

## Review

## Measuring gait speed to better identify prodromal dementia

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## ABSTRACT

Slow gait speed has been shown to predict incident dementia and cognitive decline in older individuals. We aimed to summarize the evidence concerning the association of slow gait speed with cognitive decline and dementia, and discuss the possible shared pathways leading to cognitive and motor impairments, under the unifying hypothesis that body and mind are intimately connected. This is a scoping review supported by a systematic search of the literature, performed on PubMed and Web of Science. Longitudinal studies providing information on the role of gait speed in the prediction of cognitive decline and dementia in cognitively intact people and in those with initial cognitive impairment were eligible. Of 39 studies selected, including overall 57,456 participants, 33 reported a significant association between gait speed and cognitive outcomes, including dementia. Neurodegenerative pathology and cerebrovascular burden may damage cerebral areas involved in both cognitive functions and motor control. At the same time, systemic conditions, characterized by higher cardiorespiratory, and metabolic and inflammatory burden, can affect a number of organs and systems involved in motor functions, including the brain, having ultimately an impact on cognition. The interplay of body and mind seems relevant during the development of cognitive decline and dementia. The measurement of gait speed may improve the detection of prodromal dementia and cognitive impairment in individuals with and without initial cognitive deficits. The potential applicability of such a measure in both clinical and research settings points at the importance of expanding our knowledge about the common underlying mechanisms of cognitive and motor decline.

## 1. Introduction

Due to the rapid aging of the population, people affected by dementia will triple worldwide in the next 30 years (Alzheimer Disease International, 2015; Cova et al., 2017). No effective curative treatments have been identified so far, which may be partly due to the inclusion in intervention studies of patients with an already overt cognitive impairment (Petersen, 2009). Indeed, the diagnosis of dementia comes only at an advanced stage of a long pathological process that starts several years earlier. The need to accurately intercept such a pathological trajectory as early as possible justifies the increasing efforts to identify reliable predictors of dementia (Grande et al., 2018a; Winblad et al., 2016).

Although at higher risk, almost one-third of individuals with mild cognitive impairment do not progress toward dementia, and remain clinically stable over time or even revert to normal cognition (Canevelli et al., 2016). In recent years, the inclusion of biological markers in the diagnostic approach to Alzheimer's disease (AD) has proven to enhance the accuracy of early diagnosis (Jack et al., 2018). However, several studies showed that higher brain pathological burden does not always correlate with an increased risk of developing AD dementia (Nelson et al., 2012). Finally, non-AD dementias, which account for up to 50% of dementia cases, still lack of specific diagnostic markers. To deal with this challenge, the identification of clinically valid, inexpensive and non-invasive markers of prodromal dementia is being highly advocated (Montero-Odasso et al., 2018a).

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**Table 1**

Main characteristics and findings of longitudinal studies investigating the prognostic role of gait speed for cognitive outcomes. Grey bands identify studies investigating the role of the interplay between baseline slow gait speed and cognitive impairment.

Study	N	Mean age years; (% female sex)	Cognitive decline <sup>a</sup>	Cognitive impairment <sup>b</sup>	Outcomes *		
					All-cause	AD	Vascular/non-AD dementia
Atkinson et al, 2010	1793	70; (100)	●				
Auyeung et al, 2011	2737	72; (45)	●				
Best et al, 2016	2876	74; (52)	●				
Boyle et al, 2010	761	79; (76)		●			
Bullain et al, 2016	578	93; (70)			●		
Byun et al, 2018	91	67; (44)		●			
Camargo et al, 2016	2176	62; (54)			●	●	
Demnitz et al, 2017	387	70; (19)		●			
Deshpande et al; 2009	660	75; (54)	●	●			
Doi et al; 2018	3937	74; (53)			●		
Doi et al; 2019	4011	72; (54)			●		
Donoghue et al; 2018	1740	72; (52)	●				
Dumurgier et al, 2017	3663	73; (62)			●	●	●
Gale et al, 2014	2654	69; (56)	●				
Gillain et al, 2016	13	70-74; (50)				●	
Gray et al, 2013	2619	77; (60)			●	●	●
Hackett et al; 2018	3932	60+; (55)			●		
Hooghiemstra et al; 2017	309	70; (35)	●	●	●		
Hsu et al; 2017	249	86; (0)		●			
Inzitari et al; 2007	2776	73; (53)		●			
Krall et al; 2014	395	74; (100)	●				
Kuate-Tegueu et al, 2017	1265	74; (60)			●	●	●
Lipnicki et al, 2017	873	79; (56)		●	●		
MacDonald et al, 2017	121	85; (64)	●				
Marquis et al, 2002	108	83; (63)		●			
Mielke et al, 2013	1478	80; (51)	●				
Montero-Odasso et al; 2016	252	77; (63)			●		
Montero-Odasso et al; 2017	112	76; (49)			●		
Montero-Odasso et al; 2018	154	74; (54)			●		
Park et al, 2017	620	60+; (51)		●			
Savica et al; 2017	3426	74; (50)	●				
Sibbett et al; 2018	488	79; (57)			●		
Taniguchi et al; 2012	853	75; (59)		●			
Taylor et al; 2017	134	82; (59)	●				
Tian et al; 2017	412	71; (51)	●				
Verghese et al; 2013	767	70+; (61)			●		●
Verghese et al; 2014	4555	60-108; (-)		●	●		
Veronese et al; 2016	1249	72; (59)	●	●			
Welmer et al; 2014	2232	72; (63)			●		

Legend: N = sample size; AD = Alzheimer's disease; ● = significant association; ● = not associated or non-significant association.

<sup>a</sup>Cognitive decline was defined as the change in cognitive performances across at least two time-points.

<sup>b</sup>Cognitive impairment was defined as scoring below a given threshold on one or more cognitive tests.

\*In reporting the study findings, the most adjusted statistical models were considered.

By capturing clinical and subclinical disorders across different organs and systems, gait speed demonstrates as a powerful predictor of several health-related outcomes (Studenski et al., 2011). Gait speed appears one of the most convenient ways to measure motor function in older adults and some scientists suggest to use it as an indicator of an individual's biological age (Newman et al., 2006). Interestingly, growing evidence suggests not only that a decline in gait speed predicts dementia, but also that it may precede the decline in cognitive performance (Kikkert et al., 2016; Kueper et al., 2017; Buracchio et al., 2010).

In the present review, we aim to summarize the scientific evidence concerning the association of slow gait speed with cognitive decline and dementia, and its added value in predicting dementia in people with initial cognitive impairment. We further aim to discuss a) the potential shared mechanisms and pathways leading to both cognitive and motor impairments, under the unifying hypothesis that the body and mind are intimately connected, and b) the potential implications for clinical practice and research in the field of dementia.

## 2. Methods

This is a scoping review on the association of slow gait speed with cognitive impairment and dementia, which nests a systematic search of the literature on the clinical evidence supporting such a relationship. We systematically reviewed longitudinal studies reporting information on the role of gait speed in the prediction of cognitive decline and dementia in cognitively intact people and in those with initial cognitive impairment. PubMed and Web of Science were searched for articles including terms referred to as *gait speed*, *cognitive decline*, and *dementia* (full search strategy in Table S1). Two independent assessors (GG and FT), screened titles and abstracts of the retrieved articles. All the articles selected by at least one assessor were further independently screened. Articles were excluded if they were: 1) not longitudinal; 2) not original contributions; 3) written in languages other than English; 4) considering the rate of gait speed change as exposure; and 5) not on topic. Results were extracted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

### 3. Gait speed and cognition: clinical evidence

Following the systematic search, out of 2100 retrieved articles, 39 entered the final assessment (Fig. S1). Table 1 summarizes the main characteristics and findings of the selected studies (detailed characteristics of the selected studies in Table S1). The overall number of participants was 57,456, with a mean age range of 62–93 years (max age reported 108 years), and with the proportion of females in the studies ranging from zero to 100%. Also the length of follow-ups varied greatly, ranging between 1 and 25 years. Notably, 32 out of 39 studies had a follow-up longer than 3 years. The majority of the studies included community-dwelling people, while few were conducted in specialist settings. Seventeen studies were carried out in North America, 12 in Europe, seven in Asia, and two in Australia. One multicenter study was conducted in both USA and Europe.

Objective measures were used to assess gait speed and cognition (at both baseline and follow-ups) in almost all studies (Table S2). One study defined baseline cognitive impairment as the presence of cognitive complaints (Verghese et al., 2014). Gait speed has been assessed through paths of different length, ranging from 2.4 to 40 m, although the most commonly adopted was a 6-meter path, allowing for the acceleration and deceleration phases. Gait speed was considered either as a continuous or a binary variable. In the latter case, different cutoffs have been applied (e.g., 0.8 m/s, 20th lower percentile). Fourteen studies investigated the association between gait speed and cognitive decline, which was defined as the change in global cognitive performance across at least two time-points. The Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) have been used in the majority of the studies as measures of global cognitive function (Table S1). Thirteen studies investigated the association between gait speed and incident cognitive impairment, operationalized as scoring below a given threshold on one or more cognitive tests, or on the basis of an extensive neuropsychological battery (e.g., Mild Cognitive Impairment [MCI]). Six studies operationalized cognitive impairment as a given decrease in the MMSE score (i.e. the loss of 3 or 4 points). In 12 studies, a cognitive battery was used, with the aim to cover several different cognitive domains, among which memory, executive function and perceptual speed. Finally, 18 studies investigated the association of gait speed with incident dementia, which diagnosis was mostly made according to the DSM-IV criteria, or equivalent criteria. Five studies included participants having both cognitive complaints/impairments and slow gait speed at baseline.

Of the 14 studies investigating the relationship between slow gait speed and cognitive decline, 11 reported a significant association. Twelve out of the 13 studies investigating the relation between slow gait speed and incident cognitive impairment showed a significant association. Finally, a significant association between slow gait speed and dementia was reported in 14 out of 18 studies (Fig. 1). Overall, six studies investigated dementia subtypes, of them four reported a positive association with AD dementia and four with non-AD dementias (three vascular dementia and one non-AD dementia). To note, one study showed an association between slow gait speed and dementia in participants reporting subjective cognitive complaints at baseline. When the effect of the co-occurrence of cognitive impairment and slow gait speed was investigated in relation to dementia, three out of five studies showed a significant association.

### 4. Gait speed and biological age

Gait speed is a comprehensive measure of mobility, frequently used in assessments of older individuals. It can be easily performed in clinical settings, and is highly predictive of a number of negative events (Studenski et al., 2011; Newman et al., 2006; White et al., 2013; Abellan van Kan et al., 2009; Santoni et al., 2018). Older adults with impaired or declining gait speed have more care needs, higher incident disability, and shorter survival (Newman et al., 2006; Schrack et al.,

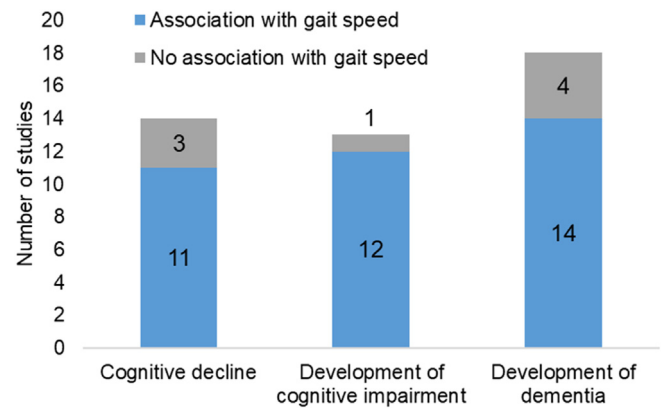


Fig. 1. Number of studies reporting an association or no association between gait speed and different cognitive outcomes.

2016). Moreover, as shown in Table 1 and Fig. 1, slow gait speed is associated with faster cognitive decline and higher incidence of dementia.

In older people, gait speed is the result of the life-long interplay between factors internal and external to the individual. It has been suggested that usual (or preferred) gait speed is quite stable across adult life and then starts to decline in old age (Schrack et al., 2016; Bohannon, 1997; Hanson et al., 2016; Gluckman et al., 2009; Hedden and Gabrieli, 2004). Walking is an energy demanding activity that requires the fine command of the central nervous system (CNS), the integrity of a number of body systems and organs (e.g., peripheral nervous system, cardiovascular) and the support of several sensorial functions (e.g., vision, hearing; Fig. 2). As a consequence, a decline in gait speed may be the result of both clinical and subclinical impairments accumulating across the above-mentioned structures and functions. For these reasons, it has been suggested as a reliable summary measure of biological age, as its faster decline is linked to accelerated aging and frailty (Studenski et al., 2011; Vetrano et al., 2018a; Calderon-Larranaga et al., 2019; Vetrano et al., 2018b; Zucchelli et al., 2018).

Several morbid conditions and factors need to be taken into account when slow gait speed is used as a predictor of cognitive decline and incident dementia, both in clinical and research settings. First, there are several demographic factors and lifestyle-related conditions that may determine slow gait speed, such as low education and physical inactivity (Welmer et al., 2013; Okada et al., 2015; Bohannon, 2008; Willey et al., 2017). Second, both acute and chronic conditions may impair walking; they include systemic (e.g., fever, pain) or organ-specific conditions (e.g., cardiovascular events and neurological diseases including stroke) (Vetrano et al., 2018a; Bano et al., 2016; Abe et al., 2016; Ayis et al., 2007). Finally, a number of external factors may affect gait speed, among which are medications (e.g., anticholinergic drugs) or the use of walking aids (Wert et al., 2010; Azmi et al., 2012). Untangling the role played by each of these conditions remains challenging.

### 5. Common underlying mechanisms of cognitive and motor decline

Cognitive and motor decline share a number of pathophysiological pathways (Ferrucci et al., 2018). As an expression of the aging process, biomolecular mechanisms including mitochondrial dysfunction, cellular senescence, genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, altered intercellular communication, and stem cell exhaustion, represent the underlying drivers of phenotypic changes that will ultimately affect both cognitive and motor function (Ferrucci and Fabbri, 2018; Lopez-

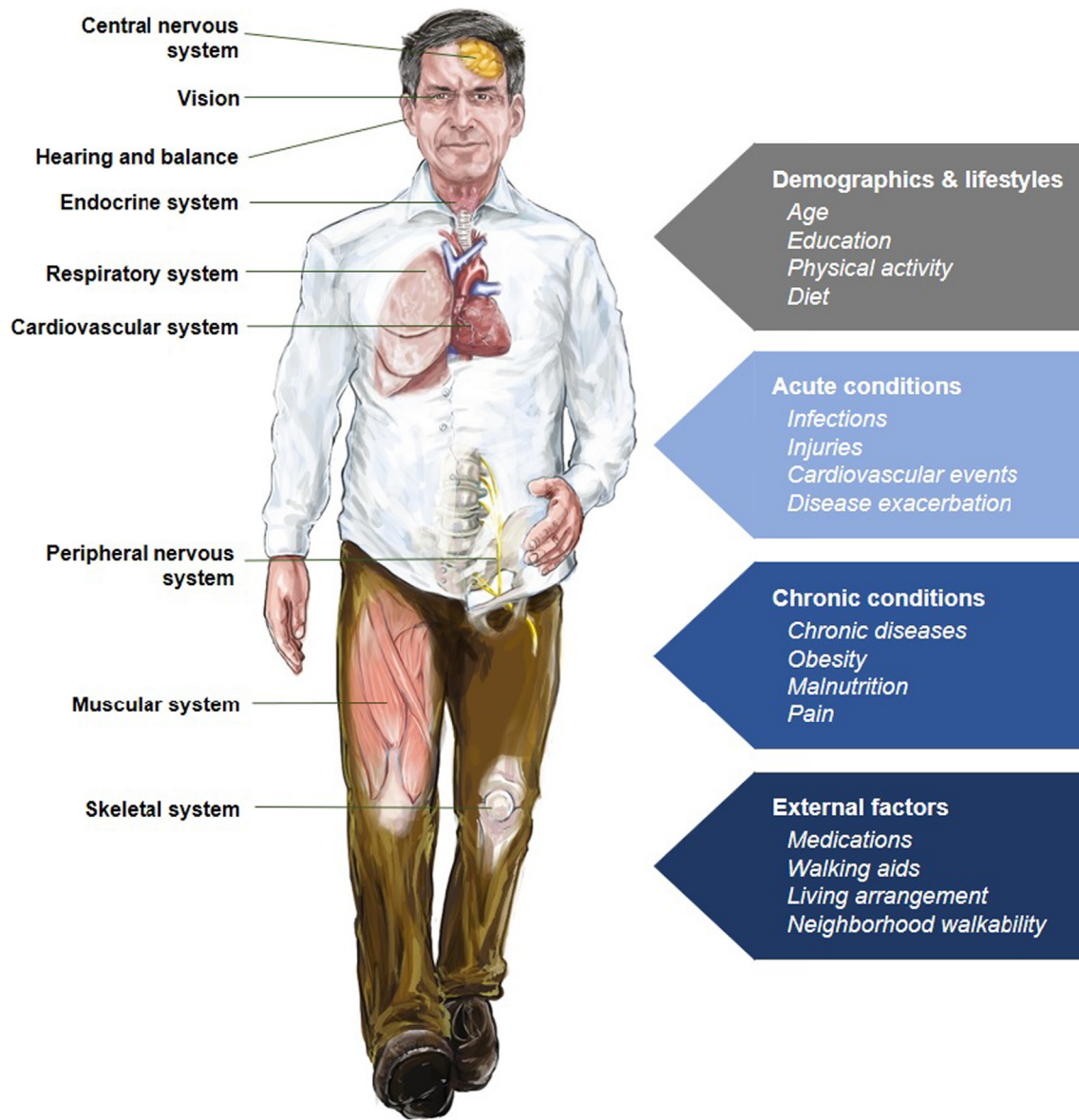


Fig. 2. Body systems involved in the maintenance of gait speed and potential affecting factors.

Otin et al., 2013). This decreasing homeostatic reserve may be the cause and consequence of several somatic conditions, which in turn will affect cognition and mobility in a more or less direct fashion (i.e., body-driven hypothesis). At the same time, motor and cognitive decline may arise from, or can be part of, morbid conditions occurring at the CNS level (i.e., brain-driven hypothesis). These two hypotheses are hereafter described.

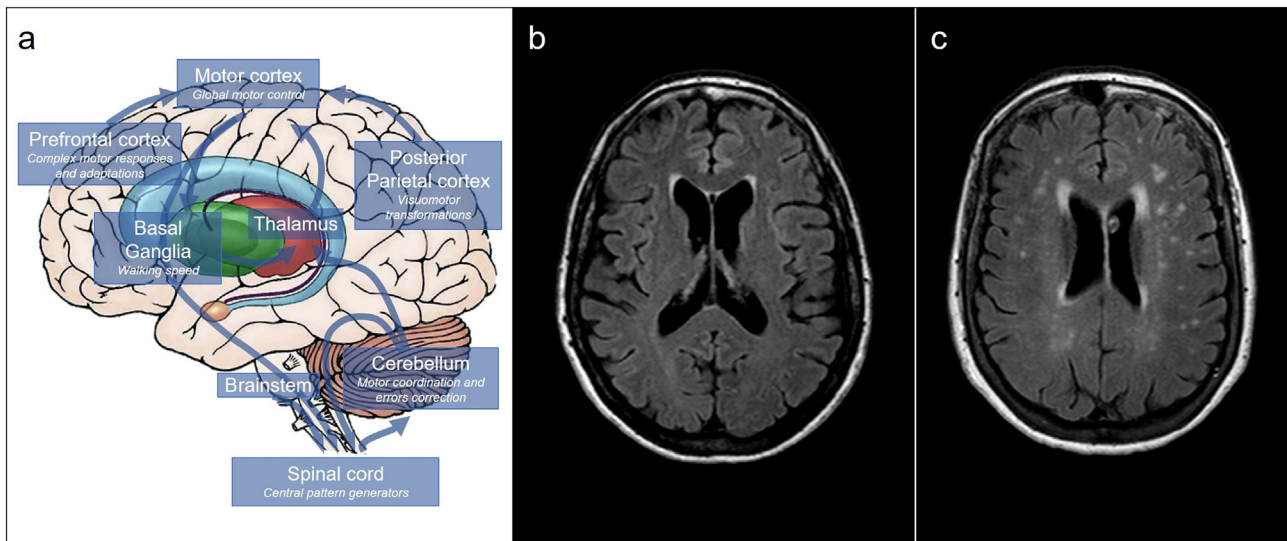
### 5.1. Brain-driven hypothesis

Even if largely consisting of automatic movements and considered a relatively simple act, human gait is a complex task requiring the coordinated integration of widespread brain regions, most of which are also involved in higher-level cognitive tasks (Rosso et al., 2017). Hence, change in gait pattern – including gait speed and dual-task performing – may underlie possible structural damages of such brain areas, which may be concurrently responsible for a decline in cognitive function (Rosso et al., 2019).

#### 5.1.1. Neurophysiology of gait control

The basic motor patterns for gait are automatically regulated at low-

order levels of the CNS (i.e. spinal cord), with a complex dynamic modulation exerted by higher brain centers (Calancie et al., 1994; Forssberg, 1985). Such fine control is known to be supported by descending signals from the supraspinal brain structures, involving the brain stem, cerebellum, basal ganglia and motor cortex. These regions, showing a rhythmic activity during gait, play different roles in the control of gait. The upper brainstem, under the control of the basal ganglia, motor cortex, and cerebellum, regulates gait initiation and cadence through its projections to the spinal cord whereas the cerebellum exerts its gait control by comparing actual movements with the intended ones (Drew et al., 2008; Mori et al., 1992). Walking speed and stride length are mainly modulated by the interplay between the basal ganglia and supplementary motor areas (Takakusaki, 2017). Finally, high-order aspects of gait entail multiple brain cortex domains: the frontal cortex produces complex motor responses closely integrating the multiple sensory inputs, including proprioceptive information, with environmental constraints (Beauchet et al., 2008); the motor cortex supports the integration of such information, generating a global motor control message (Graziano et al., 2002); and the posterior parietal cortex provides visuo-motor transformations able to control precise stepping movements and working memory processes for guiding leg



**Fig. 3.** Panel a) Brain areas involved in gait control. Except for brainstem and spinal cord, the indicated regions are also engaged in several multimodal cognitive processes. Panel b) MRI (FLAIR T2 sequence) showing progressive diffuse brain atrophy in a 56 year old female with Alzheimer's Disease. Panel c) MRI (FLAIR T2 sequence) showing subcortical white matter lesions in a 70 year old female patient with vascular dementia.

movements across obstacles in the environment (Drew et al., 2004; Pizzamiglio et al., 2018; Tian et al., 2017b) (Fig. 3, panel a).

### 5.1.2. Gait speed as a window to the brain

Neuroimaging studies using functional Magnetic Resonance Imaging (fMRI) have shown that motor control and cognitive processes share common neural substrates, in particular in the prefrontal, parietal and temporal areas (Rosano et al., 2012; Annweiler et al., 2013; Rosso et al., 2013). Interestingly, a reduced dopaminergic metabolism, due to genetic polymorphisms, is associated with both poorer cognitive and motor function, suggesting shared neural pathways (Holtzer et al., 2010; Hupfeld et al., 2018). Networks involved in both cognitive and motor control may be functionally overloaded when a motor task (e.g., gait) is simultaneously performed with a cognitive one (e.g. backward counting), and this can be used for diagnostic purposes. Both in clinical and research settings, such an approach – referred to as a *dual-task gait test* – which challenges the cognitive component of gait, provides plenty of information about the relationship between brain motor control and cognitive performance (Montero-Odasso et al., 2017; Montero-Odasso et al., 2012). The magnitude of changes in gait during a dual-task test is usually expressed as a dual-task gait cost. When cognitive reserve is reduced, dual-task gait is able to additionally stress the motor-cognitive interface, providing indirect information about the degree of cognitive impairment. Indeed, the magnitude of gait slowing during dual tasking is linearly associated with executive function, attention and memory performances in people with MCI and was shown to predict progression to AD (Camicioli et al., 1997, 1998; Montero-Odasso et al., 2009). More interestingly, even in cognitively intact individuals, dual-task effect on walking has been associated with neurodegenerative genetic and biochemical markers like apolipoprotein E  $\epsilon$ 4 and amyloid- $\beta$  (Nadkarni et al., 2017; Tian et al., 2017c). Even easier to evaluate than the dual-task test, walking speed provides insights about the clinical course of normal cognitive aging and pathological cognitive decline, which may eventually shift toward overt dementia. The clinical evidence earlier provided in this review supports this hypothesis (Table 1).

### 5.1.3. Brain pathology, cognition, and gait

Neurodegenerative and vascular processes are the two main neurobiological determinants of cognitive decline, and to some extent contribute to motor impairment. Even if not mutually exclusive, the pathogenic mechanisms underlying these two conditions have traditionally been considered separately (van der Flier et al., 2018).

Neuroimaging, bio-molecular, and cellular investigations provided evidence that the most common form of neurodegenerative dementia (i.e., AD) is supported by pathological processes leading to neuronal dysfunction and death, mainly related to the amyloid- $\beta$  peptide (A $\beta$ ) and hyperphosphorylation of the microtubule-associated protein tau (Winblad et al., 2016), eventually resulting in grey matter atrophy (Fig. 3, panel b). Neurodegenerative burden is not only cause of cognitive symptoms (Villemagne et al., 2011), but is also thought to affect walking abilities (Tian et al., 2016). Slow gait speed has been found to be associated with higher levels of amyloid  $\beta$  in key brain areas in people at risk – but not yet symptomatic – for AD, suggesting that, to a certain extent, slower gait speed may represent an early sign of such a pathological condition (Del Campo et al., 2016). Further – although indirect – evidence about the interaction between neurodegenerative processes and walking speed is provided by pharmacological studies, where acetylcholinesterase inhibitors showed effectiveness in improving gait parameters in patients with AD (Montero-Odasso et al., 2019; Assal et al., 2008). In addition to primary neurodegeneration, also impaired blood flow in the brain can lead to the death of neural tissue. A higher vascular burden is associated with endothelial dysfunction, blood-brain barrier disruption, microbleeds, and neuroinflammation, all contributing to cerebral hypoperfusion and secondary neurodegeneration (Belkhefja et al., 2018; Qiu et al., 2005; Qiu and Fratiglioni, 2015). Besides negatively impacting on cognition (Wang et al., 2017a), impaired blood flow is concurrently affecting motor function and ultimately walking abilities, as demonstrated by several studies that explored the relationship between white matter vascular lesions and decline of gait abilities (Fig. 3, panel c) (Whitman et al., 2001; Willey et al., 2013). Of note, in patients suffering from vascular dementia, gait slowing occurs usually earlier than in AD (Mc Ardle et al., 2017) and is often associated with postural instability.

### 5.2. Body-driven hypothesis

The presence of a single chronic disease may be the sole and sufficient cause of both motor and cognitive impairment. Such impairments may be either the expression of the disease itself (i.e., symptom), or the result of its detrimental effect reverberated on other organs. For instance, heart failure, a syndrome characterized by organ congestion and systemic hypoperfusion, is considered a risk factor for both motor and cognitive decline (Pulignano et al., 2016; Vetrano et al., 2016). However, in older people, single diseases very rarely stand alone. The

coexistence of multiple diseases (i.e., multimorbidity) is rather the norm, conferring an even higher burden in terms of both motor and cognitive decline (Calderon-Larranaga et al., 2019). Multimorbidity affects up to 90% of people over 60 years of age (Calderon-Larranaga et al., 2016), and it has been reported being associated with steeper cognitive and gait speed declines (Vetrano et al., 2018a). This may be due to multiple mechanisms interacting and boosting each other into a far greater burden on function (Calderon-Larranaga et al., 2019). We hereby describe the major disease-related contributors to gait and cognitive decline.

### 5.2.1. Cardiorespiratory burden

Cardiovascular and pulmonary diseases often co-occur and synergistically exert their detrimental effects virtually on every organ, system, and ultimately body function (Vetrano et al., 2018a; Qiu and Fratiglioni, 2015; Dodd, 2015; Johannes et al., 2017). Slow gait speed and exhaustion are common manifestations of conditions as heart failure and chronic obstructive pulmonary disease, which have also been consistently associated with an increased risk of dementia (Vetrano et al., 2018a; Wolters et al., 2018; Rusanen et al., 2013; Karpman and Benzo, 2014). Moreover, several risk factors for cardiovascular and respiratory diseases, like smoking, hypertension and a sedentary lifestyle have also been independently associated with cognitive and motor impairment (Heiland et al., 2017; Wang et al., 2017b). The putative pathways at play in the relationship between cardiopulmonary fitness and functional status are different and encompass, among others, hypoperfusion, thrombo-embolic phenomena and hypoxia. As discussed in the previous section, cerebral vascular damage and hypoperfusion may affect neuronal functioning and, in turn, cognition (Qiu and Fratiglioni, 2015). The same mechanisms may also impair muscle oxygen supply and metabolism, causing reduced tolerance to exercise and promoting loss of muscle mass and slower gait speed (i.e., sarcopenia) (Suzuki et al., 2018). Interestingly, as a proof of concept of the importance of cardiopulmonary fitness, active participation in multidomain interventions targeting cardiovascular risk factors, have demonstrated beneficial effects on both cognitive and motor performances (Pahor et al., 2014; Ngandu et al., 2015; Kivipelto et al., 2018).

### 5.2.2. Metabolic burden

Metabolic control may substantially contribute to motor and cognitive function (Bianchi and Volpato, 2016; Biessels et al., 2006). Insulin resistance, the tipping point for type 2 diabetes mellitus cascade, has been associated with both cognitive decline and dementia (Zhang et al., 2017; Marseglia et al., 2018), as well as reduced mobility (Allet et al., 2008). In the brain, insulin resistance has been associated with reduced beta amyloid clearance and plaque development, accelerating AD pathology progression (Craft et al., 2013). Diabetes may also contribute to impaired somatosensory function due to polyneuropathy, which in turn may lead to slow gait through balance impairment. Insulin resistance may also contribute to sarcopenia, as it may induce the activation of muscle wasting via the rapamycin and ubiquitin-proteasome pathways, and fat accumulation (Jang, 2016; Morley et al., 2014). Moreover, advanced glycation end-products due to chronic hyperglycemia induce macro- and microvascular damage, which may lead to systemic burden on nervous (central and peripheral), and musculoskeletal systems, thus resulting into gait and cognitive impairments (Jang, 2016; Srikanth et al., 2011; Marseglia et al., 2019). However, insulin resistance usually arises in the context of an extended dysmetabolic control, which is comprised of dyslipidemia, obesity, and hypertension. These factors may contribute synergistically to both physical and cognitive decline via cardiovascular burden, as well as sarcopenia and frailty development (Morley et al., 2014). Furthermore, malnutrition, a risk condition in old age (de Moraes et al., 2013), may lead to lower energy availability, loss of muscle and deficiencies in vitamins D and B12, which might ultimately hamper cognitive and

motor functional status (Goodwill and Szoek, 2017; Grober et al., 2013; Hooshmand et al., 2016; Vidoni et al., 2017; Halfon et al., 2015). Last, the metabolic rate driven by thyroid function can be implicated in both physical (Bano et al., 2016; Simonsick et al., 2016) and cognitive dysfunction (Rieben et al., 2016).

### 5.2.3. Inflammatory burden

Evidence of the role of inflammation in functional decline has been conceptualized in the inflammaging theory, by which an imbalance between inflammatory and anti-inflammatory agents might lead to phenotypical aging (Franceschi and Campisi, 2014). A low grade proinflammatory status, driven by visceral obesity, genetic predisposition, and chronic infections, is typical of the aging process, even in healthy older individuals with no risk factors or overt clinical conditions (Ferrucci and Fabbri, 2018; Newman et al., 2016). In turn, chronic inflammatory activation may contribute to a range of pathological conditions (e.g., cardiovascular disease, diabetes, sarcopenia, chronic kidney disease) and their co-existence (multimorbidity), which ultimately leads to functional decline (Ferrucci and Fabbri, 2018). Evidence from population-based studies point to a link between higher levels of C-reactive protein and inflammatory cytokines like IL-6 and IL-1, and reduced gait speed (Cesari et al., 2004; Verghese et al., 2011). Likewise, a pro-inflammatory status has been associated with lower cognitive performance and increased risk of dementia (Lai et al., 2017; Bettcher and Kramer, 2014). Interestingly, observational studies have suggested a positive impact of anti-inflammatory medications and diet on both cognitive decline and motor function (Hayden et al., 2017), although evidence from clinical trials for dementia prevention is still scarce (Veronese et al., 2017).

## 6. Discussion

Individuals presenting with slow gait speed are more likely to experience a steeper cognitive decline, and to develop dementia than those with a faster gait speed. Supported by biological evidence linking cognitive and motor function, such findings suggest an interplay between body and mind in the development of dementia. The shared underlying mechanisms affecting cognition and gait speed are not completely understood and, if any, it remains challenging to identify a unique common cause – or main pathway – implicated in both dysfunctions. In this review, we have described different pathways that intimately connect body and mind, thinking them as part of two axes.

In accordance with the *brain-driven hypothesis*, a greater neurodegenerative or vascular burden underlies both cognitive and motor dysfunctions (Fig. 4) (Qiu and Fratiglioni, 2015). However, such pathological features frequently do not correlate with functional decline (Sperling et al., 2011; Searle and Rockwood, 2015; Buchman et al., 2013). Post mortem studies have demonstrated that people with a greater burden of neuropathology may display mild or even no cognitive impairment, whereas individuals with a milder pathological

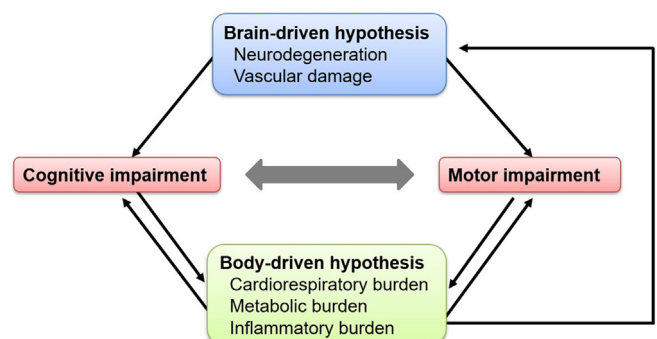


Fig. 4. Determinants and interplay of cognitive and motor impairment.

burden develop dementia (Savva et al., 2009). Such discrepancy suggests that other factors are at play, making some people more vulnerable to low degrees of brain damage. Systemic inflammation, greater cardiorespiratory and metabolic burden, stemming from conditions occurring outside the CNS, may exert further detrimental pressure on cognitive performances and concurrently explain reduced motor functions (i.e., *body-driven hypothesis*). Interestingly, in a retrospective study based on 456 brain autopsies, Wallace et al. showed that a high systemic burden conferred by diseases, symptoms, signs, and functional impairment, captured through a frailty index, strengthens the association between AD pathology and the clinical evidence of AD dementia at death (Wallace et al., 2019). Plausibly, once cognitive and/or motor impairments are established they tend to interact and boost each other into a further accumulation of damages, which in turn accelerates the aging process (Clouston et al., 2013; Robertson et al., 2013; Canevelli et al., 2015). For instance, motor impairment might increase sedentary habits, which might contribute to a further worsening of health conditions. Likewise, an impairment in cognition might lead to a lower pharmacological compliance and medical referral, with a consequent health deterioration (Grande et al., 2018b). The impact of a number of somatic conditions on cognitive decline and dementia, is supported by a recent concept, which exhibits dementia as a complex syndrome of aging rather than a single disease entity marked by a specific protein abnormality or accumulation (Wallace et al., 2019; Wallace et al., 2018). Gait speed might be considered as a marker of such underlying complexity that can help physicians to identify those frailer individuals less prone to tolerate the neuropathological burden.

Approaching cognitive and motor dimensions as distinct entities may hinder the understanding of common underlying mechanisms, and the potential for integrated preventive strategies and treatments. For this reason, during the last years several research groups have studied the combined effect of cognition and motor function. Different operationalizations have been suggested to study the combined effect of an initial cognitive impairment and motor impairment on the risk of developing dementia. Verghese et al. proposed the concept of “motoric cognitive risk syndrome”, which integrates the presence of subjective cognitive complaints with slow gait speed (Verghese et al., 2014). Montero-Odasso et al. combined slow gait speed with cognitive impairment defined by a low score on the Montreal – Cognitive Assessment test (Montero-Odasso et al., 2016, 2018a). Finally, the construct of “cognitive frailty” has been proposed based on an expert consensus, which refers to the simultaneous presence of both physical frailty (Fried’s et al. criteria) – which includes gait speed – and cognitive impairment (Kelaiditi et al., 2013). Despite the lack of agreement on the operationalization of the construct, studies constantly showed an additional prognostic value of walking speed and frailty to the standard cognitive assessment.

Our review supports the idea that gait speed might be used for risk stratification and to guide clinicians in the management of older adults with cognitive impairment. The integration of gait speed in the clinical assessment of individuals with and without cognitive impairment can be easily implemented in the clinical setting, being a simple, non-invasive, and inexpensive measure (Rodríguez-Manas and Fried, 2015). Such a multidimensional approach is highly advocated in light of the fact that the complexity of age-related conditions like dementia is determined by several and interrelated mechanisms. In addition, despite only few studies have to date investigated this issue, it is plausible to hypothesize that gait speed may confer an additional discriminative power to the assessment of people with initial cognitive impairment and thus, it can be proposed as a tool to better select the at-risk sample populations of future intervention studies, especially those testing the efficacy and effectiveness of multidomain interventions. In this regard, post hoc analyses of the Life trial, including 1635 sedentary older individuals, suggest potential benefits of a moderate-intensity physical activity program vs. a health educational program on executive functions, but only in older participants with poorer baseline physical

performance (including slow walking speed) (Sink et al., 2015).

At the same time, several knowledge gaps have been identified during the preparation of the present review. First, the great heterogeneity in gait speed assessments reported by previous work limit their direct comparison. However, in spite of such methodological differences, the majority of them reported an association of slower gait speed with cognitive decline, cognitive impairment and dementia, strengthening the hypothesis of an interplay between body and mind. Second, studies on the potential biological mechanisms underlined by both cognitive and motor dysfunction are still few. Most of the evidence comes from studies of neuroimaging or using the dual-task gait test. More research is needed to better describe the neural mechanisms underlying the motor-cognitive interface, which may involve motor and sensorimotor circuits to date neglected in studies on AD. Third, none of the few randomized controlled trials aiming at preventing cognitive decline and dementia employed measures of motor function to select their target populations. Similarly, pragmatic trials would help us to better foresee the implications of assessing gait speed in clinical practice (Canevelli et al., 2017). For these reasons, we can only hypothesize the additional role played by gait speed in selecting at-risk groups. Fourth, it is not clear if gait speed has a further prognostic role, in terms of future functional decline and other negative outcomes, once dementia has been recognized. This may have a clinical relevance for physicians and other professionals involved in the care of people with dementia.

In conclusion, the interplay of body and mind seems relevant during the development of cognitive decline and dementia. The measurement of gait speed may improve the detection of prodromal dementia and cognitive impairment in individuals with and without initial cognitive deficits. The potential applicability of such a measure in both clinical and research settings points at the importance of expanding our knowledge about the common underlying mechanisms of both cognitive and motor decline.

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## Contributorship

Conception or design of the work: GG, FT, DLV. Data extraction: GG, FT, DLV. Interpretation of the results: GG, FT, AN, A-KW, LF, DLV. Drafting the article: GG, FT, AN, DLV. Critical revision of the manuscript: GG, FT, AN, A-KW, LF, DLV. Final approval of the manuscript: GG, FT, AN, A-KW, LF, DLV. All the authors fulfil the ICMJE criteria for authorship.

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## Declaration of Competing Interest

All the authors have not conflicts of interest.

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