying constructs (latent variables). To better understand what these DGBs represent, an ad-hoc exploratory factor analysis (EFA) was performed on the DGBs used in Chapter 5 and 6. Four constructs had eigenvalues larger than 1, which were labelled walking quality, speed, quantity and distribution according to their respective measured variables with the highest loadings, as presented in Table 7.1. This finding (obtained through an unsupervised machine learning technique) that DGBs were categorized into four aspects of walking, is consistent with existing scientific understandings, and provides support for the construct validity of the algorithms.

Table 7.1 Exploratory factor analysis results

Items	1	2	3	4
Walking quality				
Step-time variability	-0.72	-0.54		
Step regularity	0.83			
Stride regularity	0.86			
8-step HR	0.87			
Step-walk Gradient	0.87			
Cadence IQR	-0.60	0.54		
Arm-swing proportion	-0.67		-0.60	
Walking Speed				
Maximal gait speed		0.80		
Usual gait speed		0.77		
Cadence Median		0.75		
Walking Quantity				
Steps per day			-0.54	
Walks=8s			0.90	
Walks=60s			0.79	
Walking Distribution				
Median walk duration				0.94
Longest walk duration	0.56			0.58
Running duration				

Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy=0.79. Factor loadings of 0.5 or larger are presented. HR, harmonic ratio; IQR, interquartile range.

In the previous chapters, I demonstrated that walking speed (Chapters 2 and 6), distribution (Chapter 4), quality (Chapter 6) and quantity (Chapter 6) are independent predictors of depression onsets in various populations of middle-age to older adults. The variation of which aspect of walking being significant might depend on subtle patient characteristics, as supported by similar results in the subgroup analysis of Chapter 6. This observation warrants collecting data from each aspect of walking to obtain a more precise prediction of depression onset across different study populations in future studies.

7.2 Strengths and Limitations

The sampling populations on which this work is based were drawn from three large, well-characterized, population-based cohort studies. Participants in Chapter 4 were randomly sampled from a mandatory electoral roll, whereas participants in Chapter 6

were randomly sampled from UK National Health Service (NHS) registrants. A comprehensive set of DGBs with high validity and reliability were extracted from daily life accelerometric data with high ecological validity. This work is also based on data with relatively long follow-up periods, ranging from 2 to 9 years.

The limitations of this thesis should be acknowledged. First, as participation in the included studies was voluntary, a resulting "healthy volunteer" selection bias may impact its representativeness. Nonetheless, observed exposure-disease relationships, which is the main focus of this work, are less dependent on population representativeness [242] and may remain widely generalizable to community-dwelling middle-age to older adults.

Definitions of depression varied across the cohorts and were based on the Patient Health Questionnaire-9 (PHQ-9), 15-item Geriatric Depression Scale (GDS-15) and the International Classification of Disease 10th Revision (ICD-10), respectively. Information was obtained from self-administered questionnaires for Chapters 3 & 4, while data in Chapter 6 were retrieved from electronic health records and documented medical diagnoses. Although these tools are all validated and widely accepted, they likely elicit differences in reported incidence and severity of depressive symptoms. Therefore, the incidence and prevalence rates of depressive symptoms reported in the included studies cannot be directly compared.

As recruitment was conducted in Australia and the United Kingdom for Chapters 3, 4 and 6, the study populations predominantly include Caucasians living in urbanized areas with high education and income levels. Hence, the generalizability of my

findings to individuals with different socio-demographic backgrounds is uncertain.

7.3 Clinical applications

The findings of this work may provide guidance to clinicians in predicting the risk of the development of depression in middle-age and older adults. Individuals at risk of developing depression generally walk less, more slowly, with more uneven steps and in shorter bouts than those not at risk of developing this condition. Walking assessments may supplement existing risk screening and assessment programs and may be collected through various methods depending on the available resources. Enquiry about walking quantity and distribution, followed by a Timed Up and Go Test (TUG) and observational gait analysis could comprise a time- and cost-efficient way to obtain such information. The TUG is preferred as it is easy to administer and incorporates assessments on multiple mobility tasks, including transitions, gait initiations and turning. If resources allow, using smart watch-based gait assessments could simultaneously measure multiple domains of daily-life walking performances objectively and, therefore, might be favoured over clinical mobility tests and related history-taking. As mobility performances may predict other adverse events, such as frailty, morbidity, hospitalization and mortality, the practicality of using an unobstructive wrist-worn wearable technology to assess daily-life walking in clinical settings remotely is further justified.

The algorithms developed in this work may have applications beyond predicting depression. As mentioned above, walking speed and quality predict functional decline, morbidity, and mortality [172]. However, conventional clinical assessments are resource-intensive [243], and remote gait assessments often use wearable devices

positioned on the waist or legs. While these devices provide valid measurements, their placement markedly limits user acceptability [174, 241]. In contrast, smart watches have almost universal uptake, which allows population-wide walking performance evaluations, which has been exemplified in the application of our algorithms on the UK Biobank dataset. Clinicians may apply our validated algorithms for remote monitoring of daily-life walking, to document disease progression, identify physical decline and evaluate the effectiveness of health improvement interventions.

Our findings also lend support to the existing body of literature on preventing and treating depression with walking [244, 245]. Given that walking speed, quality, quantity and distribution are all modifiable risk factors, gait retraining exercise for individuals with impaired step regularity, may have potential benefits for preventing depression as well as improving mobility. However, its effectiveness in this regard remains to be examined in future clinical trials.

7.4 Future Research

My findings indicate that daily-life walking speed, quality, quantity and distribution predict the risk of depression onset in middle-age to older adults. However, determining the causal relationships between these variables requires further delineation. Theoretically, mobility decline and depression can be caused by the same underlying medical conditions, such as systemic inflammation, dementia or white-matter lesion etc. Alternatively, walking difficulties may lead to psycho-social distress and/or reduced physical activity levels, eventually raising vulnerability towards affective disorders. Future multivariate analysis, including structured equation models, would help untangle the underlying pathophysiology, whereas causality

requires evidence from further clinical trials with gait retraining as an intervention. These trials can also help demonstrate the feasibility and cost-effectiveness of preventing depression by addressing gait deficits. Additionally, it is possible to evaluate sedentary behaviours with wrist accelerometers [246]. Future investigations could consider integrating sedentary-activity-related measures into depression prediction models. Further, considering that previous studies have demonstrated that gait disturbance is linked to fall-related injuries [30], frailty [247], dementia [248] and cardiovascular diseases [249], the DGBs presented in this thesis might have applications beyond depression risk screening. If daily-life mobility predicts these age-related adverse conditions, a wrist-sensor-based approach could offer complementary information for screening multiple conditions.

Future studies are warranted to support further clinical applications of our DGBs, including: (1) cross-sectional studies to establish normative values specific to age group and gender, as well as populations with specific conditions, which would help identify walking abnormalities and severity; (2) cohort studies to examine the predictive values of DGBs for other clinical conditions such as falls and fall-related injuries, frailty, cognitive impairment and mortality; and (3) clinical trials to evaluate whether quantitative feedback of walking performance can enhance the efficacy of gait retraining.

7.5 Conclusion

This doctoral thesis presents a series of novel findings in the field of human locomotion and depression. Gait quality and daily-life gait performances were identified as predictors of depression. These findings may help the development of

preventive measures for late-life depression. It also documented the development of a measurement tool to facilitate large-scale extraction of digital gait biomarkers, with potential applications in the management of other age-related conditions. Future studies should delineate the temporal associations between mobility decline and depression to contribute further to the understanding of late-life depression.

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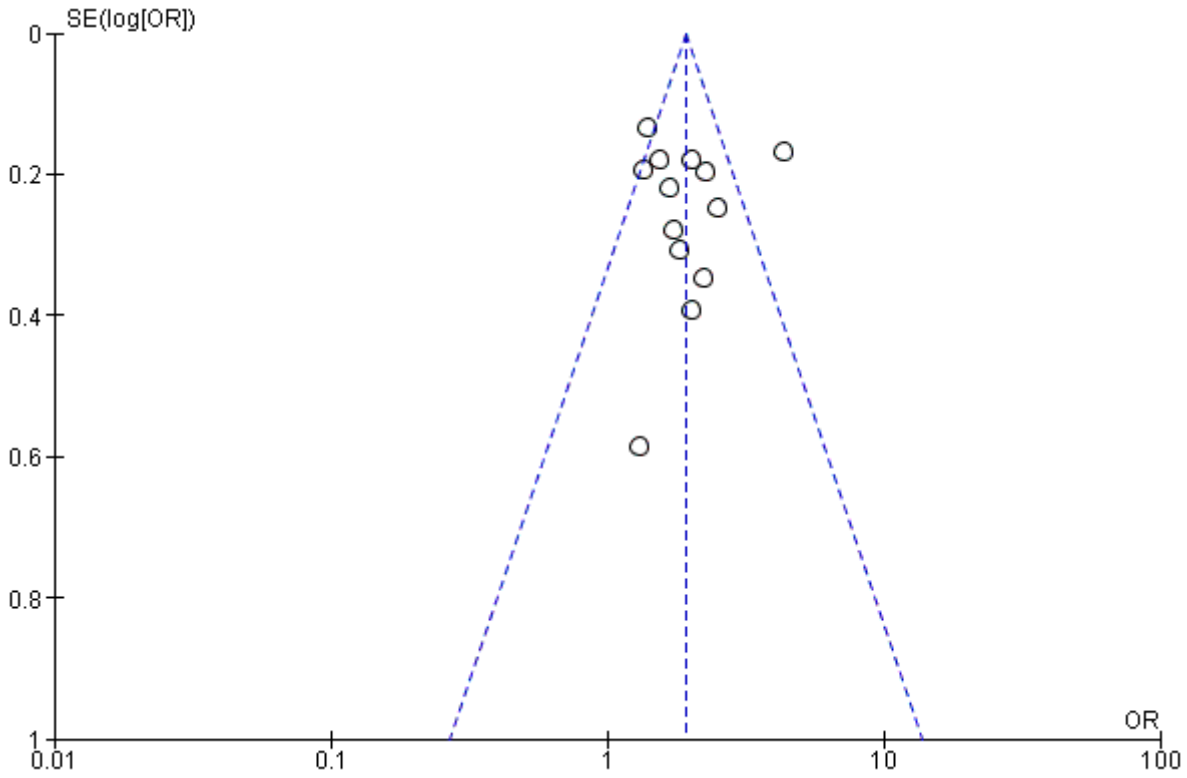
Appendix A: Supplementary material of Chapter 2

A1: Search strategy example

1	exp cohort studies/
2	cohort$.tw.
3	controlled clinical trial.pt.
4	epidemiologic methods/
5	limit 4 to yr=1971-1988
6	longitudinal stud*.mp.
7	or/1-3,5,6
8	((inciden* or developing* or predict* or develop* or new or traject* or later) adj7 depressi*).mp.
9	exp walking/
10	(gait* or walk* or mobility* or frail*).mp.
11	or/9,10
12	7 and 8 and 11

A2: Funnel Plot



A3: List of excluded titles screened

Of the 614 titles identified for potential inclusion in the review, 550 were excluded before the full-text review. The reasons for the exclusion of these studies are as follow.

Not published in English

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Of the 64 papers reviewed in full text, 50 were excluded. The reasons for the exclusion of these studies are as follow.

Conference paper

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Lack of data to assess associations

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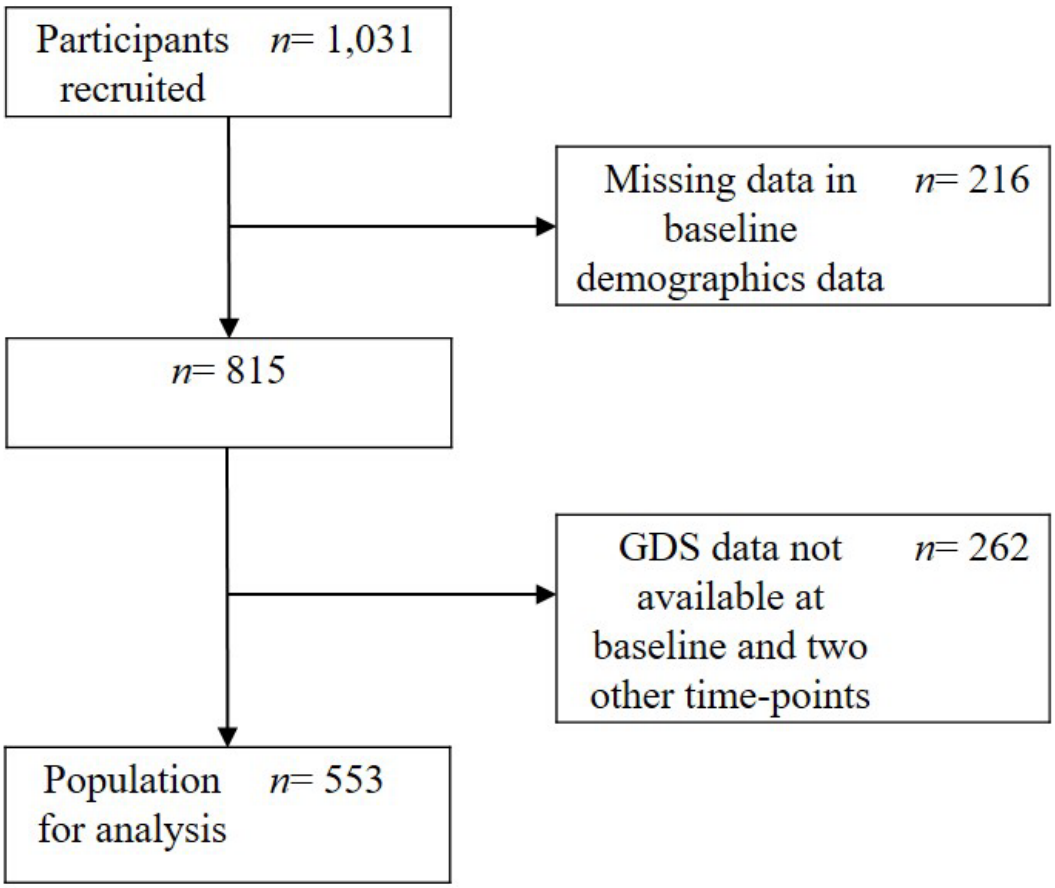
Appendix B: Supplementary material of Chapter 3

B1: Participant flow diagram



B2: Comparison between included and excluded participants

	Excluded (N=262)	Included (N=553)	Total (N=815)	p-value
Age, yrs	81.1 (5.08)	78.4 (4.53)	79.3 (4.88)	<.0001[1]
Female, n (%)	149 (56.9%)	291 (52.6%)	440 (54.0%)	0.2558[2]
Height, cm	162.0 (9.82)	164.0 (9.27)	163.4 (9.49)	0.0042[1]
Weight, kg	69.4 (14.96)	74.2 (14.74)	72.7 (14.97)	<.0001[1]
Body mass index	26.3 (4.66)	27.5 (4.88)	27.2 (4.84)	0.0013[1]
Number of medications	5.4 (3.45)	5.0 (3.20)	5.1 (3.25)	0.1885[1]
WHODAS score	20.8 (7.58)	17.9 (6.22)	18.8 (6.78)	<.0001[1]
Proprioception, deg	2.5 (1.06)	2.4 (1.55)	2.4 (1.41)	0.4002[1]
Simple reaction time, milliseconds	243.3 (34.53)	237.0 (44.13)	239.0 (41.37)	0.0431[1]
Visual contrast sensitivity, dB	20.4 (1.61)	20.7 (2.03)	20.6 (1.91)	0.0183[1]
Quadriceps strength, kg	34.5 (60.94)	28.8 (12.02)	30.7 (36.00)	0.0367[1]
Postural Sway, mm	212.7 (76.22)	187.1 (101.35)	195.4 (94.72)	0.0003[1]
Handgrip strength, kg	25.2 (6.21)	27.5 (11.01)	26.7 (9.79)	0.0015[1]
Five Times Sit to Stand Test, s	16.4 (4.90)	16.0 (4.88)	16.1 (4.89)	0.2106[1]
Six-Metre Walk Test, s	10.4 (3.79)	9.0 (2.83)	9.4 (3.24)	<.0001[1]
Timed Up and Go Test time, secs	10.7 (3.95)	9.4 (3.06)	9.8 (3.43)	<.0001[1]
Total physical activity, hours/week	31.7 (12.95)	31.2 (16.20)	31.4 (15.22)	0.2808[3]
Planned physical activity, hours/week	3.2 (2.70)	3.5 (5.09)	3.4 (4.46)	0.0031[3]
Incidental physical activity, hours/week	28.5 (12.09)	27.7 (15.92)	28.0 (14.79)	0.0814[3]
[1]Independent t-test; [2]Chi-Square p-value; [3]Wilcoxon rank sum p-value;				

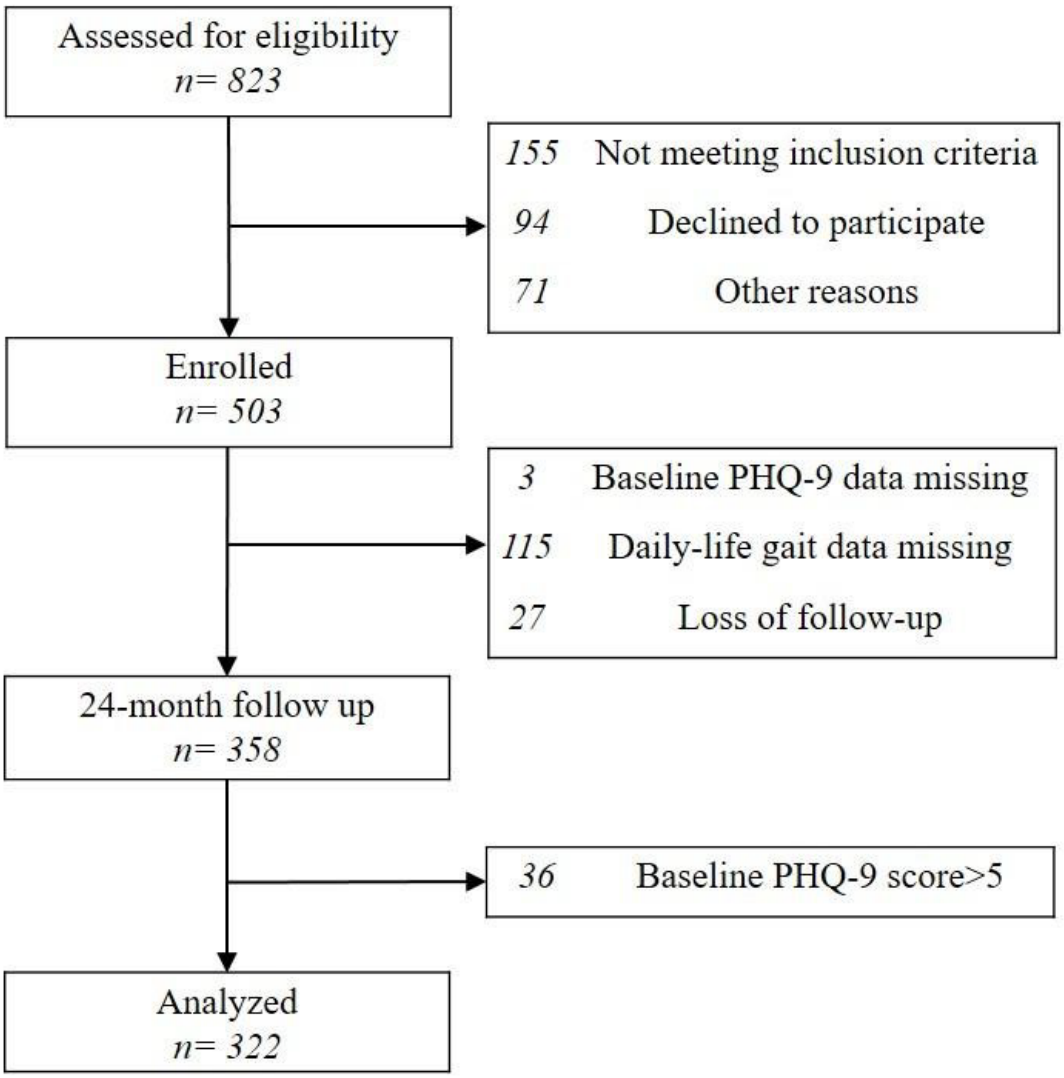
B3: Statistics for stepwise GBTM model fitting

Steps	Number of trajectory groups	Pattern of trajectories	BIC (overall sample size, N=1868)	BIC (participant sample size, N=553)	logged Bayes factor (2*ΔBIC) compared to the previous model	
Selecting the optimum number of groups						
1	1	Q	-4026.83	-4024.39	N/A	N/A
2	2	Q Q	-3841.59	-3836.72	370.48	375.34
3	3	Q Q Q	-3785.01	-3777.70	113.16	118.04
4	4	Q Q Q Q	Number of participants in group<5%			
Selecting the optimum shape of each group						
5	3	I I L	False convergence			
6	3	I I Q	-3801.83	-3796.96	N/A	N/A
7	3	I L L	False convergence			
8	**3**	**I L Q**	**-3778.58**	**-3773.1**	**46.5**	**47.72**
9	3	I Q Q	-3781.66	-3775.57	-6.16	-4.94

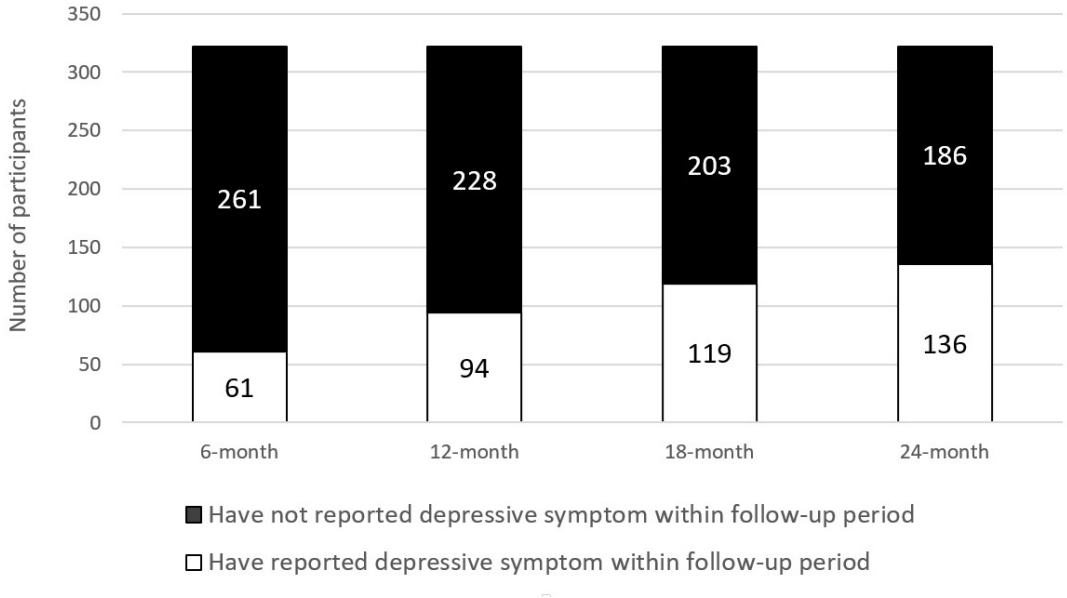
I: Intercept; L: Linear; Q: Quadratic

Appendix C: Supplementary material of Chapter 4

C1: Participant flow diagram



C2: Depressive symptom incidence bar chart



C3:Varimax-rotated factors of principal component

	Overall gait quality	ML intensity	AP intensity	ML Stability	Complexity
Walking speed	**0.73**	0.37	**0.46**	0.06	-0.03
Stride frequency	**0.40**	0.15	**0.55**	0.24	**0.44**
Root mean Square VT	**0.41**	**0.46**	**0.70**	0.07	-0.13
Root mean Square ML	-0.07	**0.83**	0.32	0.31	-0.02
Root mean Square AP	**0.43**	**0.68**	**0.47**	0.06	-0.01
Range VT	0.02	**0.50**	**0.74**	-0.03	-0.21
Range ML	-0.03	**0.88**	0.34	0.05	-0.09
Range AP	0.18	**0.62**	**0.66**	-0.05	-0.09
Magnitude of dominant period in frequency domain VT	**0.91**	0.10	0.11	0.00	-0.04
Magnitude of dominant period in frequency domain ML	-0.17	**-0.66**	-0.09	**0.58**	-0.10
Magnitude of dominant period in frequency domain AP	**0.54**	-0.02	**-0.74**	0.00	0.12
Magnitude of dominant period in frequency domain Vector	**0.92**	-0.04	-0.27	0.01	0.01
Index of harmonicity VT	**0.78**	0.12	0.11	-0.14	-0.10
Index of harmonicity ML	-0.37	**-0.75**	-0.05	0.11	-0.13
Index of harmonicity AP	-0.15	-0.25	**-0.78**	-0.08	0.04
Harmonic ratio VT	**0.73**	-0.07	0.16	0.27	-0.08
Harmonic ratio ML	0.14	0.18	-0.04	**0.86**	-0.07
Harmonic ratio AP	**0.83**	0.22	-0.04	0.09	-0.06
Mean logarithmic rate of divergence per stride VT	**-0.83**	-0.16	-0.29	-0.20	-0.28
Mean logarithmic rate of divergence per stride ML	-0.32	0.09	-0.29	**-0.79**	-0.29
Mean logarithmic rate of divergence per stride AP	**-0.78**	-0.18	-0.14	-0.22	-0.38
Sample entropy VT	-0.03	0.13	-0.34	-0.03	**0.81**
Sample entropy ML	**0.47**	-0.37	0.05	-0.31	**0.58**
Sample entropy AP	**-0.46**	-0.15	-0.03	0.31	**0.60**

C4: Correlation coefficients between predictors

	Median walking bout duration	Longest walking bout duration	Overall gait quality	ML intensity	AP intensity	ML stability	Complexity	TUG	6mWT	SPPB
Daily total walking duration	.131*	.557**	.417**	.241**	.159**	-.133*	-0.108	-.295**	-.313**	.278**
Median walking bout duration		0.088	-.249**	0.099	0.006	-0.072	-0.033	0.017	0.067	-0.084
Longest walking bout duration			.390**	.211**	.248**	0.105	0.041	-.152**	-.182**	.177**
Overall gait quality				0.000	0.000	0.000	0.000	-.381**	-.377**	.320**
ML intensity					0.000	0.000	0.000	-.331**	-.261**	.303**
AP intensity						0.000	0.000	-.174**	-.254**	.159**
ML stability							0.000	.146**	.204**	-0.091
Complexity								0.084	0.069	-0.051
TUG									.696**	-.652**
6mWT										-.592**

Appendix D: Supplementary material of Chapter 5

D1: List of machine learning features generated for selection

Feature No.	Name (unit) and description	Rank
One window before the current window		
1	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 1 to 12)	93
2	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 12 to 22	83
3	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 22 to 37	60
4	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 37 to 57	57
5	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 57 to 85	56
6	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 85 to 115	53
7	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 115 to 165	52
8	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 165 to 245	51
9	Mean of Static-block-removed Euclidean norm of acceleration signal	50
10	Standard deviation of Static-block-removed Euclidean norm of acceleration signal	49
11	**Minimum of Static-block-removed Euclidean norm of acceleration signal**	**46**
12	Maximum of Static-block-removed Euclidean norm of acceleration signal	58
13	25^{th} percentile of Static-block-removed Euclidean norm of acceleration signal	48
14	**Median of Static-block-removed Euclidean norm of acceleration signal**	**27**
15	75^{th} percentile of Static-block-removed Euclidean norm of acceleration signal	80
16	**Correlation coefficient between acceleration signal in x- and y- axes**	**18**
17	**Correlation coefficient between acceleration signal in x- and z- axes**	**43**
18	**Correlation coefficient between acceleration signal in y- and z- axes**	**14**

19	Mean of crude vector magnitude	82
20	Standard deviation of crude vector magnitude	84
21	**Minimum of crude vector magnitude**	**16**
22	Maximum crude vector magnitude	59
23	**25th percentile of crude vector magnitude**	**15**
24	**Median of crude vector magnitude**	**24**
25	**75th percentile of crude vector magnitude**	**17**
26	Number of peaks in autocorrelation	81
27	Normalised autocorrelation coefficient	47
28	Autocorrelation coefficient	65
29	Ratio between 1st and 2nd autocorrelation coefficient	75
30	**Ratio between 1st and 2nd autocorrelation time-lag**	**19**
31	Ratio between 1st and 3rd autocorrelation coefficient	89
32	Ratio between 1st and 3rd autocorrelation time-lag	79
33	Time-lag of 1st autocorrelation	85
The current window		
34	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 1 to 12)	76
35	**Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 12 to 22)**	**23**
36	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 22 to 37)	86
37	**Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 37 to 57)**	**13**
38	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 57 to 85)	90
39	**Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 85 to 115)**	**42**
40	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 115 to 165)	54
41	**Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 165 to 245)**	**10**
42	**Mean of Static-block-removed Euclidean norm of acceleration signal**	**9**
43	**Standard deviation of Static-block-removed Euclidean norm of acceleration signal**	**25**
44	Minimum of Static-block-removed Euclidean norm of acceleration signal	98
45	**Maximum of Static-block-removed Euclidean norm of acceleration signal**	**40**
46	**25th percentile of Static-block-removed Euclidean norm of acceleration signal**	**30**
47	**Median of Static-block-removed Euclidean norm of acceleration signal**	**38**

48	**75th percentile of Static-block-removed Euclidean norm of acceleration signal**	**32**
49	Correlation coefficient between acceleration signal in x- and y-axes	96
50	Correlation coefficient between acceleration signal in x- and z-axes	91
51	**Correlation coefficient between acceleration signal in y- and z- axes**	**20**
52	**Mean of crude vector magnitude**	**36**
53	**Standard deviation of crude vector magnitude**	**44**
54	Minimum of crude vector magnitude	67
55	Maximum crude vector magnitude	70
56	25th percentile of crude vector magnitude	63
57	**Median of crude vector magnitude**	**34**
58	75th percentile of crude vector magnitude	72
59	Number of peaks in autocorrelation	87
60	**Normalised autocorrelation coefficient**	**37**
61	**Autocorrelation coefficient**	**3**
62	**Ratio between 1st and 2nd autocorrelation coefficient**	**5**
63	**Ratio between 1st and 2nd autocorrelation time-lag**	**45**
64	**Ratio between 1st and 3rd autocorrelation coefficient**	**1**
65	**Ratio between 1st and 3rd autocorrelation time-lag**	**39**
66	**Time-lag of 1st autocorrelation**	**4**
One window after the current window		
67	**Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 1 to 12)**	**7**
68	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 12 to 22)	55
69	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 22 to 37)	71
70	**Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 37 to 57)**	**2**
71	**Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 57 to 85)**	**21**
72	Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 85 to 115)	62
73	**Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 115 to 165)**	**11**
74	**Wavelet coefficient in Static-block-removed Euclidean norm of acceleration signal (scales 165 to 245)**	**6**
75	**Mean of Static-block-removed Euclidean norm of acceleration signal**	**35**
76	**Standard deviation of Static-block-removed Euclidean norm of acceleration signal**	**29**

77	Minimum of Static-block-removed Euclidean norm of acceleration signal	73
78	Maximum of Static-block-removed Euclidean norm of acceleration signal	77
79	**25th percentile of Static-block-removed Euclidean norm of acceleration signal**	**41**
80	**Median of Static-block-removed Euclidean norm of acceleration signal**	**8**
81	75th percentile of Static-block-removed Euclidean norm of acceleration signal	74
82	Correlation coefficient between acceleration signal in x- and y-axes	88
83	**Correlation coefficient between acceleration signal in x- and z- axes**	**31**
84	Correlation coefficient between acceleration signal in y- and z-axes	69
85	**Mean of crude Euclidean norm of acceleration signal**	**12**
86	Standard deviation of crude Euclidean norm of acceleration signal	64
87	Minimum of crude Euclidean norm of acceleration signal	97
88	**Maximum crude Euclidean norm of acceleration signal**	**22**
89	25th percentile of crude Euclidean norm of acceleration signal	78
90	**Median of crude Euclidean norm of acceleration signal**	**33**
91	**75th percentile of crude Euclidean norm of acceleration signal**	**28**
92	Number of peaks in autocorrelation	68
93	Normalised autocorrelation coefficient	94
94	Autocorrelation coefficient	92
95	Ratio between 1st and 2nd autocorrelation coefficient	95
96	**Ratio between 1st and 2nd autocorrelation time-lag**	**26**
97	Ratio between 1st and 3rd autocorrelation coefficient	66
98	Ratio between 1st and 3rd autocorrelation time-lag	99
99	Time-lag of 1st autocorrelation	61

Bold indicates features included in the activity classification algorithm

D2: List of annotated activity categories

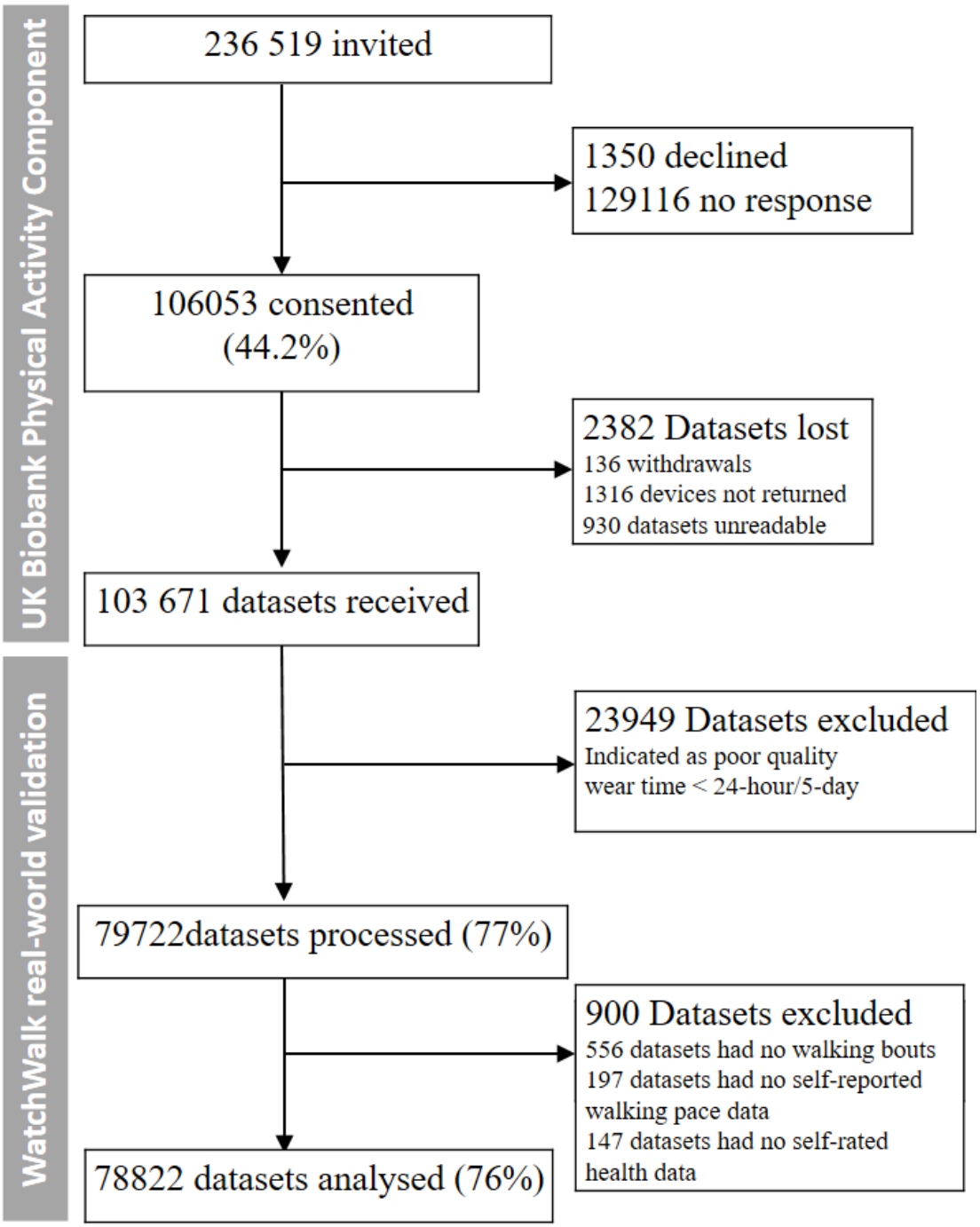
Activity class	**Category**	**Description**
Walking	Walking: Arm swing	Refers to walking with natural arm swing
	Other walking patterns	• Walking- Hands in pockets: Refers to walking with the dominant hand in a trousers/ shorts/ skirt/dress pocket • Walking- Texting : Refers to walking while holding a smart phone stably in front of the trunk with the dominant hand • Walking- Phone call: Refers to walking while holding a smart phone stably next to the head with the dominant hand • Walking- Shoulder bag: Refers to walking with the dominant hand rested on or in front of the shoulder • Walking- Briefcase: Refers to walking with the dominant arm straight on the side while carrying a heavy object
Running	Running	Refers to any running movement
Stationary	Stationary	Refers to standing or sitting with minimal or without upper limb movement
	Vehicle	Refers to standing or sitting with minimal or without upper limb movement on a moving vehicle
Unspecified Arms Activities	Unspecified arms activities while sitting/ standing	Refers to a standing or sitting with upper limb movements
	Unspecified arms activities while walking	Refers to walking with independent upper limb movements

D3: P-values of post-hoc comparison tests between different self-rated health status (n=78822).

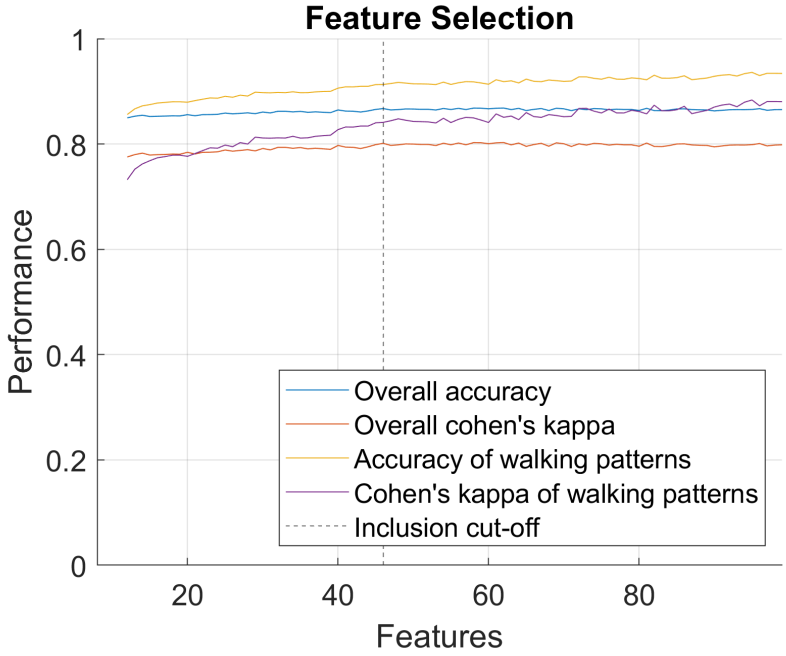
	Self-rated Health Status					
	Excellent vs Good	**Excellent vs Fair**	**Excellent vs Poor**	**Good vs Fair**	**Good vs Poor**	**Fair vs Poor**
Demographics						
Age[1]	**<0.001**	**<0.001**	0.23	0.22	**<0.001**	**<0.001**
Gait quantity and its distribution						
Steps per day[2]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Longest walk duration[1]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Arm-swing proportion[1]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Hands in pocket proportion[1]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Texting proportion[1]	0.34	**<0.001**	0.94	**<0.001**	1.00	0.43
Phone-call proportion[1]	**0.04**	**<0.001**	0.10	**<0.001**	0.53	0.99
Shoulder-bag proportion[1]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Briefcase proportion[1]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Step-walk Gradient[2]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Walks≤8s	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.01**
Walks≤60s[1]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Gait Speed (arm-swing)						
Median (usual) [1]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
95th percentile(maximal) [1]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Gait Quality						
Cadence Median[2]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Cadence IQR [2]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Mode of step-time variability[1]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
8-step HR [2]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Step regularity (arm-swing) [1]	**<0.001**	**<0.001**	**<0.001**	**0.01**	**<0.001**	**<0.001**
Stride regularity (arm-swing) [1]	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Respondents were asked to rate their overall health as “Excellent”, “Good”, “Fair” or “Poor”. Bold indicates statistical significance. [1]Dunn post-hoc test; [2]Tukey's honest significance test

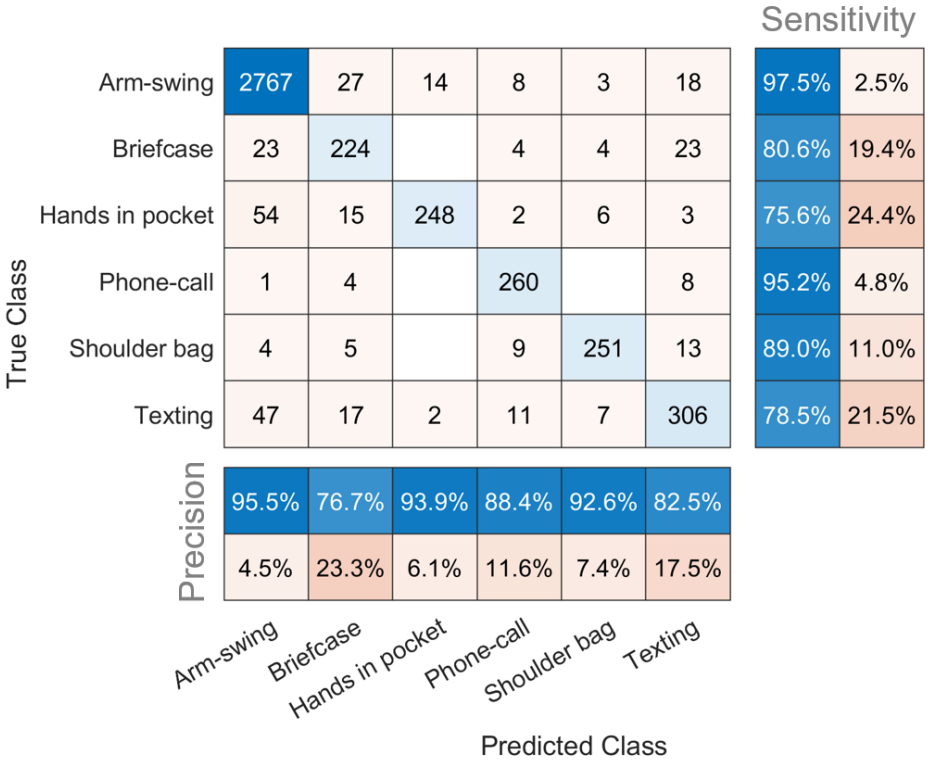
D4: Participant flow chart for Stage II study (n= 103672)



D5:Accuracy and Cohen's Kappa of the classification model by the number of features included



D6: Confusion matrix of stage 2 classification (4,388 windows from both free-living recording and structured walks)



D7: Justification of using 4-second window

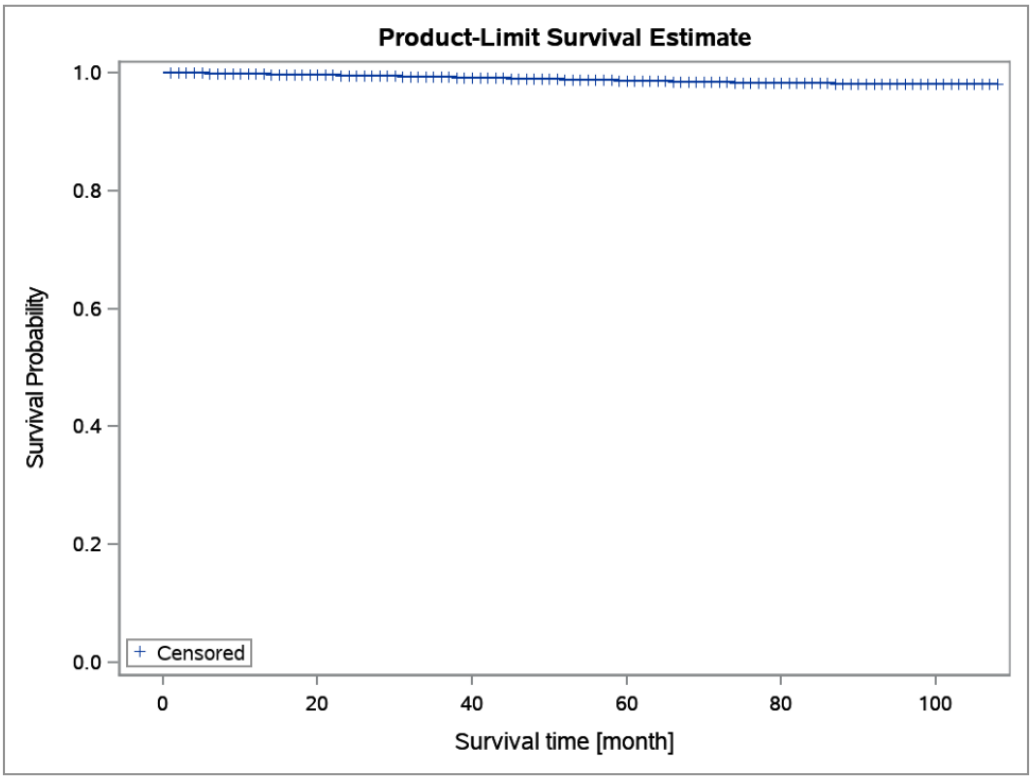
To classify movement into activity classes, data were segmented into 4-second(s) non-overlapping windows. In theory, longer window segments (e.g. >10s) provide more samples and repetitions to be extracted and therefore enhance classifier performance. However, daily activities often occur in short bouts. For instance, while entering a lift, a person stands quietly, walks and then stands quietly again all within10 s. Shorter window segments would better segment these activities and as well as reduced feedback latency and therefore better for providing real-time responses. Mannini et al have compared activity recognition performances of 12.8s, 4s and 2s window segments, and found 4s and 12.8s windows to be similarly accurate (84.2% to 84.7%).[1] Similarly, Zhang et al reported that 12.8s windows can be reduced to 6.8s windows without significantly compromising classification accuracy[2].

[1] Mannini A, Intille SS, Rosenberger M, Sabatini AM, Haskell W. Activity recognition using a single accelerometer placed at the wrist or ankle. Med Sci Sports Exerc. 2013 Nov;45(11):2193-203. doi: 10.1249/MSS.0b013e31829736d6. Erratum in: Med Sci Sports Exerc. 2015 Feb;47(2):448-9. PMID: 23604069; PMCID: PMC3795931.

[2] Zhang S, Rowlands AV, Murray P, Hurst TL. Physical activity classification using the GENEA wrist-worn accelerometer. Med Sci Sports Exerc. 2012 Apr;44(4):742-8. doi: 10.1249/MSS.0b013e31823bf95c. PMID: 21988935.

Appendix E: Supplementary material of Chapter 6

E1: Kaplan-Meier curve for time-to-depressive episode



E2: Pearson's correlation coefficients between digital gait biomarkers

	Steps per day	Running duration	Max walking speed	Usual walking speed	Cadence Median	Cadence IQR	Step-time variability	8-step Harmonic ratio	Step regularity	Stride regularity	Median walk duration	Longest walk duration
Steps per day	1.00	0.08	0.41	0.35	0.29	-0.11	-0.34	0.31	0.31	0.27	0.04	0.50
Running duration	0.08	1.00	0.10	0.11	0.06	0.03	-0.08	0.05	0.06	0.06	0.00	0.05
Max walking speed	0.41	0.10	1.00	0.64	0.73	0.10	-0.60	0.41	0.44	0.42	0.03	0.44
Usual walking speed	0.35	0.11	0.64	1.00	0.47	0.19	-0.33	0.15	0.18	0.14	0.02	0.28
Cadence Median	0.29	0.06	0.73	0.47	1.00	0.14	-0.73	0.47	0.55	0.50	0.02	0.43
Cadence IQR	-0.11	0.03	0.10	0.19	0.14	1.00	0.09	-0.57	-0.34	-0.42	-0.02	-0.40
Step-time variability	-0.34	-0.08	-0.60	-0.33	-0.73	0.09	1.00	-0.66	-0.78	-0.68	-0.01	-0.49
8-step Harmonic ratio	0.31	0.05	0.41	0.15	0.47	-0.57	-0.66	1.00	0.76	0.84	0.04	0.62
Step regularity	0.31	0.06	0.44	0.18	0.55	-0.34	-0.78	0.76	1.00	0.82	0.02	0.49
Stride regularity	0.27	0.06	0.42	0.14	0.50	-0.42	-0.68	0.84	0.82	1.00	0.03	0.52
Median walk duration	0.04	0.00	0.03	0.02	0.02	-0.02	-0.01	0.04	0.02	0.03	1.00	0.38
Longest walk duration	0.50	0.05	0.44	0.28	0.43	-0.40	-0.49	0.62	0.49	0.52	0.38	1.00
Walks ≤ 7s	-0.56	-0.05	-0.34	-0.27	-0.16	0.32	0.27	-0.53	-0.38	-0.47	-0.08	-0.44
Step-walk Gradient	0.21	0.05	0.47	0.16	0.55	-0.47	-0.66	0.80	0.70	0.78	0.05	0.65
Walks ≤ 60s	-0.33	-0.02	-0.34	-0.22	-0.24	0.25	0.22	-0.51	-0.27	-0.43	-0.13	-0.49
Shoulder bag [%]	0.10	0.04	0.28	0.08	0.30	-0.32	-0.40	0.36	0.35	0.33	-0.02	0.36
Hands in pocket [%]	0.11	0.08	0.26	0.21	0.29	-0.19	-0.35	0.31	0.32	0.30	-0.01	0.27
Briefcase [%]	0.08	0.02	0.29	-0.01	0.40	-0.30	-0.45	0.44	0.44	0.42	0.00	0.39
Arm swing [%]	0.04	-0.05	-0.18	0.09	-0.36	0.28	0.43	-0.36	-0.38	-0.37	0.03	-0.29
Phone call [%]	-0.07	0.00	-0.04	-0.07	0.11	-0.05	-0.12	0.09	0.09	0.10	-0.01	0.07
Texting [%]	-0.28	0.00	-0.17	-0.37	0.08	-0.02	-0.06	0.01	0.05	0.07	-0.03	-0.09
Total sleep	-0.22	-0.06	-0.10	-0.09	-0.08	-0.05	0.10	0.00	-0.09	-0.06	0.01	-0.04
Bedtime	0.25	0.04	0.10	0.05	0.08	0.04	-0.13	0.02	0.06	0.02	-0.01	0.07

Appendix E2. Pearson's correlation coefficients between digital gait biomarkers (Cont'd)

	Walks ≤ 7s	Step-walk Gradient	Walks ≤ 60s	Shoulder bag [%]	Hands in pocket [%]	Briefcase [%]	Arm swing [%]	Phone call [%]	Texting [%]	Total sleep	Bedtime
Steps per day	-0.56	0.21	-0.33	0.10	0.11	0.08	0.04	-0.07	-0.28	-0.22	0.25
Running duration	-0.05	0.05	-0.02	0.04	0.08	0.02	-0.05	0.00	0.00	-0.06	0.04
Max walking speed	-0.34	0.47	-0.34	0.28	0.26	0.29	-0.18	-0.04	-0.17	-0.10	0.10
Usual walking speed	-0.27	0.16	-0.22	0.08	0.21	-0.01	0.09	-0.07	-0.37	-0.09	0.05
Cadence Median	-0.16	0.55	-0.24	0.30	0.29	0.40	-0.36	0.11	0.08	-0.08	0.08
Cadence IQR	0.32	-0.47	0.25	-0.32	-0.19	-0.30	0.28	-0.05	-0.02	-0.05	0.04
Step-time variability	0.27	-0.66	0.22	-0.40	-0.35	-0.45	0.43	-0.12	-0.06	0.10	-0.13
8-step Harmonic ratio	-0.53	0.80	-0.51	0.36	0.31	0.44	-0.36	0.09	0.01	0.00	0.02
Step regularity	-0.38	0.70	-0.27	0.35	0.32	0.44	-0.38	0.09	0.05	-0.09	0.06
Stride regularity	-0.47	0.78	-0.43	0.33	0.30	0.42	-0.37	0.10	0.07	-0.06	0.02
Median walk duration	-0.08	0.05	-0.13	-0.02	-0.01	0.00	0.03	-0.01	-0.03	0.01	-0.01
Longest walk duration	-0.44	0.65	-0.49	0.36	0.27	0.39	-0.29	0.07	-0.09	-0.04	0.07
Walks ≤ 7s	1.00	-0.49	0.73	0.13	0.03	0.05	-0.34	0.24	0.51	0.04	-0.01
Step-walk Gradient	-0.49	1.00	-0.48	0.46	0.35	0.54	-0.49	0.16	0.08	0.05	-0.09
Walks ≤ 60s	0.73	-0.48	1.00	0.15	0.08	0.04	-0.25	0.13	0.31	-0.01	0.01
Shoulder bag [%]	0.13	0.46	0.15	1.00	0.26	0.43	-0.72	0.20	0.25	-0.02	0.02
Hands in pocket [%]	0.03	0.35	0.08	0.26	1.00	0.18	-0.47	0.04	0.09	-0.06	0.05
Briefcase [%]	0.05	0.54	0.04	0.43	0.18	1.00	-0.67	0.22	0.31	-0.01	0.03
Arm swing [%]	-0.34	-0.49	-0.25	-0.72	-0.47	-0.67	1.00	-0.51	-0.72	0.03	-0.03
Phone call [%]	0.24	0.16	0.13	0.20	0.04	0.22	-0.51	1.00	0.44	0.00	-0.01
Texting [%]	0.51	0.08	0.31	0.25	0.09	0.31	-0.72	0.44	1.00	-0.01	0.01
Total sleep	0.04	0.05	-0.01	-0.02	-0.06	-0.01	0.03	0.00	-0.01	1.00	-0.58
Bedtime	-0.01	-0.09	0.01	0.02	0.05	0.03	-0.03	-0.01	0.01	-0.58	1.00