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What can quantitative gait analysis tell us about dementia and its subtypes? A structured review

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Running heading: Gait analysis in dementia subtypes

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Abstract

Distinguishing dementia subtypes can be difficult due to similarities in clinical presentation. There is increasing interest in discrete gait characteristics as markers to aid diagnostic algorithms in dementia. This structured review explores the differences in quantitative gait characteristics between dementia and healthy controls, and between four dementia subtypes under single-task conditions: Alzheimer's disease (AD), dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) and vascular dementia (VaD). Twenty-six papers out of an initial 5,211 were reviewed and interpreted using a validated model of gait. Dementia was associated with gait characteristics grouped by slower pace, impaired rhythm and increased variability compared to normal aging. Only four studies compared two or more dementia subtypes. People with AD are less impaired in pace, rhythm and variability domains of gait compared to non-AD dementias. Results demonstrate the potential of gait as a clinical marker to discriminate between dementia subtypes. Larger studies using a more comprehensive battery of gait characteristics and better characterized dementia sub-types are required.

Keywords: Alzheimer's disease, Lewy body disease, biomarker, cognition, diagnosis, cognitive impairment

Introduction

Dementia is a growing global issue with 46.8 million people affected worldwide and numbers predicted to rise to 131.5 million by 2050 [1]. Dementia is identified by multiple cognitive impairments, which limit everyday functioning. It occurs predominantly in older adults and can be categorised into different subtypes. Alzheimer's Disease (AD) is the most common subtype, followed by Lewy body dementia (LBD) and vascular dementia (VaD) [2]. Alzheimer's disease is characterised by gradual onset of memory impairment and is associated with neurofibrillary tangles and amyloid beta plaques contributing to neurodegeneration, particularly focal to the hippocampal region. Dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) share symptomology and pathology; they have common key symptoms such as parkinsonism, cognitive fluctuations, visual hallucinations and REM sleep behaviour disorder, and are associated with Lewy body formation in the brainstem, limbic and neocortical areas [3, 4]. Together, these dementia subtypes are referred to as Lewy body dementia (LBD). LBD often has concurrent AD pathology, which alters clinical presentation. Vascular dementia is heterogeneous in nature and therefore cognitive changes vary greatly [5]. The most common findings are subcortical infarcts and white matter ischemia damaging frontostriatal circuits, leading to impaired attention, information processing and executive function.

Misdiagnosis of dementia subtypes is problematic in AD and DLB; it is reported that 34-65% of cases are misdiagnosed [6], due to similarities in cognitive presentation and pathology. Some dementia cases, such as AD with subcortical infarcts, have mixed pathology which can further hinder accurate diagnosis. Often the need to distinguish subtypes is disregarded, as it is not thought to influence care. However, accurate diagnosis of DLB subtype is important to prevent mistaking cognitive fluctuations, key characteristics of DLB, as delirium; prevent inappropriate use of antipsychotics; and to facilitate early identification and

treatment of motor symptoms, dysautonomia, falls and other characteristic non-psychiatric symptoms [7]. Subtypes also have different prognoses, with DLB associated with more rapid decline and entering nursing care earlier [8]. The advent of disease modifying treatments will also necessitate subtype identification and dementia stratification for the optimal use of such therapies.

Diagnostic markers for dementia, such as cerebrospinal fluid, blood samples, brain pathology and cognitive markers, are being investigated to distinguish dementia subtypes and improve accuracy of current clinical diagnoses [9]. More recently, gait (and its discrete characteristics) have been proposed as potential clinical biomarkers for dementia [10]. Gait is a complex skill requiring involvement from widespread brain regions (including those related to different cognitive functions, such as the frontal cortex and hippocampus). Changes in brain function can therefore lead to subtle changes in distinct gait characteristics, explaining why its features may be useful. Studies show a robust association between gait and cognitive function [11], and gait impairments precede and predict cognitive impairment and dementia [10, 12]. Therefore, evidence suggests quantitative gait analysis as a plausible diagnostic marker for early diagnosis of dementia. However, recent reviews have not addressed the role of gait to differentiate between dementia subtypes.

In consideration of this, the aims of this review are to establish quantitatively assessed gait differences between dementia and non-cognitively impaired older adults, review evidence for distinct gait profiles across dementia subtypes and identify recommendations for future research. This review will focus on the most common subtypes of dementia: AD, VaD and LBD (referring to DLB and PDD). This review will focus solely on single-task gait analysis as dual-task protocols (which involve walking while engaging in another task) vary widely in both methodology and type of secondary task (i.e. tests to assess different cognitive domains or manual function). Different tasks may produce different gait impairments and is therefore a

subject for further detailed investigation beyond the scope of this review. Assessing differences in gait impairment during single-task walking is clinically useful, as it is a simple task to carry out and easy to understand – an important consideration for populations with cognitive impairment. For the purposes of this review we will adopt a model of gait (Figure 1) Lord, et al. [13] as a framework to provide structure to the synthesis of literature and aid interpretation of data. We hypothesize that gait will be more impaired across multiple domains in dementia compared to controls, and that LBD and VaD will have reduced pace and increased variability when walking compared to AD, whereas AD will have more pronounced impairments in temporal characteristics of gait. Characteristics relating to reduced pace and increased variability are associated with impaired attention and executive function, whilst temporal characteristics of gait have been linked to memory [12].

Methods

Search Strategy

Six databases were used for the search: Scopus, Embase, Web of Science, Psych Articles, Medline and Psychinfo. Key terms for the search strategy are detailed in Figure 2. The search was limited to papers published from 1946 to October 2016. Other eligible papers brought to the reviewers' attention were also considered. Articles were included if they: i) included at least one dementia subtype and control/other clinical cohort (i.e. Parkinson's disease; PD) or two dementia subtypes or at least one dementia subtype at different stages of disease severity; ii) included quantitative gait characteristics, obtained from electronic gait analysis, wearable technology, motion capture analysis or other suitable means; iii) were original articles; and iv) were written in English. Where an article included another clinical cohort (e.g. Parkinson's disease or mild cognitive impairment) or other clinical characteristics (e.g. urinary symptoms), only the data relating to dementia and gait was reviewed.

Data Extraction

One reviewer (R.M.A.) screened the titles from the initial search and two reviewers (R.M.A. and B.G.) independently screened the abstracts to identify potential articles. Full-text articles were retrieved when reviewers could not determine the eligibility of the study from the title and abstract. All full-length articles were reviewed by three reviewers (R.M.A, R.M and J.W).

Data were extracted from eligible articles. The key characteristics of interest were: (i) dementia subtypes included, (ii) gait parameters assessed, (iii) method of gait analysis, (iv) main findings of the study with respect to gait. A quality assessment was conducted separately by two reviewers (R.M.A and J.W) and overall quality scores were determined for each study (see Supplementary Table 1).

Interpretation of data

Due to the wide and varying range of gait characteristics, several groups have proposed models of gait that categorize gait characteristics by domain using data reduction techniques [12, 14-16]. Although comparable, there is no standardized model - different models emphasize different characteristics and domains. The model chosen for this review was validated in older adults and PD (see Figure 1 for more details). Gait characteristics across studies were broadly mapped onto five core domains (Figure 1; hypothesized to represent different neural networks involved in locomotor control) in order to structure data presentation and interpretation of results for within this review [11].

< Insert Figure 1 >

Results

Search Yield

The search strategy generated 11,515 papers after exclusion criteria were applied. After removing duplicates, 5211 papers remained from the search (see Figure 2). The initial title search yielded 376 papers with an abstract screening leaving 55 papers eligible for data extraction. Fourteen studies were excluded as they did not specify the subtype of dementia (n=10), were not relevant to the review (n=3) or had previously reported results in a paper included in the review (n=1). Data were extracted from 42 papers. After data extraction, a further 16 papers were removed as they only reported timed gait speed or used functional tasks which required additional tasks, such as the Timed Up and Go test. All papers were published between 1983 and 2016.

Out of the remaining 26 articles, the majority of studies investigated AD (n=25; 96%), followed by DLB (n=2; 8%), Parkinson's disease dementia (PDD; n=2; 8%), Lewy body dementia (LBD; n=1; 4%), VaD (n=1; 4%) and unspecified non-AD dementia (n=1; 4%). Two studies used Parkinson's disease (PD) for comparison, four used mild cognitive impairment (MCI) and 21 used older adult control groups.

< Insert Figure 2 >

Measurement of gait in dementia

Table 1 details the specific characteristics and findings for each of the reviewed papers. Quantitative gait analysis included the use of gait walkway systems [17-25], accelerometers [26-30], motion capture analysis systems [31-35], pressurized foot-sensors [19, 36-39] and combinations of these and other methods such as forceplates [40] and digital cameras [41]. One study did not define the instruments they used [42].

To examine the wide range of reported gait parameters, all gait characteristics were mapped to one of the five domains of gait Lord, et al. [16]. Commonly described gait parameters have been described in Supplementary Table 2. All 26 papers investigated pace [17-42], 18 studies described characteristics relating to rhythm [18-20, 23-27, 29, 30, 32-35, 38, 39, 41], 13 studies reported gait variability [17, 19, 24-29, 31-33, 35, 39], two studies described characteristics of gait asymmetry [26, 27] and nine reported parameters relating to postural control [17-20, 25, 33, 34, 39, 40, 42].

< Insert Table 1 >

Gait impairments in Alzheimer's Disease

25 studies assessed gait in AD [17-24, 26-36, 38-42]; 21 of these studies compared AD to controls [17-20, 22-30, 32-36, 38, 40, 42], four studies compared AD to other dementia subtypes [18, 25, 39, 42], four compared AD to MCI [22, 26-28] and four studies compared AD severity levels [21, 31, 36, 41].

In AD, all 25 studies assessed characteristics of pace, such as step velocity, step length, step, stance and swing time variability [17-36, 38-42] (See table 2 for specific study details). People with AD typically walked with reduced pace [17-20, 22-30, 32-36, 38, 40, 42] compared to controls, and were more impaired in severe AD [32, 36]. Reduced pace was also reported in AD compared to controls with low levels of white matter subcortical hyperintensities but not compared to controls with high levels of subcortical hyperintensities [20].

In AD, 18 studies assessed characteristics of rhythm, such as step, swing and stance time [18-20, 23-27, 29, 30, 32-35, 38, 39, 41]. The majority found impaired rhythm in AD compared to controls [18, 19, 23-25, 27, 30, 33-35]. One study found impaired rhythm with

increased dementia severity [32]. One study found impaired rhythm in AD compared to controls with low levels of subcortical hyperintensities but not high levels [20].

In AD, 12 studies assessed features of variability, such as step velocity, step length and step width variability [17, 24-29, 31-33, 35, 39]. Results were inconsistent between AD and controls; five studies found increased variability in AD [17, 25, 27, 31, 33] while four did not [24, 26, 28, 35].

In AD, only two studies assessed features of asymmetry such as step time, swing and stance asymmetry [26, 27]. Both compared AD to controls and MCI cohorts; no significant differences were found between any groups. In AD, nine studies assessed postural control of gait such as step width and step length asymmetry [17-19, 25, 33, 34, 40, 42]. Typically, there were no significant differences between AD and controls for postural control characteristics of gait [17-19, 33, 34, 40, 42, 43]**.**

Gait impairments in Lewy Body Dementia

In LBD, three studies assessed gait. All studies assessed characteristics of pace [18, 37, 39] and generally found reduced pace compared to controls [18, 37]. Findings were also inconsistent between LBD and PD, with one study reporting reduced pace in LBD [39] and another study showing no group differences between PDD and PD [37]. No significant differences were found between subtypes of LBD [45]. In LBD, two studies assessed features of rhythm [18, 39] and found rhythm was impaired compared to controls [18]. One study reported impaired rhythm in LBD compared to PD but no significant differences between LBD subtypes [39]. In LBD, only one study assessed characteristics of variability [39]. It found no group differences between LBD and PD. The same study assessed postural control characteristics of gait in LBD and found no significant differences between controls and DLB. Asymmetry was not assessed in LBD.

Gait impairments in Vascular Dementia

One study assessed pace and postural control characteristics of gait in VaD [42]. It found reduced pace but no differences in postural control in VaD compared to both controls. Rhythm, variability and asymmetry were not assessed in VaD.

3.6 Differences in gait between dementia subtypes and disease severity.

People with AD demonstrated better pace compared to VaD [42]. In contrast, comparisons with LBD are inconsistent; one study found no difference in pace or rhythm between AD and DLB [18] whilst another reported reduced pace, impaired rhythm and increased variability in LBD compared to AD [39]. One study compared mild and moderate severity AD to mild and moderate severity unspecified non-AD dementia [25]; for both severity levels, non-AD dementia had reduced pace and a larger stride width (a feature of postural control). However, impaired rhythm was only found in the non-AD group in the moderate cohort and impaired variability only in the non-AD group in the mild cohort. No significant differences for postural control characteristics were found between AD and VaD or AD and DLB [18, 42]. Surprisingly, no significant differences were found in pace or rhythm between AD and PD [39].

Reduced pace was reported with increasing dementia severity. All four studies comparing dementia severity found reductions in pace in the moderate-to-severe AD groups compared to the milder groups [21, 31, 36, 41]. Results were inconsistent between AD and MCI; two studies reported slower pace in AD compared to MCI [27, 28] whilst two studies found no significant differences between these groups [22, 26]. No differences in characteristics of rhythm were found across dementia severity [22, 26, 41] and only one study reported impaired rhythm in AD compared to MCI [27]. Inconsistent results for variability were found between AD and MCI, with two studies showing increased variability in AD [26,

27] and two reporting no differences [22, 28]. One study found increased variability in moderate AD compared to mild AD [41] while another found increased variability in moderate and severe AD compared to controls; this was not found in mild AD [32]. Only one study found moderate AD had a larger stride width, a feature of postural control, compared to controls whereas mild AD did not [25]. No studies investigated asymmetry across dementia severity.

Discussion

This review aimed to summarize available data on gait differences in people with dementia compared to controls and identify distinct gait profiles in dementia subtypes. This review clarifies previous findings of gait impairment in dementia compared to controls, specifically attributing impairments to pace and rhythm domains. However, we extend previous literature by identifying that dementia subtypes differ from each other in characteristics of pace, rhythm and variability, although the number of studies comparing subtypes (Figure 3) and the range of gait characteristics described are limited.

< Insert Figure 3 >

Is gait in dementia distinct from normal aging?

Our findings provide insight into significant impairments in gait in AD, VaD and LBD compared to non-cognitively impaired older adults that are consistent with our hypothesis. Reductions in pace was reported by the majority of studies, however it was also the most commonly assessed characteristic. Other discrete gait characteristics may have identified key discrete differences and need to be assessed in order to develop distinct patterns of gait for dementia subtypes [11]. Temporal gait characteristics (i.e. those in the rhythm domain) appeared more impaired in dementia and were dependent on disease stage. Impairments in variability are inconclusive, largely due to inconsistencies in the variables measured.

Are gait impairments distinctive between dementia subtypes?

The findings of this review support the qualitative literature reporting that gait is more impaired in non-AD dementia subtypes compared to AD and emphasizes differences across pace, rhythm and variability domains, which is somewhat consistent with our hypothesis [2]. Only four studies compared gait across subtypes, highlighting a significant gap in the literature. Interestingly, no differences were found between PD and AD in one study – however, trends indicated that PD walked slower with a mean velocity of 1.13 metres per second and mean stride length of 115.82 centimetres compared to 1.2 and 125.33 respectively [39]. One study reported differences across MCI subtypes, which may relate to different dementia subtypes. For example, when compared to controls, amnestic-MCI had slower pace, while non-amnestic-MCI had slower pace and impaired rhythm [25]. This may be due to pathological differences with important implications, as a-MCI usually develops into AD, while na-MCI progresses into non-AD dementias, such as DLB or VaD [44]. Therefore, gait could act as an early marker to differentiate between dementia subtypes, however further work is needed to determine this.

Do gait impairments across dementia subtypes relate to cognitive impairments and their underlying neural correlates?

This review provides evidence for gait impairment in dementia subtypes reflecting cognitive impairments. Selective cognitive domains have been associated with discrete gait impairments which may reflect underlying pathology [12]. For example, characteristics of rhythm have been associated with memory, affected early in AD, while reduced pace and increased variability have been associated with impaired attention and executive function, affected early in LBD and VaD [11]. These cognitive impairments relate to the underlying neural correlates and pathological changes in different dementia subtypes. Our findings suggest that gait impairments may similarly reflect these differences. Dementias such as LBD have associated motor impairments due to disease pathology, such as neurodegeneration of the

substantia nigra, which produces key motor impairments of which gait asymmetry and postural control may be a feature. It is worth noting however, that despite these impairments, diagnosis in the early stages is still difficult. Therefore while the differences in gait may not all be mediated by cognitive deficits and associated neural correlates, additional motor impairments may contribute to early differentiation.

< Insert Figure 4 >

An interesting question to ask is; do gait impairments reflect shared cognitive and pathological correlates consistent with different dementia subtypes? Alzheimer's disease is associated with amnestic memory deficits predominantly due to amyloid deposition in the entorhinal cortex and hippocampus [45]. Atrophy of the hippocampus (involved in navigation and memory) is associated with decreased pace and variability [46], with speculative links between rhythm and the hippocampus; temporal aspects of gait have been associated with memory [12]. Reduced pace and increased variability are associated with frontal lobe atrophy and white matter hyper-intensities affecting frontal subcortical circuits in both dementia and older adults – areas that mediate attention and executive function [46, 47]. Frontal white matter lesions are key characteristics of VaD [5] and frontal neuronal loss is associated with Lewy body disease, lending explanation to pace and variability deficits. There are also correlations between increases in gait impairment with dementia severity and reduced frontal cerebral blood flow becoming more widespread [32], suggesting gait impairment is reflective of ongoing neural changes in dementia. However, the majority of research associating gait with specific brain regions focuses on gait speed – further research needs to be completed before drawing any conclusions in this area.

Limitations of current research and recommendations for the future

There are a number of discrepancies with the current research regarding quantitative gait assessment in dementia. Several additional studies using functional tasks (i.e. timed up and go) were identified but not included in this review, as they did not provide standardized measures of gait. This prevents comparison across studies and may be subject to confounding variables, such as impaired movement initiation. Of the studies that were included, distance walked, number of strides and steps, type of walk (i.e. continuous or intermittent) and gait analysis technique used (i.e. instrumented walkways, body worn sensors) varied. This limited interpretation when collating the results. Development of a standardized single-task gait protocol suitable for use in any clinic would be beneficial to aid generalizability of findings. This should include measuring at least 30 steps to assess variability characteristics [48]. Intermittent walks may be more suitable for dementia populations, particularly as the disease progresses – allowing for rest breaks as needed. Gait characteristics across studies also varied, with some studies limited to velocity and others assessing a wider range, such as stance time, step width, etc. Only two studies assessed features of asymmetry; this may be an oversight when considering dementias with notable asymmetric pathology, such as PDD, as asymmetric pathology may be reflected in gait outcomes. Studies should strive to assess a large range of spatial and temporal aspects of gait, to establish distinct gait profiles across dementia subtypes.

There was also a limited number of studies comparing dementia subtypes, as seen in Table 2. The majority focused on differences between AD and controls, with only five studies investigating non-AD dementias. Although non-AD dementias such as LBD and VaD have notable gait impairments as described in the qualitative literature [2], quantitative gait assessment is needed to tease out subtle differences that may support diagnosis. More studies comparing subtypes are necessary. There were also discrepancies across studies regarding severity measures – a number of rating scales, such as the MMSE or the CDR, were used to

establish stage of disease with inconsistent ratings determining disease stage. Studies were also restricted by small sample sizes and may not have provided a true picture of gait in dementia due to influence of outliers – studies should be adequately powered. Overall, the majority of studies were only of mediocre quality (see Supplementary Table 1 for more details). Therefore, we have provided key recommendations in Table 2 to guide future research.

< Insert Table 2 >

Clinical implications

While gait impairments are recognisably present and often early markers of dementia subtypes such as VaD, PDD or DLB [2], clinical recognition of gait deficits in AD is an emergent area of research. The National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) includes gait disturbances in their exclusion criteria for a diagnosis of AD [49, 50]. However the findings from this review and previous qualitative studies show that gait impairments are more common in AD compared to controls [2]. Qualitative literature suggests that gait impairments are not present in mild AD; however, quantitative gait analysis reveals subtle discrete deficits in mild AD that progressively worsen. Equally, while parkinsonism is a core feature of DLB according to the latest diagnostic criteria [51], specific gait impairments have not been described, and the revised DLB criteria suggests that at least one clinical marker and a biomarker suggestive of Lewy body disease are necessary for early diagnosis. Although limited, the current evidence suggests that dementia subtypes have distinctive patterns of gait impairment. While more research is necessary in order to establish unique gait profiles in dementia subtypes, the end-result could complement current diagnostic criteria and show potential utility as a biomarker. Similar to acknowledging the specific cognitive domains impaired early in disease onset (e.g. episodic memory in AD), specific gait domains may also be impaired early (e.g. rhythm in AD). Changes in gait are also found prior to onset of cognitive

decline; therefore, gait analysis at early intervals could contribute to early diagnosis of dementia. With advancing technology, quantitative gait analysis techniques are becoming smaller, portable and more cost-effective and could prove a useful addition to a clinician's toolbox.

Conclusion

Gait is impaired in dementia compared to cognitively intact older adults. Dementia subtypes may have discrete gait profiles but more research is necessary to establish these. Use of standardized protocols and assessment of a comprehensive range of spatiotemporal gait characteristics are necessary when studying gait in dementia and its subtypes. Future research should endeavor to establish quantitative gait analysis as a cost-effective and easily applicable clinical biomarker for dementia.

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Conflicts of Interest/Disclosure Statement

The authors have no conflict of interest to report.

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Table 1: Descriptive information and methodology of all cross-sectional studies

Study	Participant Characteristics	Diagnostic Criteria	Severity Rating	Gait analysis tool (distance)	Gait parameters measured (units)	Main study findings
Merory, et al. [18]	10 AD; 8M/2F, age: 76±6, MMSE: 28.7±1.2, UPDRS: 2.7±4.2 10 DLB; 8M/2F; age: 73±5, MMSE: 23.5±4, UPDRS: 27.1±9.4 10 Controls; 8M/2F, age: 72±7, MMSE: 28.7±1.2	AD: NINCDS-ADRDA DLB: McKeith	Not specified	GAITRite (8.3m x 0.89m)	Velocity (not specified) Cadence (not specified) Stride length (not specified) Step width (not specified) Double support time (not specified)	AD and DLB: slower velocity, shorter stride length and increased double support time compared to controls. No significant differences between AD and DLB
[17]	Groups split by subcortical hyperintensity severity: (+) high severity, (-) low severity 42 AD; 60%F, age: 74±8, MMSE: 25±3, UPDRS: 7±7. 21 AD -; 68%F, age: 71±9, MMSE: 24±3, UPDRS ±3±3 21 AD+; 52%F, age: 77±6, MMSE: 25±2, UPDRS: 11±9 33 Controls; 47%, age: 73±8, MMSE: 29±1, UPDRS, 3±4 18 Controls -; 44%F, age: 69±7, MMSE: 29±1, UPDRS: 1±3 15 Controls +; 53%F, 76±7, MMSE: 28±1.3, UPDRS: 3±3	NINCDS-ADRDA – probable AD	MMSE ≥ 20. Dementia Rating Scale	GAITRite (2 x 12ft)	Velocity (cm/s) Stride Length (cm) Cadence (Steps/min) Step width (cm)	Controls -: faster velocity compared to controls +, AD – and AD +. Stride length longer and cadence higher compared to AD – and AD +
Ries, et al. [21]	20 mild-moderate AD; 60%F, age: 81.05±9.48, MMSE: 17.4±4.5 31 moderate-severe AD; 70.7%F, age: 80.48±8.43, MMSE: 10.20±8.83	Not specified	FAST 4/5: mild – moderate AD FAST 6/7: moderate – severe AD	GAITRite (15ft)	Gait speed (cm/s)	Moderate-severe AD had a slower gait speed on the GAITRite.

Gras, et al. [23]	13 AD; 10M/3F, age: 72.9±4.7, MMSE: 24.8±2.6 13 Controls; 10M/3F, age: 72.6±4.6, MMSE: 29±1	NINCDS-ADRDA	CDR 0.5: very mild AD	GAITRite (4.88m)	Velocity (m/s) Stance time (s) Step length (m)	AD: slower velocity, longer stance time, shorter step length compared to controls.
Visser [24]	11 AD; 2M/9F, age: 78.8±2.5. 11 Controls; 2M/9F, age: 78.3±2.6	Not specified	Set Test (Isaacs & Akhtar): severe dementia - < 10, moderate dementia – 10-20	Specially designed walkway with sensors (6m)	Speed (m/s) Step frequency (steps/sec) Step length (cm) Double support ratio (%) CV step length (%)	AD: slower walking speed, shorter step length, lower step frequency and increased double support ratio compared to controls
Gillain, et al. [26]	6 AD; 9%M, 9%F (overall sample), age: 73.66, MMSE: 22.83±2.14, education: 9.33±3.78 14 MCI; 21%M, 21%F, age: 72.85, MMSE: 26.71±1.68, education: 13.64±3.3 14 Controls; 19%M, 21%F, age: 75.53, MMSE: 28.21±1.58, education: 13.71±3.73	AD: NINCDS-ADRDA MCI: Confirmed isolated cognitive disorder that doesn't affect activities of daily living	CDR 0.5: MCI CDR 1: AD MMSE ≥ 24 – MCI MMSE ≥ 20 - AD	Tri-axial accelerometer (40m x 2 times)	Gait speed (m/s) Stride frequency (hz) Stride length (m) Regularity (dimensionless) Symmetry (dimensionless) Stops	AD: Slower speed and shorter stride length compared to controls. AD had reduced regularity compared to MCI. MCI had reduced stride frequency compared to controls.
Maquet, et al. [27]	6 AD; 3M/3F, age: 74±4 14 MCI; 7M/7F, age: 73±4 14 Controls; 7M/7F, age: 74±5	AD: NINCDS-ADRDA a-MCI: Pearson et al, 2001 na-MCI: Winblad et al, 2004	CDR 0.5: MCI CDR 1: AD MMSE 24≥ - MCI MMSE 20≥ - AD	Accelerometer (45m x 2times)	Walking speed (m/s) Stride frequency (hz) Stride length (m) Symmetry (au) Regularity (au) Stops (au)	AD: slower walking speed, lower stride frequency, shorter stride length and decreased regularity compared to controls. AD: slower walking speed, lower stride frequency, shorter stride length and decreased regularity

						compared to MCI. MCI: reduced stride frequency compared to controls.
Choi, et al. [28]	10 AD; 4M/6F, age: 77.2±6.84 7 MCI; 4M/3F, age: 72.9±6.28 6 Controls; 4M/2F, age: 71.6±5.78	Not specified	Not specified	Tri-axial accelerometer (100m)	Stride time (not defined) CV stride time Detrended fluctuation analysis Spectral analysis (LF/HF ratio)	AD: increased CV stride time compared to controls. AD: increased CV stride time compared to MCI. MCI: slower stride time, increased CV stride time and increased LF/HF ratio compared to controls.
Lamoth, et al. [29]	13 AD; 4M/9F, age: 82.62±4.29, MMSE: 18±3.54 13 Controls; 6M/7F, age: 79.38±5.55, MMSE: 28.23±1.09	Criteria of Alzheimer's Association	MMSE < 23	Tri-axial accelerometer	Speed (m/sec) Stride frequency (stride/sec) Stride time (sec) CV stride time (%) Phase variability index (%) Stride-to-stride variability (%)	No significant differences found between groups
Nakamura, et al. [31]	10 mild AD fallers; 2M/8F, age: 75.4±2.5, MMSE: 17.8±2.1, disease duration: 2.9±0.7 40 mild AD non-fallers; 9M/31F, age: 74.6±2.7, MMSE: 18±1.8, disease duration: 3.1±0.5 18 moderate AD fallers;	NINCDS-ADRDA – probable AD DSM-III-R	MMSE CDR 1: Mild A CDR 2: Moderate AD	Motion capture analysis system (10 strides)	Speed Stride length CV stride length (%)	Moderate AD had a slower walking speed, shorter stride length and increased

	5M/13F, age: 74.8±2.3, MMSE: 11.3±2.6, disease duration: 6.0±0.8 29 moderate AD non-fallers: 8M/21F, age: 76±3, MMSE: 12.2±2.1, disease duration: 5.8±1					CV stride length compared to mild AD.
Nakamura, et al. [32]	45 AD; 13M/32F, age: 76.8 (73-82) – Split by severity levels. 15 CDR1; 5M/10F, age: 75.9±3.6, MMSE: 18.6±1.7, disease duration: 2.2±1.8 15 CDR2; 4M/11F, age: 77.5±4.0, MMSE: 11.4±2.6, disease duration: 4.3±1.6 15 CDR3; 4M/11F, age: 78.1±3.2, MMSE: 6.8±2.4, disease duration: 7.0±2.1 15 Controls; 5M/10F, age: 77.1±3.4, MMSE: 27.4±1.3	DSM-III-R criteria for probable AD. NINCDS-ADRDA	MMSE CDR1: Mild CDR2: Moderate CDR3: Severe	Motion capture analysis system (10m)	Walking speed (m/s) Stride length (m) Double support time (s) CV stride length (%)	AD -Moderate and severe: slower walking speed, shorter stride length, increased double support time, increased CV stride length compared to controls. AD – mild: did not differ from controls. Statistical comparisons between dementia severity groups not reported but trend implies that gait impairments worsen with progression of dementia.
Barbieri, et al. [33]	15 AD; age: 78.33±5.23, MMSE: 17.73±3.93. 15 Controls: age: 77.44± 6.19, MMSE: 27.4±2.38.	Not specified	CDR Neuropsychiatric inventory	Motion capture analysis system (8m)	Stride length (cm) Step width (cm) Stride duration (s) Stride velocity (cm/s) Double support duration (%)	AD: shorter stride length, double-support duration, longer stride duration, slower stride velocity, increased CV stride length, increased CV double

					CV stride length (%) CV step width (%) CV stride duration (%) CV stride velocity (%) CV double support duration (%)	support time and increased CV stride duration compared to controls.
Simieli, et al. [34]	18 AD; 4M/15F, age: 78.33±5.23 15 Controls; age: 77.44±6.19	DSM-IV-TR and International Disease Code	CDR 1 and CDR 2 Neuropsychiatric inventory	Motion capture analysis system (8m)	Stride length (cm) Step width (cm) Single support duration (s) Double support time (s) Stride duration (s) Stride velocity (cm/s)	AD: shorter stride length, shorter stride width, slower stride velocity, increased single support duration, increased double support time and longer stride duration compared to controls
Lin, et al. [35]	10 AD; 2M/8F, age: 74±8.6, MMSE: 17.7±4.1. 10 Controls, 2M/8F, age: 73.8±6.1, MMSE: 29.4±0.7	Criteria not specified.	CDR: 0.8±0.3 - mild	Motion capture analysis system (8m)	Velocity (leg length/sec) Cadence (steps/min) Stride length (leg length) CV stride length (%) Stride time (s) CV stride time (%)	AD: slower velocity, decreased cadence and longer stride time compared to controls.
Goldman, et al. [36]	40 very mild AD; 19M/21F, age: 71.98±7.51, education: 13.72±3.36 20 mild AD; 9M/11F, age: 73.68±7.82, education: 12.05±3.63 43 Controls; 21M/22F, age: 73.22±7.70, education: 14.44±3.26	NINCDS-ADRDA	CDR 0.5: very mild CDR 1: mild	Electric contact footpads with pressure-activated foot-switches (10m)	Velocity (distance/time)	Mild AD: slower velocity compared to controls. Very mild AD: did not differ from controls

						Mild AD: slower velocity compared to very mild AD.
Goldman, et al. [37]	22 PDD; 19M/3F, age: 71.6±7.8, education: 13.7±3.7 58 PD; 42M/16F, age: 69.7±6.0, education: 14.8±3.1 43 Controls; 21M/22F, age: 73.2±7.7, education: 14.4±3.3	Not specified	CDR 0.5: Questionable dementia	Electric contact footpads with pressure-activated foot-switches (10m)	Velocity (cm/s)	PDD: slower velocity compared to controls but did not differ from PD.
Nadkarni, et al. [19]	40 AD; 55%F, age: 74±8, MMSE: 25±3, UPDRS: 7±8. 34 Controls; 45F, age: 73±8, MMSE: 29±1, UPDRS: 2±4	NINCDS-ADRDA	MMSE Dementia Rating Scale	GAITRite (2 x 12ft). Footswitches with motorised treadmill.	**GAITRite:** Velocity (cm/s) Cadence (steps/min) Stride length (cm) Cycle time (s) Stride width (cm) Double support time (s) **Treadmill:** Belt speed (cm/s) Cadence (steps/min) Cycle time (s) Double support time (s) CV cycle time (%) CV double support time (%)	**GAITRite:** AD had a slower velocity, decreased cadence, shorter stride length, longer cycle time and longer double support time than controls. **Treadmill:** AD had a slower belt speed and decreased cadence than controls compared to controls.

Nadkarni, et al. [20]	24 AD; 60%F, age: 75±9, MMSE: 25±3, UPDRS: 6±7 20 Controls; 47%F, age: 72±8, MMSE: 29±1, UPDRS: 3±4	NINCDS-ADRDA – probable AD	MMSE Mattis Dementia Rating Scale	Footswitches on a motorised treadmill.	Overground gait speed (m/s) Self-selected treadmill walking speed (m/s) Cadence (not defined) Cycle time (not defined) Double support time (not defined)	AD: slower overground gait and slower self-selected treadmill walking speed compared to controls.
Fritz, et al. [39]	21 AD; 13M/8F, age: 75.05±4.96, MMSE: 22.43±4.25, education: 14.67±2.13, UPDRS: 3.9±3.62 21 LBD; 13M/8F, age: 73.95±4.78, MMSE: 22.57±3.57, education: 15.57±2.58, UPDRS: 25.95±5.82 LBD group split into subtypes DLB and PDD. 11 DLB; 6M/5F, age: 73.7±4.59, MMSE: 24.45±4.46, education: 15.54±2.38, UPDRS: 24.45±6.3 10 PDD; 7M/3F, age: 74.2±5.16, MMSE: 27.6±2.51, education: 15.6±2.91, UPDRS: 27.6±5.04 21 PD; 13M/8F, age: 72.38±4.72, MMSE: 27.81±1.36, education: 14.86±2.31, UPDRS: 25.52±5.89	AD: NINCDS-ADRDA – probable DLB: McKeith PDD: Emre	Not defined	GAITRite	Velocity (m/s) Stride length (m) Swing (%) Swing time (s) Stance(%) Double support (%) CV step time (%) CV step length (%) CV stride length (%) CV swing time (%) CV stance time (%) CV double support time (%)	LBD: slower velocity, shorter stride length, increased stance time, increased double support time, decreased CV double support time compared to PD. AD: No differences found between AD and PD. CV measures were not investigated between AD and PD. LBD vs AD: slower velocity, shorter stride length, decreased swing, increased stance time,

						increased double support time, increased CV step time, increased CV step length, increased stride length, CV swing time and took longer to complete TUG compared to AD. DLB vs PDD: No significant differences between groups – CV differences not reported between groups.
Suttanon, et al. [40]	25 AD; 9M/16F, age: 81 (78.4-83.5), MMSE: 21.1 (19.2-23) 25 Controls; 9M/16F, age: 80.4 (78-82.7), MMSE: 29.2 (28.5-29.8)	Not specified	MMSE ≥ 10 – mild-moderate dementia	Forceplate (360cm)	Step width (cm) Step length (cm) Walking speed (m/s)	AD: slower walking speed and shorter step length compared to controls.
Coelho, et al. [41]	12 Mild AD; age: 75.7±6.8, MMSE: 22±2.2, education: 5.5±3.0. 11 Moderate AD; age: 80.1±7.5, MMSE: 16.2±2.2, education: 3.5±1.1	DSM IV - TR	CDR 1: Mild CDR 2: Moderate	Digital camera with passive marker (8m x 1.4m).	Stride length (m) Stride speed (m/s) Cadence (strides/sec)	Moderate AD had a shorter stride length and slower stride speed compared to mild AD.
Tanaka, et al. [42]	15 AD; 15F, age: 79.8±4.6 15 VaD; 15F, age: 80.3±4.4 15 Controls; 15F, age: 78.3±6.9	DSM IIIR	MMSE, CDR	10m walkway 3 times. Measurement of gait parameters not specified.	Walking velocity (m/s) Step length (mm) Step width (mm)	VaD and AD: slower velocity and shorter step length compared to controls VaD: slower velocity and shorter step length compared to AD.

	10 AD; 7M/3F, age: 77.6±5.5, MMSE: 18.9±3.9 10 Controls; 7M/3F, age: 72.4±6.5, MMSE: 28.4±1.7	NINCDS-ADRDA	Not specified	GAITRite (8m)	Speed (m/s) Stride length (m) CV stride length (%) Step width (cm) CV step width (%)	AD: slower speed, shorter stride length and increased CV stride length compared to controls.
Allali, et al. [25]	196 mild AD; 134F, age: 82.5±5.1 177 moderate AD; 121F, age: 83.9±5.6 126 mild non-AD; 71F, age: 81.9±5.1 91 moderate non-AD; 52F, age: 83.3±5.2 108 a-MCI; 40F, age: 76.7±7.9 286 na-MCI; 134F, age: 75.5±6.6 735 Controls; 374F, age: 73.9±6.3	Dementia subtypes: DSM-IV apart from TASCOG cohort (self-report, medical review, cognitive testing, clinical interview) MCI subtypes: spontaneous cognitive complaints and objective impairment in memory/multiple domains	Mild dementia: CDR 1, MMSE ≥20 Moderate: CDR 2, MMSE 19-10	GAITRite (ranging from 4.6m to 7.9m)	Walking speed (cm/s) Stride length (cm) Stride time (ms) Swing time (ms) Stance time (ms) Single support time (ms) Double support time (ms) Stride width (cm) Stride velocity (m/s) CV stride length (%) CV stride time (%) CV swing time (%) CV stance time (%) CV single support time (%) CV double support time (%) CV stride width (%) CV stride velocity (%)	All dementia groups (mild/moderate AD and non-AD) had slower walking speed, shorter stride length, increased CV stride length, longer stride time, increased CV stride time, longer stance time, increased CV stance time, increased CV single support time, longer double support time, increased CV double support time, slower stride velocity and increased CV stride velocity compared to controls. All dementia groups except mild AD demonstrated

							larger stride width and reduced CV stride width variability compared to controls. Only mild AD showed increased single support time compared to controls. Mild dementia: OD had increased CV stride length, larger stride width, reduced CV stride width and increased CV stride velocity compared to AD. Moderate dementia: OD had slower walking speed, shorter stride length, longer stance time, increased CV stance time, larger stride width, and slower stride velocity compared to AD. a-MCI: slower walking speed, increased CV stance time, slower stride velocity and increased CV stride

						velocity compared to controls. na-MCI: slower walking speed, shorter stride length, increased CV stride length, slower stride time, increased CV stride time, longer stance time, increased CV stance time, increased CV single support time, longer double support time, increased CV double support time, slower stride velocity and increased CV stride velocity compared to controls.
Muir, et al. [22]	23 AD; 14F, age: 77.5±5, MMSE: 24.2±2.3, education: 12.3±3.4 29 MCI; 17F, age: 73.6±6.2, MMSE: 27.5±1.9 22 Controls; 19F, age: 71±5, MMSE: 29.5±0.6, education: 13.4±3.1	AD: NINCDS-ADRDA MCI: Subjective memory complaint, report of cognitive deterioration, objective memory impairment in cognitive tests with lack of functional impairment and absence of clinical dementia	CDR 0.5: MCI MMSE 20≥ - AD	GAITRite (600cm x 64cm)	Gait velocity (cm/s) Stride time (ms) CV stride time (%)	No significant differences between groups
Hsu, et al. [30]	21 AD; 10M/11F, age: 61.48±4.85, MMSE: 23±3.23 50 Controls; 20M/30F, age: 59.86±4.62, MMSE: 28.38±1.55	Not specified	Not specified	Wearable device with tri-axial accelerometer, bi-axial gyroscope, uni-axial gyroscope, microcontroller and micro SD flash card	No. of strides (count) Walking time (s) Stride length (m)	AD: higher number of strides, slower walking time, shorter stride length,

	Stride frequency (hz) Stride speed (m/s) Stride cadence (stride/min) Stride time (s) Stance time (s) CV stride time (%) CV stance time (%) CV swing time (%) Stance period (%) Swing time (%) CV stance period (%) CV swing period (%)	slower stride speed, longer stance time, longer stance period, shorter swing period, increased CV stance period and increased CV swing period compared to controls.

Table 2: Recommendations for future research

Key recommendations for future research
• Development of a standardized single-task gait protocol. • Adopting a standardized framework to inform selection of gait characteristics – such as models suggested by Hollman, et al. [14], Lord, et al. [16], Verghese, et al. [52] • More studies are needed to compare gait across the most common subtypes, i.e. AD, DLB, PDD and VaD. • Follow recommended diagnostic criteria for dementia to ensure accuracy of diagnosis in order to compare dementia sub-types (Dubois, et al. [49], McKhann, et al. [50], McKeith, et al. [51], Emre, et al. [53]). • Adherence to guidelines regarding measures for assessing stage of dementia [54, 55]

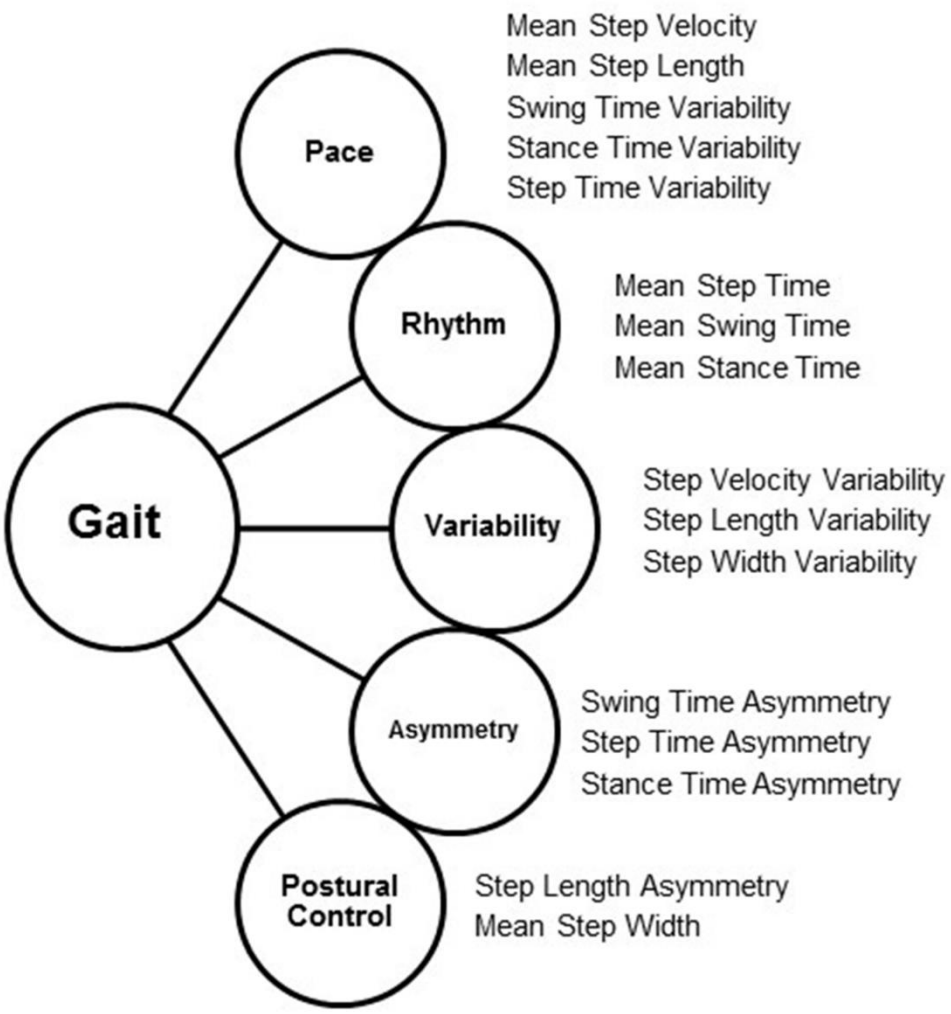


Figure 1: Lord, et al. [16]'s model of gait for older adults. Gait domains include pace, rhythm, variability, asymmetry and postural control.

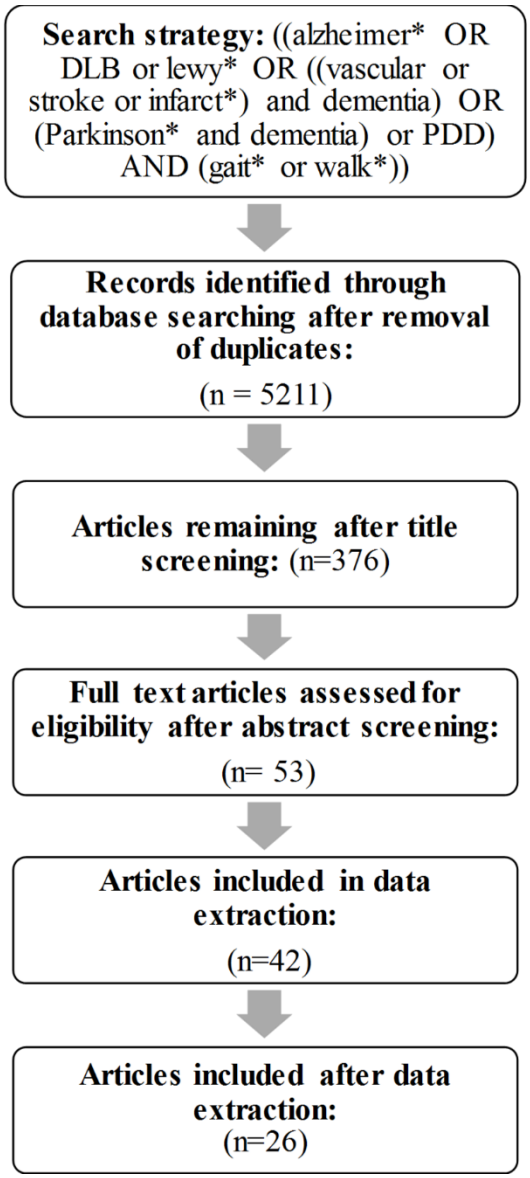
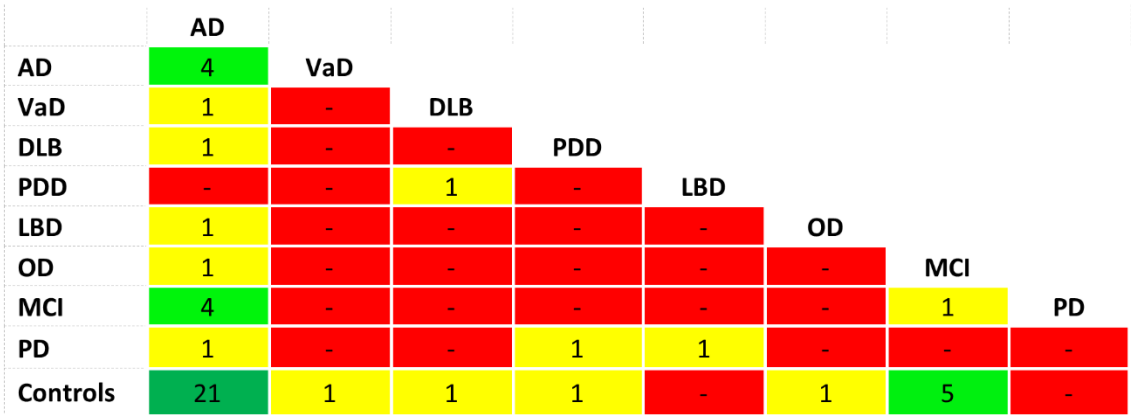


Figure 2: Flowchart of search strategy and extraction of eligible studies.



	AD	VaD	DLB	PDD	LBD	OD	MCI	PD
AD	4							
VaD	1	-						
DLB	1	-	-					
PDD	-	-	1	-				
LBD	1	-	-	-	-			
OD	1	-	-	-	-	-		
MCI	4	-	-	-	-	-	1	
PD	1	-	-	1	1	-	-	-
Controls	21	1	1	1	-	1	5	-

Figure 3: Heat map detailing number of studies comparing groups. AD = Alzheimer's Disease, VaD = Vascular dementia, DLB = Dementia with Lewy bodies, PDD = Parkinson's disease with dementia, LBD = Lewy body dementia, OD = unspecified non-AD dementias, MCI = mild cognitive impairment, PD = Parkinson's disease.

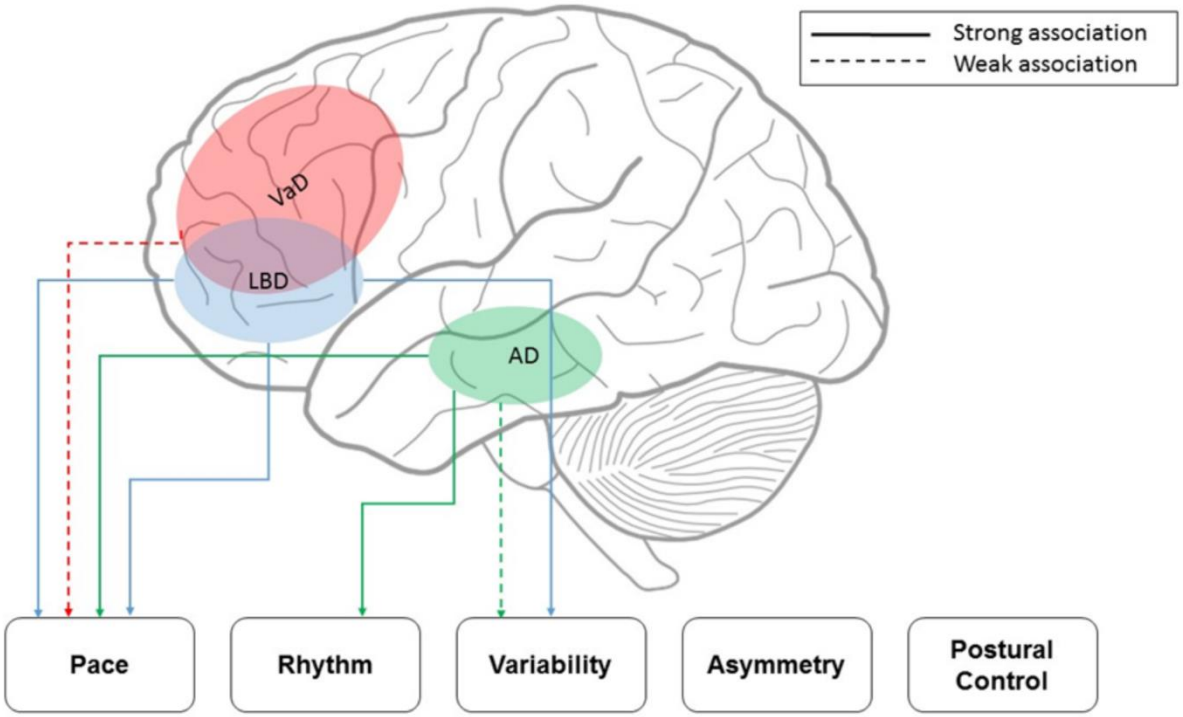


Figure 4: Associations between dementia subtypes and gait implied by the current literature, using Lord, et al. [16]'s as a framework to interpret results.

Supplementary Materials

Supplementary Table 1: Quality assessment of all studies included in this review, as conducted by reviewers R.M.A and J.W.

Study	**Was the research question or objective in this paper clearly stated?**	**Was the study population clearly specified and defined?**	**Were withdrawals reported and explained?**	**Were inclusion and exclusion criteria for participants defined and determined prior to the study onset?**	**Was a sample size justification, power description, or variance and effect estimates provided?**	**Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?**	**Were clinical diagnostic criteria and severity ratings for dementia reported and adhered to?**	**Were key potential confounding variables measured and adjusted statistically for their impact on the outcome(s)?**	**Quality Assessment: Reviewer 1 (R.M.A.)**	**Quality Assessment: Reviewer 2 (J.W.)**
Visser [1]	Yes	No	Yes	No	No	No	No	No	Poor (2/8)	Poor (2/8)
Tanaka, et al. [2]	Yes	Yes	n/a	No	No	No	R.M.A Yes	No	Poor (3/8)	Poor (2/8)

							J.W. No			
Nakamura, et al. [3]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Mediocre (6/8)	Mediocre (6/8)
Nakamura, et al. [4]	Yes	Yes	n/a	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Goldman, et al. [5]	Yes	Yes	No	Yes	No	Yes	R.M.A No J.W. Yes	Yes	Mediocre (5/8)	Mediocre (6/8)
Goldman, et al. [6]	No	Yes	R.M.A Yes J.W. No	Yes	No	Yes	No	Yes	Mediocre (5/8)	Mediocre (4/8)
Webster, et al. [7]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Mediocre (6/8)	Mediocre (6/8)
Merory, et al. [8]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Mediocre (6/8)	Mediocre (6/8)
Gillain, et al. [9]	Yes	Yes	n/a	Yes	Yes	Yes	Yes	No	Mediocre (6/8)	Mediocre (6/8)

Nadkarni, et al. [10]	Yes	Yes	n/a	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Nadkarni, et al. [11]	Yes	Yes	n/a	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Ries, et al. [12]	Yes	Yes	Yes	Yes	No	Yes	R.M.A. No J.W. Yes	No	Mediocre (5/8)	Mediocre (6/8)
Maquet, et al. [13]	Yes	Yes	n/a	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Choi, et al. [14]	Yes	No	n/a	No	No	Yes	No	No	Poor (2/8)	Poor (2/8)
Lamoth, et al. [15]	Yes	Yes	n/a	Yes	No	Yes	Yes	No	Mediocre (5/8)	Mediocre (5/8)
Coelho, et al. [16]	Yes	No	R.M.A. Yes J.W. No	R.M.A. No J.W. Yes	No	Yes	Yes	No	Mediocre (4/8)	Mediocre (4/8)
Muir, et al. [17]	Yes	Yes	n/a	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)

Nadkarni, et al. [18]	Yes	Yes	n/a	Yes	No	No	Yes	Yes	Mediocre (5/8)	Mediocre (5/8)
Suttanon, et al. [19]	Yes	Yes	n/a	Yes	R.M.A. No J.W. Yes	Yes	No	Yes	Mediocre (5/8)	Mediocre (6/8)
Hsu, et al. [20]	No	Yes	n/a	Yes	No	Yes	No	No	Poor (3/8)	Poor (3/8)
Barbieri, et al. [21]	Yes	No	R.M.A. Yes J.W. n/a	No	No	Yes	No	Yes	Mediocre (4/8)	Poor (3/8)
Gras, et al. [22]	Yes	No	n/a	No	No	Yes	No	Yes	Poor (3/8)	Poor (3/8)
Simieli, et al. [23]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)
Allali, et al. [24]	Yes	Yes	Yes	Yes	No	No	No	Yes	Mediocre (4/8)	Mediocre (5/8)
Fritz, et al. [25]	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Mediocre (6/8)	Mediocre (6/8)

Lin, et al. [26]	Yes	Yes	n/a	No	No	Yes	No	Yes	Mediocre (4/8)	Mediocre (4/8)
									Total: **0 Good** **21 Mediocre** **5 Poor**	**Total:** **0 Good** **20 Mediocre** **6 Poor**

Supplementary Table 2: Definitions for commonly described characteristics of gait.

Gait Terms:	**Definition:**
Step	Every time a leg goes forward during walking
Step Length	Distance between the heel of a trailing foot and the heel of the leading foot.
Stride	When both a left and right footstep have been taken
Stride time	The time it takes to make a stride – also referred to as **gait cycle duration.**
Stance	When the foot is on the ground during walking – also referred to as **single support duration.**
Swing	When the foot is not on the ground during walking
Double Support	When both feet are on the ground during walking.
Velocity	Refers to the **speed** of walking – calculated as distance/time
Cadence	Number of steps per defined time measure (e.g. steps per minute)
Step width	Mediolateral distance between heels during double support
Pace	How fast or slow someone walks
Rhythm	Refers to temporal characteristics of walking, such as swing, stance and step time.
Variability	Changes in spatio-temporal parameters of gait, usually regarding step-to-step fluctuations. E.g. how much step length changes from one step to the next.
Asymmetry	The ratio between right and left steps
Postural control	Referring to characteristics contributing to keeping individuals upright during walking.

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