



REVIEW

Stages of mild cognitive impairment and Alzheimer's disease can be differentiated by declines in timed up and go test: A systematic review and meta-analysis



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ABSTRACT

Motor dysfunction increases in the moderate and severe stages of dementia. However, there is still no consensus on changes in mobility during its early stages. This meta-analysis aimed to measure the level of single-task functional mobility in older subjects with mild cognitive impairment (MCI) and/or Alzheimer's disease (AD). In a search of the PubMed, ISI Web of Knowledge, and Scopus databases, 2728 articles were identified. At the end of the selection, a total of 18 studies were included in the meta-analysis. Functional mobility was investigated using the timed up and go (TUG) test in all studies. When compared to healthy elderly (HE) adults, the following mean differences (MD) in seconds were found for the investigated subgroups: no amnesic MCI (MD = 0.26; CI_{95%} = -0.77, 1.29), amnesic MCI (MD = 0.86; CI_{95%} = -0.02, 1.73), very mild AD (MD = 1.32; CI_{95%} = 0.63, 2.02), mild AD (MD = 2.43; CI_{95%} = 1.84, 3.01), mild-moderate AD (MD = 3.01; CI_{95%} = 2.47, 3.55), and mild-severe AD (MD = 4.51; CI_{95%} = 1.14, 7.88); for the groups, the following MD were found: MCI (MD = 0.97; CI_{95%} = 0.51, 1.44) and AD (MD = 2.66; CI_{95%} = 2.16, 3.15). These results suggest a transition period in motor capacity between healthy aging and dementia, wherein functional mobility analysis in a single-task (TUG) can contribute to the diagnosis and staging of prodementia states and AD.

1. Introduction

A higher incidence of neurodegenerative diseases is associated with an increase in the elderly population. The age-standardized prevalence in dementia varies five to seven percent in most world regions, with a higher and lower prevalence in the Latin America and African areas, respectively (Prince et al., 2013). From 1990–2016, global dementia diagnosis has an increase of over than fifty percent (Nichols et al., 2019). Currently, Alzheimer's disease is the type of dementia who represent the major public health challenge. The diagnosis is made according to standard clinical criteria that include an insidious onset and progressive decline in memory and other cognitive functions (McKhann et al., 1984). Although motor declines can be observed in all stages of AD (Boyle et al., 2007), some studies have shown the absence of these deficits on early stages (Donoghue, Feeney, O'Leary, & Kenny, 2018). A

prodromal dementia phase defined as mild cognitive impairment (MCI) can be classified as no amnesic (na-MCI) or amnesic (a-MCI). Furthermore, AD also can be separated into mild, moderate, and severe stages.

Different brain networks sustain complex movements in older persons without any central nervous system (CNS) pathology, but this compensation missing in individuals with dementia (Franssen, Souren, Torossian, & Reisberg, 1999). Kikkert, Vuillerme, van Campen, Hortobagyi, and Lamoth (2016) proposed that cognitive and motor functions share neuroanatomical structures and can be related with the mobility decline, especially in AD patients (Beauchet et al., 2014; Tolea, Morris, & Galvin, 2015). Other studies have suggested that several changes observed during walking may be related not only to AD, but also MCI (Bahureksa et al., 2017). Therefore, the severity of the motor impairment may also be associated with the stage of disease

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(Nakamura, Meguro, & Sasaki, 1996). A decrease in gait velocity and difficulty in turning around in a functional mobility test are the most highlighted motor changes (Benavent-Caballer et al., 2016; Cruz-Jimenez, 2017).

Older adults with functional mobility preserve can sit, stand, and walk a few meters, essential functions for activities of daily living (ADLs) (Podsiadlo & Richardson, 1991). AD patients can show impairments in their mobility over time (Zidan et al., 2012), but those with MCI subtypes still should be investigated. The timed up and go (TUG) test, get up and go (GUG) test, and 8-foot up-and-go test are simple tests to assess functional mobility in the elderly. Initially, these tests had clinical utility in diagnosing the risk of falls in the elderly population, but recent studies (Nordin, Rosendahl, & Lundin-Olsson, 2006; Ries, Echternach, Nof, & Gagnon Blodgett, 2009; van Iersel, Benraad, & Rikkert, 2007) have demonstrated their excellent test-retest reliability in individuals with AD in different dementia stages.

The literature shows the influence of cognitive impairment in the decrease of mobility (Halliday et al., 2018; Montero-Odasso et al., 2015). Although AD patients can understand the tests instructions and perform cognitive and motor tasks, simultaneously (Bossers, van der Woude, Boersma, Scherder, & van Heuvelen, 2012). Frequently, dual-task assessments are used to differentiate HE, MCI, and AD. However, the influence of the scholarly level on dual-task tests in dementia not yet evident. Older adults with a low cognitive reserve can show worse performances in the dual-task (cognitive and motor), mainly due to the education level (Gomes et al., 2015). A systematic review found that mobility decline can follow the course of dementia (van Iersel, Hoefsloot, Munneke, Bloem, & Olde Rikkert, 2004). Despite, there is still no consensus on the existence of mobility deficits on single-tasks in pre-dementia stages of AD. The goal of this meta-analysis is to determine the level of single-task functional mobility in different stages of MCI and AD.

2. Methods

The registration of this systematic review and meta-analysis has been approved in the International Prospective Register of Systematic Reviews (PROSPERO) with the protocol number CRD42017074895. We followed the PICOS strategy (Akobeng, 2005) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). The recommendations of the Cochrane Collaboration (Higgins & Green, 2006) were used as a complementary guide.

2.1. Eligibility criteria

2.1.1. Types of studies

All studies had to be cross-sectional with control (healthy elderly), MCI and/or AD and/or subtypes groups (na-MCI, a-MCI, very mild AD [VMAD], mild AD, moderate AD, and severe AD). To the risk of bias reduce, conference proceedings and unpublished studies were not used (Higgins et al., 2011). No restrictions on the language or publication date of the studies were applied. The selected studies show inter-group comparisons through functional mobility performance.

2.1.2. Participants

We included studies with participants over 60 years of age of both genders divided into three distinct groups: healthy elderly (HE) and subjects presenting with MCI or AD subtypes. Only individuals with no physical impairment or neurodegenerative comorbidities were included. The use of walkers and canes was not allowed in the selected studies. The same criteria were used to track the diagnosis of HE, MCI, and AD in all studies (Folstein, Folstein, & Mchugh, 1975; Morris, 1993; Petersen et al., 1999).

2.1.3. Outcomes

The average time required to perform the test, which reflects the functional mobility of each group, was the outcome of interest for this meta-analysis. Therefore, the expected result for this measure in all groups (HE, MCI, AD, and subtypes) should have been obtained by either the TUG (Podsiadlo & Richardson, 1991), GUG (Mathias, Nayak, & Isaacs, 1986), or 8-foot up-and-go test (Langhammer & Stanghelle, 2015).

2.1.4. Information sources

The PubMed, Scopus, and ISI Web of Knowledge databases were searched on July 20, 2018. No filters were used to search any of the databases in order to conduct the broadest search and reduce the risk of bias (Higgins et al., 2011). Three additional records identified through bibliographic references were included in the analysis.

2.1.5. Search

The Medical Subject Headings (MeSH) and search-indexed descriptors were used to refine the data search (Huang, Neveol, & Lu, 2011). Three thematic word groups with MeSH terms were used to conduct the searches. Within each group, the terms were combined using the Boolean operator OR, and interaction between sets using the operator AND to form a phrase. The searches were conducted in October 2017 and updated on July 2018 using the following terms: (gait or walking or "functional mobility" or "dynamic balance") AND (older or aging or elderly) AND (Alzheimer or "Mild Cognitive Impairment").

2.1.6. Study selection

Two reviewers selected the studies and extracted the data. Disagreements were analyzed, and another independent researcher was requested. The studies identified were tabulated on a worksheet (Microsoft Corporation, Redmond, USA) to confirm if they met the eligibility criteria. All titles and abstracts of identified articles were screened, and the full-text articles were assessed for potential inclusion by the principal investigator. After exclusion following review of the complete text, studies were included in the qualitative synthesis. To finish the selection, we identified all studies that presented a high risk of bias and finally included all quality studies in a quantitative synthesis for the meta-analysis.

2.1.7. Appraisal of methodological quality

The quality of the selected studies was appraised using the Newcastle-Ottawa Scale (Palmeri V & La Torre, 2016). For cross-sectional studies, the following dimensions were analyzed: selection (three items; maximum, three points); comparability (one item; maximum, two points); and outcomes (two items; maximum, two points). The maximum score is seven points. The articles underwent descriptive and critical analysis of quantitative synthesis.

2.2. Data selection

We looked into the following characteristics in all studies: 1) the total number and age of patients in each group; 2) probable diagnosis, global cognitive status, and disease stage of the subjects; 3) the test used to assess functional mobility; and 4) the data used to calculate the effect size (n, means and standard deviation).

Regarding pre-selected articles that did not present the necessary data in the text, the values were requested from the authors by e-mail; only three authors answered the request. For other pre-selected articles that presented the median and range of outcomes in the text, the values of the mean and variance were calculated according to the method devised by Hozo, Djulbegovic, and Hozo (2005).

2.3. Risk of bias

The risk of bias in the studies was assessed using qualitative analysis

for each included study, and each risk of bias item present on the Newcastle-Ottawa Scale (NOS). This scale has been adapted for cohort studies to provide a quality assessment of cross-sectional studies, with scores ranging from 0 to 4 for unsatisfactory and 5 to 7 for satisfactory studies (Palmeri V & La Torre, 2016). To analyze the risk of publication bias, we used visual inspection of the funnel plot. The risk between studies was assessed using the results of heterogeneity present in the forest plot. Heterogeneity was measured using the τ^2 , χ^2 , and I^2 tests. In the τ^2 test, $\tau^2 > 1$ suggests the presence of substantial statistical heterogeneity. If the χ^2 value is statistically significant ($p < 0.05$), there is also evidence of heterogeneity. In the I^2 test analysis, the percentage of the variance attributed to the heterogeneity of the study, ranges from low ($25\% < I^2 < 50\%$) to moderate ($50\% < I^2 < 75\%$) to high ($I^2 > 75\%$) (Higgins et al., 2011).

2.4. Summary measures

The analyses were performed considering two different groups, MCI, and AD, and six different subgroups: na-MCI, a-MCI, VMAD, mild AD, mild to moderate AD, and mild to severe AD. In the first group, we included all patients diagnosed with MCI and those into three subgroups: na-MCI, a-MCI, and VMAD (pseudodementia staging or clinical dementia rating [CDR] of 0.5). For the second group, patients were identified with a probable diagnosis of AD based on a CDR between 1 and 3. The lack of CDR stratification in some studies for the AD group led to subjects being classified in the mild AD or CDR 1 subgroup. The other outcomes were separated into subgroups of mild to moderate AD or CDR 1–2 (mild-mod AD) and mild to severe AD or CDR 1–3 (mild-severe AD). For the statistical analysis performed in this meta-analysis, the HE data were replicated and compared with the MCI, AD, and subgroups in their own studies. For multiple comparison groups in the same study, the HE group had the sample divided based on the number of groups that existed for comparison (Borenstein, 2009). This is to maintain the correct sample size of the HE group and give the correct weight to groups or subgroups with more subjects.

The mean difference (MD) was calculated considering the average time on functional mobility tests and standard deviation for each study. This outcome was reported on a meaningful scale, and all studies in the analysis used the same scale (seconds). The subgroup and group meta-analysis were performed directly on the raw difference in means. The MD in this review was calculated based on the random-effects model with 95% confidence intervals (CI: 95%), including the assumption of heterogeneity of the studies and their participants. Analyses of forest and funnel plots were performed using the Review Manager (RevMan) Version 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

3. Results

3.1. Study selection and characteristics

A total of 2731 articles were found (PubMed = 736; Scopus = 1053; ISI Web of Knowledge = 939; Identified through other sources = 3). After applying the exclusion criteria for eligibility, a total of 20 studies were subjected to a qualitative analysis. After this, 18 studies were included, and six studies were excluded from the meta-analysis. Fig. 1 shows the screening flow used in the study selection.

Table 1 shows 20 studies selected for the quality assessment score based on the NOS check-list. Regarding the cross-sectional studies evaluated, scores ranged between 3 and 7 points (mean = 5 points). Two studies (Christofolletti, Andrade, Beinotti, & Borges, 2014; Woellner et al., 2010) scored 3, indicating unsatisfactory quality, and were excluded.

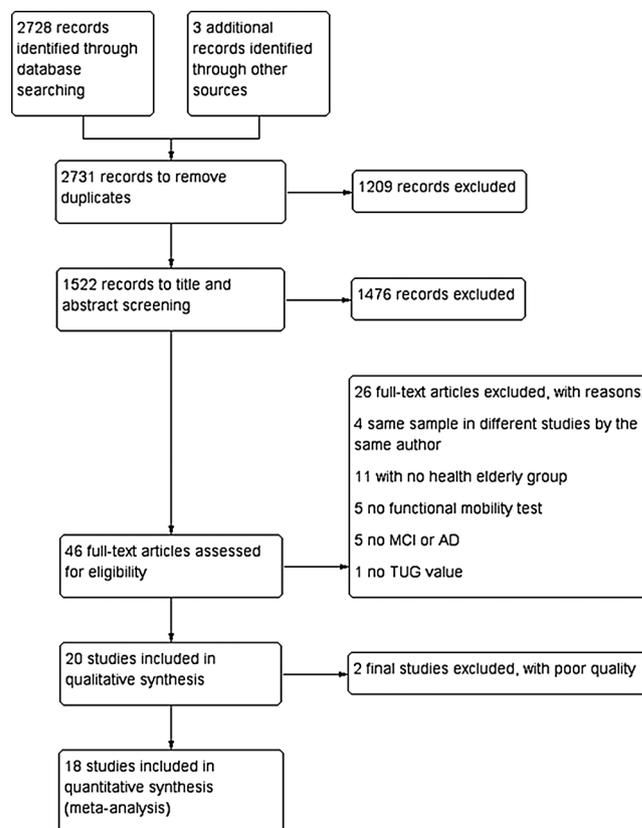


Fig. 1. Study flow diagram.

3.2. Summary of the studies

The 18 studies included in the meta-analysis provided a total sample size of 2973, with a mean age ranged from 57 to 83 years, with both genders and investigation in different countries. The Mini-Mental State Examination (MMSE) scores varied between 15.9 and 30.0 and the CDR between 0 and 3. They were used in all studies to evaluate the neuropsychological status and perform the staging of the disease in patients. No coexisting neurodegenerative diseases or physical frailty were found among the participants. In all selected articles, the TUG was used as the evaluation method for elderly functional mobility. The characteristics of the studies are described in Table 2.

3.3. Mean difference (MD)

Two studies (Allali, Annweiler, Predovan, Bherer, & Beauchet, 2015; Rajtar-Zembaty, Salakowski, Rajtar-Zembaty, Starowicz-Filip, & Skalska, 2018) included na-MCI, four studies (Allali et al., 2015; Fujisawa et al., 2017; Rajtar-Zembaty et al., 2018; Tseng, Cullum, & Zhang, 2014) included a-MCI, eight studies (Ansai et al., 2018; Borges, Radanovic, & Forlenza, 2015; Eggermont et al., 2010; Gillain et al., 2009; Gras et al., 2015; Mirelman et al., 2014; Nishiguchi, Yorozu, Adachi, Takahashi, & Aoyama, 2017; Pettersson, Olsson, & Wahlund, 2005) included VMAD, nine studies (Ansai et al., 2018; Borges et al., 2015; Cedervall, Kilander, & Aberg, 2012; Fujisawa et al., 2017; Nadkarni, Mawji, McIlroy, & Black, 2009; Pedroso et al., 2018; Pettersson, Engardt, & Wahlund, 2002, 2005; Wang et al., 2015) included mild AD, two studies (Fujisawa et al., 2017; Suttanon et al., 2012) included mild to moderate AD, and two studies (Eggermont et al., 2010; Gillain et al., 2009) mild to severe AD participants in their research. The mean difference (MD) was calculated according to the comparisons made in the studies (na-MCI × HE; a-MCI × HE; VMAD × HE; mild AD × HE; mild-mod AD × HE, and mild-severe

Table 1
Evaluation of the methodological quality of the cross-sectional studies by the NOS.

Cross-sectional study	Selection			Comparability Subjects are comparable. Confounding factors are controlled	Outcome		Total 7 points
	Representativeness of the sample	None respondents	Ascertainment of the exposure		Assessment of the outcome	Statistical test	
Allali et al. (2015)	1	1	NA	0	2	1	5
Ansai et al. (2017)	1	1	NA	2	2	1	7
Borges et al. (2015)	1	1	NA	0	2	1	5
Cedervall et al. (2012)	1	1	NA	0	2	1	5
Christofolletti et al. (2014)	1	1	NA	0	0	1	3 #
Eggermont et al. (2010)	1	1	NA	0	2	1	5
Fujisawa et al. (2017)	1	1	NA	0	2	1	5
Gillain et al. (2009)	1	1	NA	0	2	1	5
Gras et al. (2015)	1	1	NA	0	2	1	5
Mirelman et al. (2014)	1	1	NA	0	2	1	5
Nadkarni et al. (2009)	1	1	NA	0	2	1	5
Nishiguchi et al. (2017)	1	1	NA	0	2	1	5
Pedroso et al. (2018)	1	1	NA	0	2	1	5
Pettersson et al. (2002)	1	1	NA	0	2	1	5
Pettersson et al. (2005)	1	1	NA	0	2	1	5
Rajtar-Zembaty et al. (2018)	1	1	NA	0	2	1	5
Suttanon et al. (2012)	1	1	NA	0	2	1	5
Tseng et al. (2014)	1	1	NA	0	2	1	5
Wang et al. (2015)	1	1	NA	0	2	1	5
Woellner et al. (2010)	1	1	NA	0	0	1	3 #

NA: Not applicable; #: Unsatisfactory quality.

AD × HE). The forest plot for the MCI group (Fig. 2) shows the MD in three subgroups: na-MCI (MD = 0.26; CI_{95%} = -0.77, 1.29), a-MCI (MD = 0.86; CI_{95%} = -0.02, 1.73), and VMAD (MD = 1.32; CI_{95%} = 0.63, 2.02). Regarding the compared global data between MCI and HE groups, the raw mean difference was approximately one second (MD = 0.97; CI_{95%} = 0.51, 1.44). The forest plot for the AD group (Fig. 3) shows the MD in three subgroups: mild AD (MD = 2.43; CI_{95%} = 1.84, 3.01), mild-mod AD (MD = 3.01; CI_{95%} = 2.47, 3.55), and mild-severe AD (MD = 4.51; CI_{95%} = 1.14, 7.88). Regarding the compared global data between AD and HE groups, the raw mean difference was approximately three seconds (MD = 2.66; CI_{95%} = 2.16, 3.15). This result indicates that there is a difference in functional mobility between groups, corroborating the hypothesis presented in the present study (Fig. 4).

3.4. Risk of bias

A visual analysis of the funnel plot showed a small asymmetry in the data within the selected studies. Two studies (Gillain et al., 2009; Pedroso et al., 2018) were shown outside the cone or pseudo-confidence interval (CI 95%) revealing a possible heterogeneity within these selected studies. Because of the risk of bias also, between the selected studies, a heterogeneity test was applied and showed a significant value for the MCI subgroups (Higgins et al., 2011), I² equal to 81% (p = 0.02) for na-MCI, 67% (p = 0.03) for a-MCI, and 64% (p = 0.007) for VMAD. A heterogeneity test showed a non-significant value for the AD subgroups (Higgins et al., 2011), I² equal to 26% (p = 0.21) for mild AD, 0% (p = 0.86) for mild-mod AD, and 44% (p = 0.18) for mild-severe AD. Regarding the overall effect in the MCI group, significant heterogeneity with I² equal to 69% (p < 0.0001), and the overall effect in the AD group, non-significant heterogeneity with I² equal to 30% (p = 0.15), were also observed. The p-value was also significant (< 0.05) for the different stages of MCI disease and

combined data, confirming their heterogeneity, but not for AD. However, τ² only demonstrated significant heterogeneity in the mild-severe AD subgroup (Fig. 5).

4. Discussion

This meta-analysis aimed to examine studies to determine the level of functional mobility in a single-task in HE, MCI, and AD subjects. The crescent-shaped MD reflects a significant cognitive-motor deficit between groups and subgroups, without a second related cognitive task. This differential decline between groups suggests that the single-task assessment of functional mobility, specifically with the TUG, could be suitable in assisting the diagnosis and identification of dementia stages. Presenting a good alternative for immigrants, illiterate or elderly with poorly educated that may have their performance impaired in a dual-task by the low-education or because come from the other culture. In this case, older people that show some difficulty in functional mobility, with a temporal decline atypical for their age, must be observed and undergo further evaluation. Early identification of cognitive decline facilitates not only the clinical analysis of the disease but also how the patient can execute the most appropriate intervention (Kikkert et al., 2016).

Although the relationship between brain structures involved in locomotion and neural lesions in MCI and AD is not yet fully understood, some theories have been established. For example, Annweiler et al. (2012) believe that quantitative gait disorders (e.g., speed) are associated with injuries in frontotemporoparietal network and basal ganglia, including the dopaminergic nigrostriatal system. Qualitative gait disorders (e.g., dynamic balance) would be correlated with lower hippocampal volume and function, including the basal cholinergic forebrain and brain stem complex systems. Image studies revealed that differences in the lower limbs performance occur in different damage areas, such as: dorsolateral prefrontal cortex, cingulate gyrus,

Table 2
Characteristics of selected studies (mean ± SD).

Cross-sectional study	Country of samples population	Sex	Groups	N	Age, years	MMSE, score	CDR
Rajtar-Zembaty et al. (2018)	Poland	M/F	Control	651	68.87 ± 4.91	28.88 ± 1.02	0
			na-MCI	59	69.93 ± 5.29	27.14 ± 1.04	0.5
			a-MCI	88	72.28 ± 6.19	26.86 ± 1.33	0.5
Ansai et al. (2017)	Brazil	M/F	Control	40	73.5 ± 6.2	25.8 ± 2.9	0
			MCI	40	75.8 ± 6.3	22.9 ± 3.5	0.5
			AD	38	77.7 ± 6.2	17.2 ± 5.8	1
Fujisawa et al. (2017)	Japan	M/F	Control	194	74.5 ± 5.8	28.0 ± 2.1	0
			a-MCI	261	76.3 ± 6.0	24.7 ± 3.1	0.5
			mild AD	164	78.8 ± 5.7	22.7 ± 2.2	1
			mod AD	181	79.4 ± 5.6	15.9 ± 2.6	2
Nishiguchi et al. (2017)	Japan	M/F	Control	38	73.2 ± 6.4	28.9 ± 1.2	0
			MCI	25	72.8 ± 6.2	24.7 ± 1.7	0.5
Allali et al. (2015)	France	M/F	Control	80	69.8 ± 3.5	28.8 ± 1.2	0
			na-MCI	25	70.6 ± 4.6	26.9 ± 1.9	0.5
			a-MCI	66	70.3 ± 4.0	27.6 ± 1.6	0.5
Borges et al. (2015)	Brazil	M/F	Control	36	72.6 ± 5.4	28.6 ± 1.4	0
			MCI	42	75.5 ± 5.3	27.4 ± 2.1	0.5
			AD	26	74.3 ± 5.6	22.6 ± 3.0	1
Gras et al. (2015)	United States	M/F	Control	13	72.6 ± 4.6	29.0 ± 1.0	0
			MCI	13	72.9 ± 4.7	24.8 ± 2.6	0.5
Wang et al. (2015)	Taiwan	M/F	Control	25	57.14 ± 5.97	28.40 ± 1.31	0
			AD	21	65.47 ± 7.62	23.43 ± 3.28	1
Pedroso et al. (2018)	Brazil	M/F	Control	30	74.1 ± 5.6	24.6 ± 4.0	0
			AD	24	76.9 ± 5.3	19.8 ± 4.5	1
Mirelman et al. (2014)	United States	M/F	Control	280	82.7 ± 4.2	–	0
			MCI	67	83.3 ± 3.5	–	0.5
Tseng et al. (2014)	United States	M/F	Control	10	61.8 ± 6.5	28.9 ± 1.0	0
			a-MCI	16	64.4 ± 5.3	28.8 ± 1.5	0.5
Cedervall et al. (2012)	Sweden	M/F	Control	25	71 (56–79)*	30 (28–30)*	0
			AD	25	71 (55–79)*	25 (21–30)*	1
Suttanon et al. (2012)	Australia	M/F	Control	25	80.4 (78.0–82.7)*	29.2 (28.5–29.8)*	0
			AD	25	81.0 (78.4–83.5)*	21.1 (19.2–23.0)*	1 - 2
Eggermont et al. (2010)	United States	M/F	Control	22	76.5 ± 7.4	29.4 ± 0.9	0
			MCI	22	76.3 ± 8.1	28.4 ± 1.5	0.5
			AD	22	77.1 ± 9.6	21.6 ± 4.8	≥ 1
Gillain et al. (2009)	Belgium	M/F	Control	14	73.53	28.21 ± 1.58	0
			MCI	14	72.85	26.72 ± 1.68	0.5
			AD	6	73.66	22.83 ± 2.14	≥ 1
Nadkarni et al. (2009)	Canada	M/F	Control	34	73 ± 8	29 ± 1	0
			AD	40	74 ± 8	25 ± 3	1
Pettersson et al. (2005)	Sweden	M/F	Control	31	57 ± 9.2	29 (27–30)*	0
			MCI	59	60 ± 7.3	28 (15–30)*	0.5
			AD	21	68 ± 9.9	24 (17–30)*	1
Pettersson et al. (2002)	Sweden	M/F	Control	18	74.5 (64–84)*	29.5 (27–30)*	0
			AD	17	74 (67–82)*	25 (21–29)*	1

AD: Alzheimer’s disease; MCI: mild cognitive impairment; na-MCI: non-amnestic MCI; a-MCI: amnestic-MCI; N: total sample; MMSE: Mini-Mental Statement Exam; CDR: Clinical Dementia Rating; *: median (minimum-maximum).

association areas of the parietal lobe (precuneus), basal ganglia, and medial temporal lobes, particularly in the hippocampus (Allali et al., 2015; Eggermont et al., 2010; Lo et al., 2017). Montero-Odasso et al. (2015) conclude that cognitive function plays a crucial role in mobility regulation in ADLs.

Patients with MCI or VMAD and their subgroups can use a compensatory mechanism to maintain essential functions (Cohen, Verghese, & Zwerling, 2016). The neurodegeneration caused by AD results in gradual cognitive and functional declines, follow to ADLs impairments since prodromal stages of AD (Zidan et al., 2012). It is believed that a-MCI and VMAD are significant risk factors for the development of AD, while na-MCI is not (Petersen et al., 1999). Our meta-analysis, as well as Waite et al. (2005), confirms this viewpoint, and we propose the incorporation of non-cognitive clinical assessments even in the pre-dementia stage. Furthermore, mobility can be measured quickly, easily, and in small spaces, without expensive equipment or sophisticated training. Thus, it is reasonable to put forward the assumption that functional mobility may be a useful motor biomarker for MCI and AD patients.

This review has some limitations that should be considered. Regarding the database search, some keywords are not included in the

MeSH terms used for indexing articles in PubMed. This might have reduced the extent of the search scope. Regarding the heterogeneity, the random-effects model results in broader confidence intervals around the point estimates. However, it is a more conservative choice for the analysis (Higgins & Green, 2006). Specifying TUG performance based on cognitive status, gender, age, and even different countries or regions will provide to researchers and clinicians a more precise representation of functional mobility among older adults. Although all selected subjects in this study did not exhibit frailty, this is common in elderly as well as in cognitive decline, and both can impact on the gait velocity impairment. Other confounding variables, such as the number of comorbidities, and medications, were not reported in these studies. The literature has shown a cut-off value of TUG test indicating functional disability in older adults, defined as ≥ 9 s (Makizako et al., 2017) and 12 s (Bischoff et al., 2003). Though, another study with Parkinson disease and TUG showed a score of 3.5 s as a minimal detectable change (MDC) beyond random measurement error (Huang, Hsieh et al., 2011). Future studies should investigate the MDC, prevalence, and incidence of the TUG in MCI and AD patients.

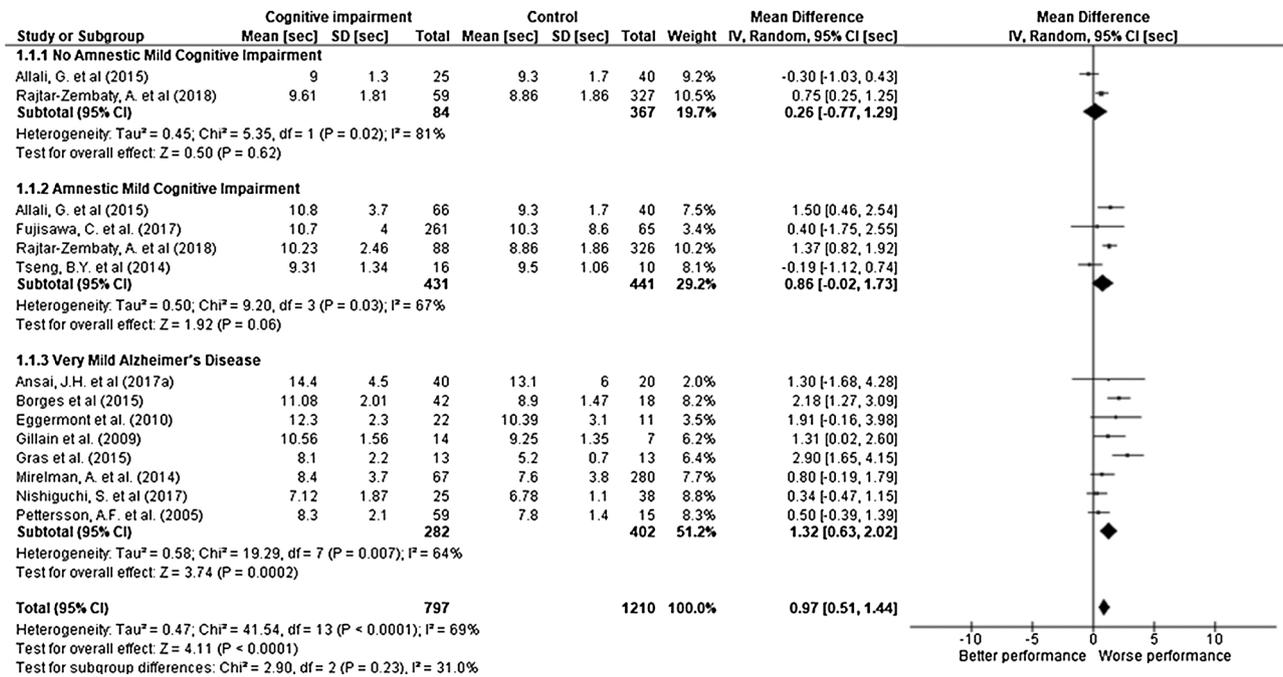


Fig. 2. Forest plot for TUG comparison between groups and subgroups: MCI vs. HE.

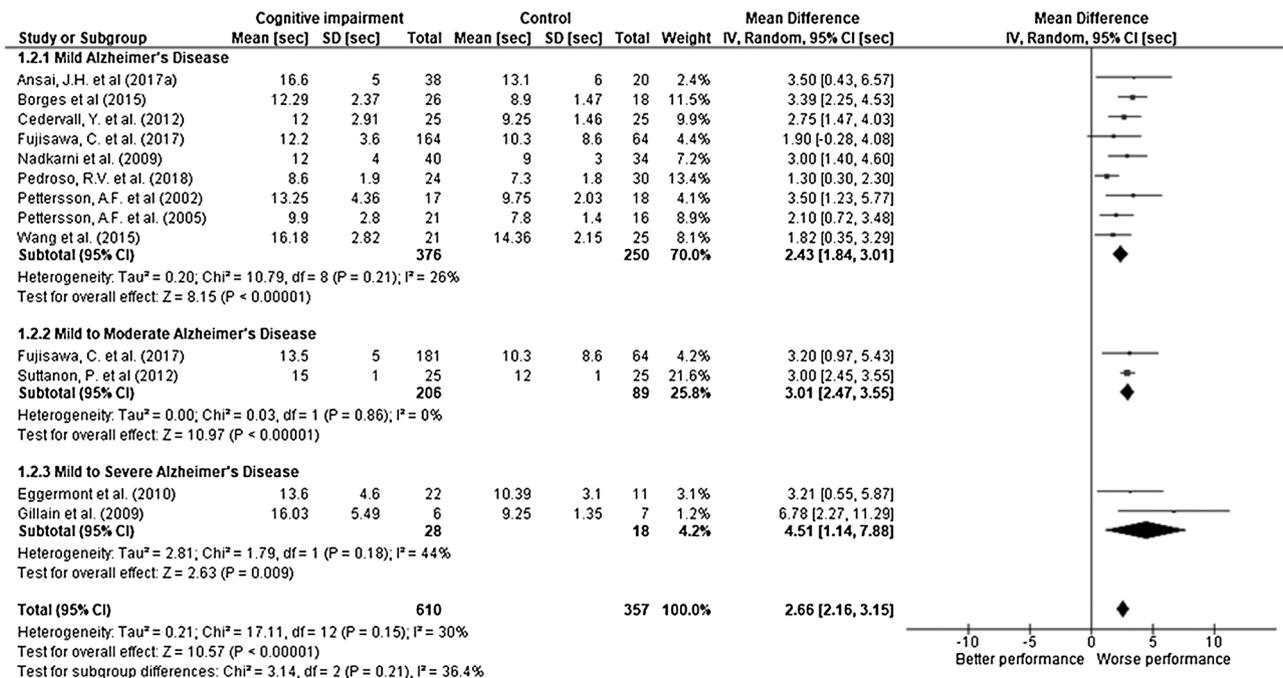


Fig. 3. Forest plot for TUG comparison between groups and subgroups: AD vs. HE.

5. Conclusions

The cognitive impairment caused by MCI and AD promotes a decline in functional mobility not only in the intermediate and advanced stages of the disease, but also in prodementia stages (a-MCI, VMAD, and mild AD). Therefore, a clinical evaluation of single-task functional mobility in older adults using the TUG can also contribute to understanding the clinical diagnosis and respective stage of the disease. Brain circuits involved in cognitive and functional mobility may be partially compromised as early as in the prodromal and initial period of AD, but this needs to be investigated further.

Declaration of Competing Interest

The authors declare no conflicting interests.

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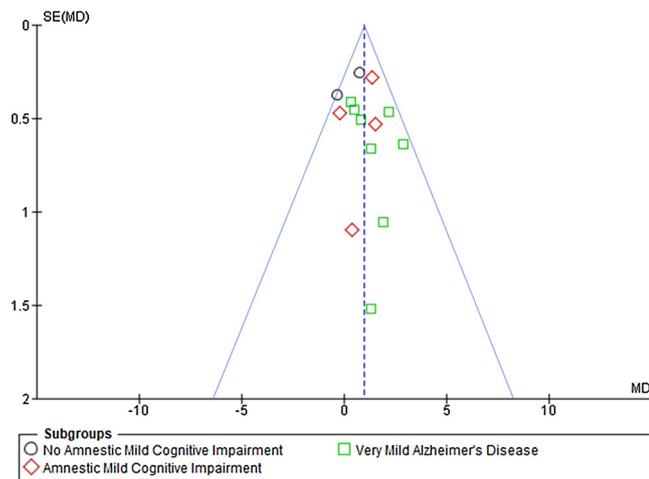


Fig. 4. Funnel plot for studies with MCI subgroups.

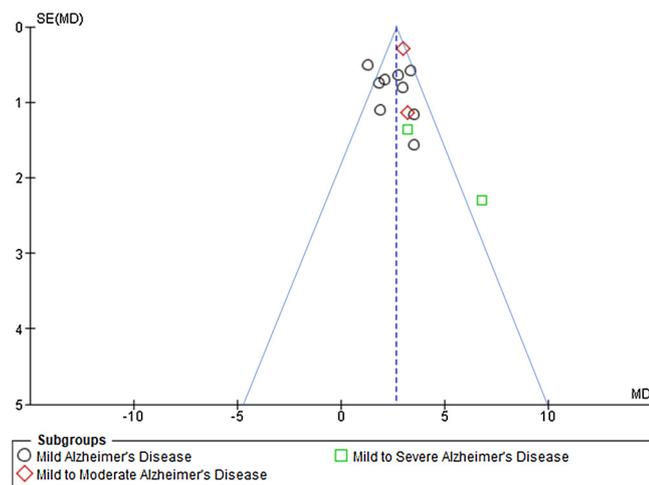


Fig. 5. Funnel plot for studies with AD subgroups.

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