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Gait characteristics as indicators of cognitive impairment in geriatric patients

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WALKING ABILITY TO PREDICT FUTURE COGNITIVE DECLINE IN OLD ADULTS: A SCOPING REVIEW

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ABSTRACT

Early identification of individuals at risk for cognitive decline may facilitate the selection of those who benefit most from interventions. Current models predicting cognitive decline include neuropsychological and/or biological markers. Additional markers based on walking ability might improve accuracy and specificity of these models because motor and cognitive functions share neuroanatomical structures and psychological processes. We reviewed the relationship between walking ability at one point of (mid)life and cognitive changes at follow-up. A systematic literature search identified 20 longitudinal studies. The average follow-up time was 4.5 years. Gait speed quantified walking ability in most studies (n=18). Additional gait measures (n=4) were step frequency, variability and step-length. Despite methodological weaknesses, results revealed that gait slowing (0.68-1.1 m/sec) preceded cognitive decline and the presence of dementia syndromes (maximal odds and hazard ratios of 10.4 and 11.1, respectively). The results indicate that measures of walking ability could serve as additional markers to predict cognitive decline. However, gait speed alone might lack specificity. We recommend gait analysis, including dynamic gait parameters, in clinical evaluations of patients with suspected cognitive decline. Future studies should focus on examining the specificity and accuracy of various gait characteristics to predict future cognitive decline.

Keywords: Dementia, cognitive impairment, biomarker, gait, MCI, prediction models



INTRODUCTION

Rationale

The increase in the number of old adults nearly parallels the incidence of age-associated dementia worldwide [1, 2]. Data suggest that the pathophysiological processes of dementia may start several years or even decades before the eventual diagnosis [3, 4]. Patients progress from a preclinical phase during which the disease might have already started in the brain without overt clinical symptoms, followed by a period characterized by the presence of Mild Cognitive Impairments (MCI), culminating in a diagnosis of dementia [5]. In the absence of a cure, key strategies of disease management include early diagnosis, delaying disease onset, and a slowing of disease progression [6, 7]. Therefore, identifying markers that predict dementia is a major subject of current interest [8, 9].

Prediction of dementia is often studied in the context of MCI [10], which is a transitional state between a cognitively intact condition and dementia [11]. Patients with MCI have cognitive dysfunctions beyond those expected as a result of normal aging, yet the level of impairment is not severe enough to compromise the ability to perform activities of daily living [12]. Even though the published values vary, a recent review analysing population data (> 300 participants) estimated the prevalence of MCI to range from 16 to 20% in patients over age 60. Approximately 10 to 15% of these patients develop dementia annually [13]. This conversion rate is high, making it important to differentiate between patients who will develop dementia and those who will remain cognitively fit. Early identification of patients at risk for dementia might help to select those individuals who would benefit most from future interventions to delay disease onset and slow the progression of neurodegeneration [14].

Biomarkers in prediction models for dementia

Biomarkers are used to identify pre-dementia symptoms and can be broadly classified as (1) cognitive markers (test scores measuring cognitive functioning such as memory and executive function) and (2) biological markers (such as measures derived from cerebrospinal fluid and brain imaging). The most accurate predictors are memory tasks measuring long-delay free recall [15-19], the cerebrospinal fluid (CSF) markers A β 1-42/t-tau ratio [15, 20-22], and volumes of the hippocampal and entorhinal cortices [15, 20, 23-25]. However, single predictors seem to be insufficiently sensitive to predict conversion from MCI to dementia. Therefore, prediction models ultimately employ a combination of markers [26]. Nevertheless, such predictions are far from perfect, as age, duration of follow-up, subtype of MCI diagnosis, degree of cognitive decline (early versus late stage of MCI), and outcome (e.g., AD, mixed dementia) all seem to affect conversion rates [16]; [27]; [28]. For example, a recent study showed that both neuropsychological assessment and MRI variables can predict conversion to AD with 63% to 67% classification accuracy in patients with MCI both younger and older than 75, while CSF biomarkers reached this rate only in patients younger than 75 years old [16]. A systematic review about risk prediction models for dementia concluded that sensitivity and specificity values vary broadly between studies, (Area Under the Curve ranging from AUC = 50 to AUC = 87). In particular, specificity is low in numerous prediction models [29], complicating the clinical use of such models.

Taken together, these observations show that it remains a persistent challenge and should be a research priority to develop dementia prediction models that ultimately employ a combination of markers to differentiate between old adults who will and who will not develop dementia. Current prediction models show low to moderate predictive ability with large variability, making it necessary to explore new markers. A possible candidate is motor function, in which walking ability may serve as a potential marker in the prediction of cognitive decline [30-32].

Walking ability as a predictor of cognitive decline

The original observation of a correlation between motor and cognitive impairments was reported nearly two decades ago. The data suggested that motor slowing (e.g., low walking speed) precedes cognitive decline in healthy older adults [33], a finding substantiated by the relationship between reductions in gait function and the development of dementia [34]. Numerous cross-sectional and longitudinal studies have recently confirmed these initial findings [35-38].

Viewing walking as a complex task could increase its validity to serve as a marker for early cognitive decline. Indeed, imaging and brain stimulation studies suggest that higher brain centres are involved in the planning and execution of normal human locomotion [39] and balance [40, 41]. The widespread network of brain areas that control walking involves regions responsible for attentional, executive and visuospatial functions as well as areas needed to perform and control motor tasks, such as the cerebellum, basal ganglia and motor cortex [42]. Thus, there is an overlap between areas that control walking and areas that control cognitive functioning, explaining the relationship between dementia-related pathology and gait dysfunction. The co-occurrence of decline in both cognitive and gait function favours a 'common-cause' mechanism [43]. There is considerable evidence for the role of white matter damage in age-related cognitive decline and dementia [44, 45]. In addition, reduced grey and white matter volumes in multiple brain regions and white matter hyperintensities are associated with gait dysfunction (gait speed of <0.5 m/s) in old adults free from dementia [46].

Perhaps the simplest demonstration of the interrelationship between gait and cognition comes from dual task studies in which subjects perform a walking and cognitively demanding task concurrently [47]. 'Dual task cost', i.e., the magnitude of deterioration in gait performance measured during single vs. dual tasking, arises from the two interfering tasks competing for the same cortical resources [48]. It is noteworthy that dual task costs are often higher in cognitively impaired compared to cognitively intact elderly [48-51].

The effects of decline in cognition on walking are especially expressed in the slowing of gait. A ubiquitous observation from cross-sectional studies is the reduction of gait speed in patients with MCI [52-54] and dementia [37, 38, 51, 55]. In addition to gait speed, spatial variability and stride time variability (STV) tend to increase in patients with MCI [56, 57]. However, for the time being, most studies have cross-sectional designs and are restricted to gait speed as a measure of walking ability.



Aims

The co-occurrence of gait dysfunction and decline in cognitive function as derived from cross-sectional studies suggests that measures of walking ability could serve as a marker in the identification of individuals at risk to develop dementia. To verify the possibility that gait dysfunction precedes cognitive decline, we set the aim of the present review to scope evidence from longitudinal studies that assessed whether or not there is a relationship between walking ability at one point of (mid)life and cognitive decline years later. In addition, we critically evaluate and discuss methodologies used to determine this relationship and to formulate recommendations for future studies to expand the preclinical phase of dementia.

METHODS

Scoping review

A scoping review method was adopted to explore the depth of evidence for the putative role of walking ability in the prediction of cognitive decline. A scoping review provides an appropriate method to systematically scan and evaluate evidence within a specific area of research and to identify gaps in the existing literature, allowing variation in methods between studies selected for inclusion [58, 59].

Literature search

A systematic literature search was performed for studies published from 1980 till May 2015 in PubMed and Embase using keywords specific to Embase thesaurus (EMtree) and to PubMed in the form of Medical Subject Headings (Mesh), combined with non-specific terms. We used a cognitive term (cognitive decline, MCI, cognitive impairment, dementia), combined it with a walking term (gait, walking, locomotion, motor performance, motor slowing), and terms representing a longitudinal study design (follow-up, longitudinal, long-term, prospective, cohort, predict). Filters further focused the search by removing various clinical conditions. Figure 1 presents the syntax.

Inclusion, exclusion criteria

The inclusion criteria were specified as followed: (1) Quantitative gait analysis measurements at baseline, (2) Study populations consisting of older adults with a mean age of 65 or older with significant cognitive decline or cognitive decline clinically diagnosed (e.g., MCI, dementia, Alzheimer's disease) at follow-up, (3) a longitudinal study design, and (4) English as publication language. The exclusion criteria were specified as followed: 1) Cognitive impairment with clinical diagnosis other than related to dementia (e.g., Multiple Sclerosis, Huntington's disease, and Parkinson's disease), 2) animal research, and 3) case studies. Duplicates and reviews were removed. Two reviewers were involved in the literature search and independently selected studies for in- and exclusion. Disagreement between the researchers was discussed until they reached consensus.

Data analysis

The literature revealed two types of studies investigating the relationship between walking ability and future cognitive decline, which are presented separately in the review: 1) longitudinal studies that examined associations between baseline walking ability and

within-person change in cognition at follow-up (with most results presented as beta-values) and 2) longitudinal studies that established risk estimates for cognitive decline at follow-up, with measures of walking ability as predictors (with most results presented as hazard ratios or odds ratios).

RESULTS

Literature search

The literature search revealed 431 studies of which after screening for title and abstract, 50 were assessed for eligibility by full-text analysis. Finally, 20 articles met the criteria for inclusion. A flowchart of the literature search and selection process is presented in figure 1.

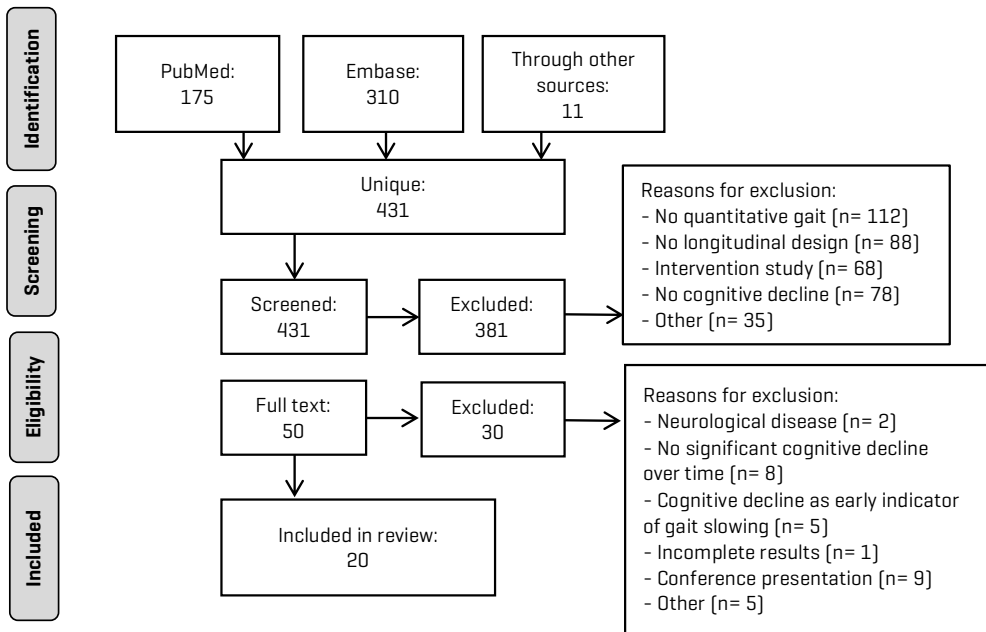



Figure 1. Syntax of literature search and selection process.

Study characteristics

Studies included in the current review were heterogeneous in terms of number of participants (ranging from 52 to 2776), age (> 60 to > 80) and length of follow-up (ranging from 2 to 9 years) and are based on data from 24,368 participants. Retention rate was 71% between baseline and follow-up measurement (n = 19 studies), with mortality accounting for most of the attrition. Two studies (10%) were sex-homogeneous (Table 2; Ref. 2 & 14) and sixteen studies (80%) showed large age ranges (> 10 years) or high standard deviations from the mean age (> 3 years). Patients were cognitively healthy at baseline in most studies (n = 17). Three studies included patients with pre-dementia syndromes at baseline [60-62]. Statistical models were adjusted for cofounding variables grossly representing the



following domains: sociodemographic (age, sex, education, gender), behavioural (physical activity, smoking), clinical conditions (heart disease, stroke, diabetes mellitus, hypertension, osteoporosis, arthritis, depression and pain), visual functioning (visual acuity), health-related (BMI, blood pressure) and genetic factors (APOE ε4 allele).

Measures of walking ability and cognitive function

Walking ability was mainly quantified using gait speed ($n = 18$ studies; 90%), either measured over a certain distance or by the completion of a bidirectional walk. Only a few studies ($n = 3$, Table 1; Ref 2 & 8 and Table 2; Ref 9) quantified walking by other gait characteristics such as step frequency, stride length, cadence, stance time, swing time and double support time. One study assessed multiple aspects of walking as revealed by factor analysis, namely pacing (loading on gait speed and step length), rhythm (loading on cadence and timing measures) and variability (loading on stride length variability and swing time variability) [63]. For the assessment of cognition as main outcome at follow-up, four studies (20%) used measures of global mental state (assessed by mini mental state examination (MMSE) or modified versions) (Table 1; Ref 1, 2, 4 & 5), four studies (20%) used measures of specific cognitive functions (e.g., memory, executive functioning and processing speed) (Table 1; Ref 3, 6, 7 & 8), and twelve studies (60%) used diagnoses of dementia syndromes (e.g., dementia, AD, MCI, vascular dementia) (Table 2; Ref 1, 2, 3, 4, 6, 8, 9, 10, 11, 12, 13 & 14). Cognitive state at baseline was assessed using various measurement instruments to indicate global mental state, such as the MMSE, and guidelines to indicate dementia syndromes, such as DSMM IV and clinical dementia rating (CDR) scale.

The relationship between walking ability and future cognitive decline

Longitudinal studies that examined associations between baseline walking ability and within-person change in cognition at follow-up

Table 1 presents the eight studies that determined the relative association between baseline walking ability and within-subject change in cognition at follow-up ($n = 9,984$). Baseline walking ability was quantified with gait speed in five studies (62.5%) with a mean habitual gait speed of 1.00 m/s ($n = 7,532$) measured on a straight course with distances ranging from 2.5 meters to 7 meters. The other three studies could not serve as a reference because the authors reported gait speed as ranges instead of a mean value (Ojagbemi et al., 2015) or used walking tasks involving a turn that slows gait and would bias the data in the present patient description (Alfaro-Acha et al., 2007; Katsumata et al., 2011).

Standardized beta-coefficients were reported as outcome measure with positive values indicating a yearly increase or preservation of cognition in relation to a unit higher gait performance at baseline, and negative values indicating a yearly decline in cognition in relation to a unit lower gait performance at baseline. For example, a unit increase in time to walk 8-feet predicts 0.21 points decline in MMSE score per year ($\beta = -0.21$, [64]). One study reported estimated test scores on mental state to indicate cognitive decline in relation to baseline walking ability and found an increase of 2.00 and 2.31 in square root of number of errors in the Japanese version of the MMSE, for slow and fast TUG time respectively [65]. All associations were relative to baseline walking ability of the reference group.

With respect to studies using measures of mental state as main outcome, slow gait speed at baseline was associated with decline in MMSE score at follow-up ($\beta = -0.21, p < 0.01$) (Table 1; Ref 1). In addition, longer step length in men at baseline was associated with preserved MMSE score at follow-up ($\beta = 0.162, p < 0.05$) (Table 2; Ref 2). Furthermore, faster gait speed at baseline correlated with preserved MMSE score at follow-up, but only under fast speed instructions ($\beta = 0.038, p < 0.05$) (Table 1; Ref 4). Finally, longer time to complete the TUG test was associated with decline in the Japanese version of the MMSE ($p = 0.03$) (Table 1; Ref 5). With respect to studies using measures of specific cognitive functions as main outcomes ($n=4$), faster gait speed at baseline was associated with preservation of executive functioning ($\beta = 0.036, p < 0.01$; $\beta = 0.060, p < 0.01$) (Table 1; Ref 3 & 6), memory ($\beta = 0.031, p < 0.05$; $\beta = 1.24, p < 0.01$) (Table 1; Ref 3 & 7), processing speed ($\beta = 0.025, p < 0.05$) [36] and visuospatial functioning ($\beta = 0.042, p < 0.05$) (Table 1; Ref 6) at follow-up. In addition to gait speed, impaired pacing at baseline was associated with a decline in the digit symbol test and letter fluency task (both relying on executive functioning) at follow up ($\beta = -0.73, p < 0.001$ and $\beta = -0.46, p < 0.001$, respectively) (Table 1; Ref 8). Impaired rhythm at baseline was associated with decline in memory at follow-up ($\beta = -0.15, p < 0.05$) (Table 1; Ref 8).

In summary, slow gait speed (under habitual and fast speed instructions) at baseline was related to decline in global mental state, executive function, memory performance, processing speed and visuospatial function, after a mean follow-up period of 4.3 years. Shorter step length in men and longer time to complete the TUG test at baseline were associated with decline in measures of global mental state at follow-up. Impaired rhythm at baseline was associated with decline in memory functioning and impaired pacing with decline in executive functioning at follow-up. The results indicate that slow gait speed precedes decline in mental state as well as in specific cognitive functions. Although there is limited evidence for gait characteristics other than gait speed, the results signify that dysfunctions in those characteristics also precede cognitive decline.

Longitudinal studies that established risk estimates for cognitive decline, with measures of walking ability as predictors

Table 2 summarizes 14 studies that examined the relative risk for cognitive decline, predicted by walking ability at baseline ($n = 14,384$). Participants developed dementia (43%), Alzheimer's disease (29%), vascular dementia (14%), MCI (7%) or other diagnosed cognitive impairment (50%), in which some studies examined multiple syndromes. Mean baseline gait speed of participants who remained free from significant cognitive decline at follow-up was 1.11 m/s, based on four studies providing this information ($n = 2,921$). In contrast, mean baseline gait speed of participants who developed dementia, MCI and cognitive impairment was respectively 0.8 m/s ($n = 2631$), 0.91 m/s ($n = 204$) and 0.68 m/s ($n = 85$). The other seven studies either used gait speed ranges, gait variability, pace or rhythm measures, or did not distinct between cognitive subgroups. Gait speed was measured over walking distances ranging from 2.5 meters to 9 meters.

Outcomes are presented as risk ratios (hazard ratio, odds ratio or relative hazard). Odds ratios (OR) were reported most often, with values above one signifying a higher relative risk compared to the reference group. For example, patients with slow versus fast gait speed at baseline were 2.28 times more likely to be diagnosed with dementia at follow-up



[66]. Second, hazard ratios (HR) were reported with values < 1.0 indicating a risk reduction in cognitive decline with better gait performance at baseline and values > 1.0 indicating increased risk at cognitive decline predicted from gait performance at baseline, both proportionally to a comparison group. For example, patients with motoric cognitive risk (MCR) syndrome had an 11-fold risk (HR = 11.1) to develop dementia at any given point in time [60]. One study reported a relative hazard of 1.57 [67], meaning that patients with slower gait speed at baseline were 1.57 times more likely to have developed dementia after 7 years compared to the reference group. Another study reported a transition point in the acceleration of gait speed decline 12.1 years prior to cognitive decline [68], indicating that changes in gait were already visible 12.1 years prior to significant cognitive decline.

With respect to studies using dementia as main outcome, slow gait speed at baseline was related to an increased risk for dementia at follow-up (OR = 2.28, $p < 0.05$; RH = 1.57, $p < 0.05$; HR = 2.72, $p < 0.05$; OR = 5.6; OR = 10.4; HR = 0.79, $p < 0.001$; HR = 0.78, $p < 0.01$; OR = 1.61, $p < 0.05$) (Table 2; Ref 1, 2, 11-14, respectively). Also, impaired rhythm and high variability at baseline were related to increased risks for dementia at follow-up (HR = 1.48, $p < 0.05$ and HR = 1.37, $p < 0.05$, respectively) (Table 2; Ref 10). In addition to studies examining the risk for dementia, several studies revealed that slow gait speed at baseline was also related to increased risk for Alzheimer's disease (OR = 3.38, $p < 0.05$; HR = 0.81, $p < 0.01$) (Table 2; Ref 1 & 13) as well as vascular dementia (HR = 11.10, $p < 0.001$) (Table 2; Ref 11) at follow-up. Note that in some studies patients were diagnosed with MCI at baseline (Table 2), explaining the large risk ratios [38, 61, 62]. Impaired pacing was also related to increased risk for vascular dementia (HR = 1.61, $p < 0.05$) (Table 1; Ref 10). The risk for significant cognitive impairments other than dementia syndromes at follow-up was determined using various definitions, for example > 3 points decline in MMSE score, > 0.5 points at the CDR scale, and more than 9 points decline in digit symbol substitution test (DSST) score. All studies concluded that slow gait speed at baseline predicted a significant increase in risk for cognitive impairment at follow-up. One study found shorter step length to be related to increased risk for cognitive decline and found higher risks for step length compared to gait speed and for gait under fast speed instructions compared to habitual gait speed [69].

In summary, slow gait speed at baseline was related to an increased risk for dementia, Alzheimer's disease, and significant cognitive decline as defined in specific studies, after a mean follow-up period of nearly 5 years. In addition, poor gait rhythm and high gait variability were related to increased risk for dementia, and worse performance on the pace factor was related to increased risks for vascular dementia. Altogether, the longitudinal data shows that slowed gait speed appears before cognitive decline is detected. Despite the limited number of studies reporting on other gait characteristics, the results of these studies point in the same direction.

DISCUSSION

The present scoping review aimed to examine the relationship between walking ability and future cognitive decline. The main finding supported the hypothesis that walking ability at baseline, independent of gait characteristic, has the potential to predict future cognitive decline through (1) an association between poor walking ability at baseline and within-person decline in cognition at follow-up and (2) a higher risk for cognitive impairment/dementia with poor walking ability at baseline as predictor variable. We provide an in-depth analysis of methodological inequalities between studies and synthesize the information into one key recommendation, i.e., clinicians should add walking ability as a quantitative and simple preclinical measurement to the array of tests used to predict cognitive decline in old adults.

The analyses of the longitudinal studies, with a mean follow-up period of 4.3 years, that examined associations between baseline walking ability and within-person change in cognition at follow-up (Table 1) revealed that slow gait speed (1.00 m/s) at baseline preceded decline in global mental state as well as in specific cognitive functions. A role for walking ability in the prediction of cognitive decline is supported by the finding that slower gait speed at baseline predicted increased risks for diagnostic outcomes related to dementia, after a mean follow-up period of nearly 5 years (Table 2). Mean baseline gait speed of old adults who developed dementia, MCI and cognitive impairment was respectively 0.8 m/s (n = 2631), 0.91 m/s (n = 204) and 0.68 m/s (n = 85), in contrast to mean baseline gait speed of participants who remained free from significant cognitive decline (1.11 m/s). Mean gait speed values are far beneath standard values of 1.15 [70], 1.22 (Hortobágyi et al., 2015), and 1.30 m/s [71] reported previously. In contrast, a mean gait speed of 1.00 m/s or lower is often used as a cut-off point for high risks for negative health outcomes such as hospitalization and death [72]. To rule out frailty, a reference of > 0.90 m/s is used [73]. Together, subject and gait characteristics suggest that the results are relevant to older adults who are cognitively healthy at baseline, mostly not frail, but less fit than healthy older adults. (Table 2).

Walking ability in the prediction of cognitive decline

Gait speed is most often used to evaluate the relationship between walking ability and future cognitive decline. This finding is not unexpected because gait speed is associated with many adverse health and clinical outcomes in healthy and mobility-impaired old adults [72, 74]. Slowing of habitual gait speed represents an important characteristic of reduced physical capacity as a result of the aging process, with slowing of gait speed up to 16% per decade in individuals over 60 [66, 71, 75]. A possible explanation for slow gait speed preceding the development of cognitive decline is that it may represent a marker of lesions in the brain resulting from pathophysiological changes related to cognitive decline. Age-related cognitive decline and dementia have been associated with white matter damage [44, 45]. This damage in white matter volumes in turn has been found to affect gait speed (gait speed of <0.5 m/s), even in older adults free from dementia [46]. Thus, slowing of gait speed might be an early indicator of the presence of brain lesions. An additional explanation for the association between slow gait speed and cognitive decline may be found in the relationship between muscle strength and slow gait speed. Loss of muscle strength has been associated with high levels of inflammatory markers, low levels of corticosteroids and high oxidative

Table 1. Walking ability in the prediction of cognitive decline: longitudinal studies that examined associations between baseline walking ability and within-person change in cognition at follow-up.

Author, Year	Study	No. of participants	Follow-up (years)	Base-line age	Baseline gait (mean \pm SD)	Baseline cognition
Alfaro-Acha et al., 2007 [64]	Hispanic Established Population for the Epidemiological Study of the Elderly	1218	7	>65	Timed 8-foot walk (s): 7.7 \pm 6.4	MMSE: 26.5 \pm 2.9
Auyeung et al., 2011 [79]	General Population of Older Chinese	1514 men	4	>65	Gait speed (m/s): 1.04 \pm 0.21 Step length (m): 0.58 \pm 0.07	MMSE: 27.4 \pm 2.25
		1223 women	4		Gait speed: 0.94 \pm 0.19 Step length: 0.51 \pm 0.07	25.8 \pm 2.80
Gale et al., 2014 [36]	The English Longitudinal Study of Ageing	2654	6	60-90	Gait speed (m/s): 0.92 \pm 0.27	EF ^a : 19.57(5.85) Verbal memory ^b : 9.53(3.13) Proc speed ^c : 18.8(5.50)
Deshpande et al., 2009 [84]	The InCHIANTI study	584	3	>65	Gait speed (m/s): Usual: 1.23 \pm 0.26 Fast: 1.49 \pm 0.33 Dual-task: 0.98 \pm 0.28	MMSE: N.A.
Katsumata et al., 2011 [65]	Keys To Optimal Cognitive Aging (KOCO) Project	192	3	>80	- Fast or normal TUG time (<14s) - Slow TUG time (>14s)	JMMSE: N.A EF: N.A Memory: N.A
Mielke et al., 2013 [96]	Mayo Clinic Study of Aging	1158	4	70-89	Gait speed: 1.09 (95% CI 0.95,1.27)	Memory ^d : 0.21(-0.39,0.86) Language ^e : 0.26(-0.30,0.82) EF ^f : 0.34(-0.26,0.83) Visuospatial ^g : 0.26(-0.38,0.80) Global cognition ^h : 0.30(-0.25,0.90)

To be continued on the next page

Follow-up cognition	Main results	Change in cognition (in relation to baseline gait)
N.A.	Subjects in the lowest 8-foot walk time quartile (≥ 9 s) had greater cognitive decline over 7 years than those in the highest quartile (< 4 s) ($p < 0.001$). A unit increase in walk time predicts 0.21 points decline in MMSE score per year.	<u>Timed 8-foot walk:</u> β (SE) MMSE: -0.21 (0.06)**
N.A.	Shorter step length in men was associated with a lower MMSE score after 4 years ($p < 0.05$). A unit increase in step length predicts 0.162 points increase in MMSE score per year.	<u>Step length men:</u> β (95% CI) MMSE: 0.162 (0.013, 0.309)*
EF ^a : 19.03(6.28) Verbal memory ^b : 9.21(3.34) Proc speed ^c : 17.57(5.45)	Slower gait speed at baseline was associated with cognitive decline at follow-up in all domains ($p < 0.01$; $p = 0.015$; $p = 0.038$ respectively). A unit increase in gait speed is associated with 0.036, 0.031 and 0.025 less decline in cognitive functioning per year, respectively.	<u>Gait speed:</u> β (SE) EF: 0.036(0.013)** β (SE) verbal memory: 0.031(0.013)* β (SE) proc speed: 0.025(0.012)*
> 3 points decline in MMSE score	Slow gait at fast speed was a predictor of cognitive decline over 3 years ($p < 0.021$). A unit increase in gait speed was associated with 0.038 less decline in MMSE score per year.	<u>Gait speed:</u> β (SE) MMSE: 0.038(0.016)*
JMMSE: N.A EF: N.A Memory: N.A	Slow TUG time was associated with decline in JMMSE functioning after 3 years ($p = 0.03$) but was only cross-sectional associated with EF and memory. An increase of 2.00 and 2.31 in square root of number of errors in the JMMSE, for slow and fast TUG time respectively.	<u>Estimated test score global cognitive functioning:</u> Slow TUG (95% CI): 2.00(1.85,2.15) Normal TUG (95% CI): 2.31(2.08,2.55)
Memory ^d : N.A. Language ^e : N.A. EF ^f : N.A. Visuospatial ^g : N.A. Global cognition ^h : N.A.	A faster gait speed at baseline was associated with less cognitive decline in the following domains (EF $p = 0.001$, visuospatial $p = 0.013$, global cognition $p = 0.001$). A 1 m/s increase in gait speed was associated with a 0.060, 0.042 and 0.049 higher z-score in cognitive domains per year, respectively.	<u>Gait speed:</u> β (SE) EF: 0.060 (0.016)** β (SE) visuospatial: 0.042 (0.017)* β (SE) global: 0.049 (0.013)**



Table 1. Continued

Author, Year	Study	No. of participants	Follow-up (years)	Base-line age	Baseline gait (mean ± SD)	Baseline cognition
Ojagbemi et al., 2015 [97]	Ibadan study of aging (ISA)	1042	2	>65	Gait speed N.A. Gait quartiles	10-word delayed recall test: N.A.
Vergheze et al., 2007 [63]	Einstein Ageing Study	399	5	>70	Gait factors: Pace Rhythm Variability	Memory ⁱ : N.A. Digit symbol: N.A. Letter fluency: N.A. Digit Span: N.A.

NOTE. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

a. EF measured with animal naming b. Measured with intermediate and delayed recall c. Measured with the letter cancelation task d. Wechsler Memory Scale-Revised Logical Memory and Visual Reproduction tasks and the Auditory Verbal Learning task e. Boston naming test and category fluency f. Free and Cued Selective Reminding Test g. Picture completion and block design h. Global cognitive test scores i. Trial making test B and Digit Symbol Substitution subtest. SD= standard deviation, SE= standard error, CI= confidence interval, SD= standard deviation, EF= executive functioning, (J)MMSE= (Japanese version of) the Mini Mental State Examination, proc. Speed= processing speed, TUG= Timed Up and Go, N.A.= not available.

Follow-up cognition	Main results	Change in cognition (in relation to baseline gait)
10-word delayed recall test: 11.49±0.32	A slower baseline gait speed was independently associated with poorer follow-up cognition ($p=0.001$). The slowest gait category (>6.52s 3m) had 1.24 less words recalled at follow-up, compared to the fastest gait category (<4.82s 4m).	<u>Gait speed:</u> β (95% CI) recall test: 1.24 (0.48,2.00)**
Memory [†] : N.A. Digit symbol: N.A. Letter fluency: N.A. Digit Span: N.A.	Impaired pace and rhythm scores predicted cognitive decline in memory ($p=0.02$), digit symbol ($p<0.001$) and letter fluency ($p<0.001$). A 1 point increase in rhythm was associated with 0.15 points decrease in memory per year. A 1 point increase in pace score was associated with 0.73 and 0.46 decrease in digit symbol and letter fluency per year, respectively.	<u>Rhythm factor:</u> β (95% CI) memory: -0.15(-0.28,-0.02)* <u>Pace factor:</u> β (95% CI) digit symbol: -0.73(-1.15,-0.31)*** β (95% CI) letter fluency: -0.46(-0.82,-0.11)***

Table 2. Walking ability in the prediction of cognitive decline: longitudinal studies that established risk estimates for cognitive decline, with measures of walking ability as predictors.

Author, Year	Study	No. of participants	Follow-up (years)	Age	Baseline gait (by final diagnosis)	Baseline cognition
Abellan van Kan et al., 2012 [66]	The EPIDOS-Toulouse Cohort	647	7	>75	Gait speed (m/s): CH: 0.9±0.2 Dementia: 0.8±0.2	CH: SPMSQ >8
Abbott et al., 2004 [67]	The Honolulu-Asia Aging Study	2257	7	71-93	Timed 10 feet walk: N.A.	CH: CASI >74
Buracchio et al., 2010 [98]	Oregon Brain Aging Study (OBAS)	204	9	>65	Gait speed (m/s): CH: 0.96±0.23 MCI: 0.91±0.24	CH: MMSE ≥24, CDR=0, no depression (GDS)
Camicioli et al., 1998 [33]	Oregon Brain Aging Study	85	3	>65	Timed 30-foot walk (s): CH: 9.6±2.3 IC: 13.2±4.5	CH: CDR=0
Deshpande et al., 2009 [84]	The InCHIANTI study	584	3	>65	Gait speed (m/s): Usual: 1.23±0.26 Fast: 1.49±0.33 Dual-task: 0.98±0.28	CH: MMSE: N.A.

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Clinical decline or diagnosis at follow-up (cognitive measure)	Main results	Change in cognition (in relation to baseline gait)
<u>AD:</u> National Institute of Neurological Disorders/Alzheimer's Disease and Related Disorders Association <u>Dementia:</u> DSMM IV	Gait speed decline was an independently associated factor for subsequent dementia and AD as a continuous (m/s) and as a categorical variable ($p < 0.05$).	<u>Continuous gait speed:</u> OR (95% CI) dementia: 2.28(1.32,3.94)* OR (95% CI) AD: 3.38(1.80,6.33)* <u>Categorical gait speed:</u> OR (95% CI) dementia: 2.38(1.28,4.43)*
<u>Dementia:</u> DSMM III	Men who walked 10 feet in > 6 seconds, incidence was 20.2/1000 person-years compared with 13.1 per 1000 person years for those with gait times of 3 seconds or less.	<u>Timed 10 feet walk:</u> RH (95% CI) dementia: 1.57(0.77,3.21)*
<u>MCI:</u> CDR ≥ 0.5	The decrease in gait speed accelerated by 0.02 m/s/year ($p < 0.001$) occurring 12.1 years prior to the onset of MCI. Approximately 14 years prior to diagnosis in men, and 6 years in women.	<u>Change point</u> Years (95% CI): Men: 14.2(8.7,UNK) Women: 6.0(4.6,9.5) Combined: 12.1(8.1,UNK)
<u>Impaired cognition:</u> CDR: > 0.5	Patients who developed cognitive impairments had longer time to walk 30 feet at baseline compared to patients who remained cognitively intact ($p < 0.001$). Every 1-second increase was associated with an increased odds of cognitive impairment of 1.26 ($p = 0.05$).	<u>Timed 30-foot walk:</u> OR (95% CI) IC: 1.26(1.01,1.6)*
<u>Significant cognitive decline:</u> > 3 points decline in MMSE score	Participants in the slowest quartile of usual (< 1.08 m/s) and 'dual task' speed (< 0.81) were more likely to develop SCD ($p = 0.019$ and $p = 0.024$). Participants in the third (1.49-1.30m/s) as well as fourth (< 1.30 m/s) quartile of fast speed were more likely to develop SCD ($p = 0.005$ and $p = 0.002$). All compared to the fastest gait quartile.	<u>Usual gait speed:</u> OR (95%CI) (< 1.08) SDC: 2.32(1.15-4.90)* <u>Fast gait speed:</u> OR (95% CI) (third) SCD: 2.71(1.35-5.46)** OR (95% CI) (fourth) SGD: 3.17(1.50-6.68)** <u>Dual-task gait speed:</u> OR (95% CI) (< 0.81) SCD: 2.08(1.10-3.93)*



Table 2. Continued

Ho et al., 2001 [99]	General Population of Older Chinese	988	3	>70	Timed 16-foot walk (s): 11.2±5.76	<u>CH:</u> CAPE [®] : Score >8
Inzitari et al., 2007 [100]	Health Aging and Body Composition Study	2776	5	70-79	Gait speed: N.A. Gait quartiles	<u>CH:</u> DSST: 37±0.29
Marquis et al., 2002 [101]	The Oregon Brain Aging Study	108	6	>65	Time 30 feet walk (steps/s): CH: 1.73±0.31 PCI: 1.66±0.42	<u>CH:</u> MMSE ≥24
Taniguchi et al., 2012 [69]	General Population of Older Japanese	266 men 400 women	2.7	>70	Gait speed, step length, step frequency: N.A. Gait tertiles	<u>CH:</u> MMSE ≥24
Verghese et al., 2007 [63]	Einstein Ageing Study	399	5	>70	Gait factors: Pace Rhythm Variability	<u>CH:</u> N.A.
Verghese et al., 2013 [38]	Einstein Aging Study	767	3	>70	Gait speed (m/s): N.A.	<u>MCR:</u> IC, slow gait, intact IADL and no dementia (DSMM, IV) <u>Not-MCR</u>

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<u>Impaired cognition:</u> CAPE [®] : Score ≤ 7	Slow 16-foot gait time, was a predictor of cognitive impairment in men and women ($p < 0.05$). Every 1-second increase was associated with an increased odds of cognitive impairment of 1.03 in women and 1.06 in men ($p = 0.05$).	<u>Timed 16-foot walk:</u> OR (95% CI) IC: women: 1.03(1.0,1.07)* men: 1.06(0.98,1.15)*
<u>Impaired cognition:</u> DSST $< 31.2 \pm 0.5$	Participants with a relatively slow gait speed ($< 1.05\text{m/s}$) were more likely to decline in DSST (> 9 points) compared to participants with a high gait speed ($\geq 1.35\text{m/s}$) ($p = 0.01$).	<u>Gait speed:</u> OR (95% CI) IC: 1.74(1.21,2.51)**
<u>PCI:</u> CDR ≥ 0.5	Time to walk 30 feet contributed independently to the time of onset PCI. A 1-second increase in time to walk 30 feet increased risk of 1.14 times of developing PCI ($p = 0.09$).	<u>Timed 30-foot walk:</u> HR PCI: 1.14*
<u>Impaired cognition:</u> > 3 points in MMSE	Men in the slowest gait tertile of fast speed were 4.42 times as likely to develop cognitive decline compared to men in the fastest gait tertile ($p < 0.01$) for step length.	<u>Fast gait speed:</u> <u>Step length:</u> OR (95% CI) IC: 4.42(1.65,11.84)**
	Women in the slowest gait tertile at usual gait speed were 2.43 ($p < 0.05$) times for gait speed and 5.76 ($p < 0.01$) times for step length as likely to develop cognitive impairment compared to women from the fastest gait tertile. At fast gait speed, these risks are 2.45 ($p < 0.05$) and 3.18 ($p < 0.01$) for respectively gait speed and step length.	<u>Usual gait speed:</u> OR (95% CI) IC: Gait speed: 2.43(1.03,5.72)* Step length: 5.76(2.15,15.44)** <u>Fast gait speed:</u> OR (95% CI) IC: Step length: 3.18(1.35,7.49)** Gait speed: 2.45(1.02,5.89)*
<u>Dementia:</u> DSMM, IV <u>AD:</u> DSMM, IV + neuroimaging <u>Vascular dementia:</u> DSMM, IV + neuroimaging	A 1 point increase on baseline rhythm and variability factor scores was associated with increased risk of dementia with 1.48 ($p = 0.03$) and 1.37 ($p = 0.02$) respectively and a 1 point increase on baseline pace was associated with an increased risk of vascular dementia with 1.60 ($p = 0.02$).	<u>Rhythm:</u> HR (95% CI) dementia: 1.48(1.03,2.14)* <u>Variability:</u> HR (95% CI) dementia: 1.37(1.05,1.78)* <u>Pace:</u> HR (95% CI) vascular: 1.60(1.06,2.41)*
<u>AD:</u> DSMM, IV <u>Vascular dementia:</u> DSMM IV + neuroimaging	Participants with MCR were at higher risk of developing dementia ($p = 0.013$) and vascular dementia ($p < 0.001$).	<u>Gait speed:</u> HR (95% CI) dementia: 2.72 (1.24,5.97)* HR (95% CI) vascular: 11.10(4.00,30.82)***



Table 2. Continued

Waite et al., 2005 [62]	The Sydney Older Persons Study	630	3 and 6	>75	5 meter- returned walk time: N.A. gait quartiles	<u>CH Dementia</u> <u>Preclinical</u> <u>phase</u>
Wang et al., 2006 [61]	Adult Changes in Thought (ACT) study	2288	6	>65	Timed to walk 10 feet: N.A. gait quartiles	<u>CH:</u> CASI >86 <u>MCI:</u> CASI ≤90
Welmer et al., 2014 [102]	Swedish National study on Aging and Care in Kungsholmen	1985	6	>60	Gait speed: 1.1±0.4 CH: 1.2±0.3 Dementia: 0.8±0.3	<u>CH:</u> MMSE >24

NOTE. ***p<0.001, ** p<0.01, *p<0.05.

SE= standard error , SD= standard deviation, CI= confidence interval , RH = relative hazard, OR= odds ratio, HR= hazard ratio, AD= Alzheimer's disease, IC= impaired cognition, MCI= mild cognitive impairment, PCI= persistent cognitive impairment, SPMSQ= short portable mental status questionnaire, CASI= cognitive abilities screening instrument, DSM-IV= diagnostic and statistical manual of mental disorders, CH= cognitively healthy, CDR= clinical dementia rating scale, GDS= geriatric depression scale, MCR= motoric cognitive risk syndrome, preEP= pre-extrapyramidal features, MMSE= Mini Mental State Examination, CAPE= clifton assessment procedure for the elderly, DSST= digit symbol substitution test, IADL= instrumental activities of daily living, SCD= significant cognitive decline, UNK= unknown, N.A.= not available.

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<p><u>Dementia:</u> DSMM IV + CDR <u>Impaired cognition:</u> mild or moderate dysfunction in cognition, insufficient for dementia</p>	<p>Those with cognitive impairment in combination with gait and motor slowing (preEP) were the most likely to dement over the 3- and 6-year period compared to CH elderly. Sensitivity levels are high (80.4%) but specificity levels low (36.9%)</p>	<p><u>5-meter returned walk:</u> OR (95% CI) dementia: over 6 years 5.6(2.5,12.6) over 3 years 10.4(3.6,30).</p>
<p><u>PreEP:</u> Slowed 5 meter-returned walk + (bradykinesia, tremor and/or rigidity). <u>Dementia and AD:</u> DSMM IV + National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer’s Disease and Related Disorders Association</p>	<p>Better performance of 10-foot timed walk at baseline was associated with less risk of dementia ($p<0.001$) and AD ($p<0.01$), per 1 point increase in test score. In MCI patients, better gait performance was associated with lower risk of dementia ($p<0.01$).</p>	<p><u>Timed 10-foot walk:</u> HR (95% CI) dementia: 0.79(0.70,0.81)(0.71,0.81) HR (95% CI) with MCI at 0.78(0.66,0.91)</p>
<p><u>Dementia:</u> DSMM IV</p>	<p>Each SD slower baseline gait speed increased the likelihood of incident dementia. Slowing of gait speed appears to occur secondary to slowing of processing speed in the path leading to dementia.</p>	<p><u>Gait speed:</u> OR (95% CI) dementia: 1.61(1.31,1.98)</p>



stress [76, 77], which in turn are strongly related to cognitive decline [78]. Slow gait speed might thus represent a hallmark for a loss of muscle strength, resulting from the early pathophysiological changes in the process of cognitive decline. Taken these observations together, a plausible assumption is that physical impairment is one of the core features in the development of cognitive decline. Therefore, gait speed may be a useful proxy in the prediction of cognitive decline in old adults.

While gait speed is an important marker of mobility and cognitive function, focusing on gait speed alone might be overly simplistic. Explaining, when gait was expressed in one of its elements (step length), the relation with cognitive decline in women was stronger than with gait speed [69]. Furthermore, step length in men correlated with future cognitive decline, while the association between gait speed and cognitive decline remained non-significant [79]. Thus, the relationship between gait slowing and future cognitive decline is presumably strengthened when gait speed is expressed in its more specific elements.

A more comprehensive gait analysis that moves beyond gait speed, including dynamic metrics of gait (e.g., gait smoothness, regularity, stability; [37, 51]0)), could increase the specificity of the relationship with future cognitive decline. For example, studies included in the present review showed that pace, rhythm and variability of gait were uniquely related to decline in specific cognitive functions and types of dementia [80]. Because comorbidities and other conditions (e.g., low back pain, osteoarthritis, medication) and their detrimental effects on gait speed are common in older adults, dynamic metrics of gait compared with gait velocity might be more sensitive to predict cognitive decline. For example, cross-sectional studies showed that indices of gait variability have the potential to distinguish between fallers and non-fallers [81, 82], age-groups [83], and patients with different conditions [37, 50, 51]. Therefore, measures of gait variability and stability could possibly strengthen the gait cognition link.

The type of gait test in terms of speed instructions or dual tasking can also affect the sensitivity of the prediction of cognitive decline. Compared with habitual gait speed and gait speed during 'walking-while-talking' in 660 old adults aged over 65, only fast gait speed (1.49 m/s) was associated with cognitive decline at 3-year follow-up [84]. However, the speed of the gait test may interact with gender because step length at maximum walking speed predicted cognitive decline in men but not in women during a median follow-up of 2.7 years in the 16.5% of the originally cognitively intact 853 old adults age over 70 [69]. While intuitively it seems attractive to propose that fast vs. habitual gait speed is more effective in predicting cognitive decline, additional longitudinal studies are needed that assess variants of gait tests along the continuum of gait challenges. One way to improve the interpretation of dual-task performance is to measure performance in each single task and also in the dual task condition and determine whether or not the decline in gait speed during dual tasking is caused by insufficient cognitive recourses or rather by an over-allocation of resources to the cognitive task [85]. In addition, gait might be differentially affected by the complexity and type of the dual task [50]. Considering these observations, the relationship between walking ability and future cognitive decline is likely to be influenced by speed instructions as well as by the type of cognitive task.

Methodological considerations

Studies included in the present scoping review were heterogeneous in terms of number of participants, age, duration of follow-up, and measures used to indicate walking ability and cognitive state. In some cases, assessable information was inconsistent and/or incomplete. For example, it appeared difficult to interpret the exact size of the effect on cognitive function because absolute or 'net' change in cognitive decline when measured at follow-up was rarely reported. Predictions reached significant values whereas effects sizes appeared to be small, which might be the result of a large number of participants included.


In addition to methodological considerations regarding interpretation of clinical relevance, critical notes with respect to measures indicating walking ability and cognitive function needs to be addressed. For example, some studies used a very short distance, such as 8 feet, to indicate gait speed. Considering acceleration and deceleration phases, this distance might be too short to measure gait speed [86]. In addition, measures of global mental state were often used to indicate baseline cognitive state as well as to determine cognitive decline at follow-up. However, the MMSE has been proposed solely suitable as a screening tool to indicate whether patients need further cognitive testing [87]. Thus, measures of MMSE optimally should be expanded with more specific neuropsychological testing. Despite such methodological limitations, the results converge towards a consensus that measures of walking ability could serve as a marker in the prediction of cognitive decline.

Public health priority

The composition of accurate markers in the prediction of cognitive decline/dementia is crucial to select those individuals who might benefit most from intervention strategies. Evidence from longitudinal studies show that the presence of vascular risk factors, including for example diabetes, high blood pressure, smoking, high cholesterol and being overweight increases the risk for developing dementia later in life [88, 89]. Additionally, physical activity and individualized diet reduce the risk for dementia [90-93]. Modifying vascular risk factors by adopting a healthy lifestyle might thus preserve cognitive functions and/or postpone dementia. As a result, several large-scale prevention studies target vascular and lifestyle related risk factors, aiming to develop multi-domain interventions to prevent cognitive decline among older adults: the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), the Prevention of Dementia by Intensive Vascular Care (PreDIVA), the Multi-domain Alzheimer Preventive Trial (MAPT) and the European Dementia Prevention Initiative (EDPI) project. In summary, the effectiveness of interventions to slow the process of neurodegenerations starts with the selection of individuals at risk for cognitive decline, emphasizing the need to improve current dementia prediction models.

Limitations and recommendations

A possible limitation of our review is that we excluded studies that used observational gait analysis, which reduced the number of studies included in the review. However, sub-clinical gait abnormalities might be underestimated by observational gait analysis in the absence of quantitative methods [94]. Furthermore, the included studies may have suffered from the 'survival effect', meaning people who reached vs. those who dropped out were healthier at baseline. Such a bias tends to underestimate how accurately walking ability



can predict cognitive decline in the future. We also note the limitation that only 4 studies reported results separately for men and women. Therefore, we cannot be totally sure that the conclusions are not biased by combined analysis for men and women, supporting future studies to take into account sex-differences. Moreover, it is worth mentioning that the present study exclusively examined the relationship between walking ability and future cognitive decline, while the literature has shown more variables that predict cognitive decline, and that are also correlates of walking ability (such as medication use, diabetes and obesity). Therefore, prediction models should employ a combination of variables. Finally, the large heterogeneity between studies made it impossible to make a direct comparison between studies by means of a quantitative meta-analysis. Although we did not perform a meta-analysis but rather qualitatively discussed the results, the literature was searched systematically.

The results imply that there is an urgent need to examine the relationship between various gait characteristics on the one hand, and specific cognitive functions and dementia syndromes on the other hand. While there is a clear conceptual basis for the sensitivity of for example measures of gait variability in the prediction of cognitive decline, as derived from cross-sectional studies, longitudinal evidence is currently lacking. In addition, there is a need to develop guidelines that standardize administration, instructions, and distances for tests assessing walking ability [95]. Considering measures of cognitive state, consistent and specific measures could increase clinical interpretation, as for now the MMSE is mostly used to indicate and to rule out cognitive decline, while the MMSE has found to be unsuitable for such purposes. Finally, the types of task in terms of speed or dual task seem to influence the relationship between walking ability and future cognitive decline. It remains to be seen whether more vs. less challenging gait tests actually predict cognitive decline more accurately, as for now the longitudinal data are inconclusive.

Conclusions

It is a health priority to improve dementia prediction models. The present scoping review aimed to determine the relationship between walking ability at baseline and future cognitive state. The results emerging from 20 studies demonstrated that gait slowing preceded cognitive decline in mental state, specific cognitive functions and syndromes related to dementia, and support the hypothesis that measures of walking ability could serve as a marker in the prediction of cognitive decline. Therefore, we recommend to include quantitative gait analysis in the clinical routine evaluation of individuals with suspected cognitive decline. Future research should reduce methodological inequalities and specify the relationship between various gait characteristics and specific cognitive functions and dementia syndromes. The next step would be to examine whether the incorporation of walking ability in dementia prediction models actually increases disease prediction and classification accuracy.

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