



**DECLINO COGNITIVO-
FUNZIONALE:
CARATTERISTICHE E
POSSIBILI DETERMINANTI DEL
FENOTIPO COGNITIVO-
MOTORIO**

Journal Club

Brescia, 18 marzo 2016

Andrea Crucitti

OUTLINE

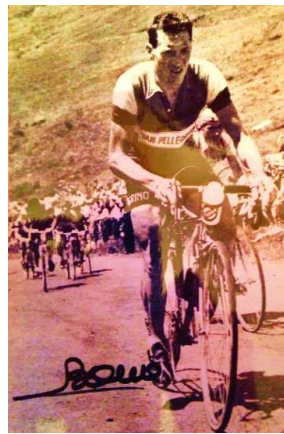
- Mobilità e cammino
- Attività fisica e rischio mortalità
- Disturbo della marcia e disabilità
- Qualità del cammino e cadute
- “Riserva motoria”
- Mobilità e stato cognitivo
- “Motoric Cognitive Risk syndrome” e rischio di demenza

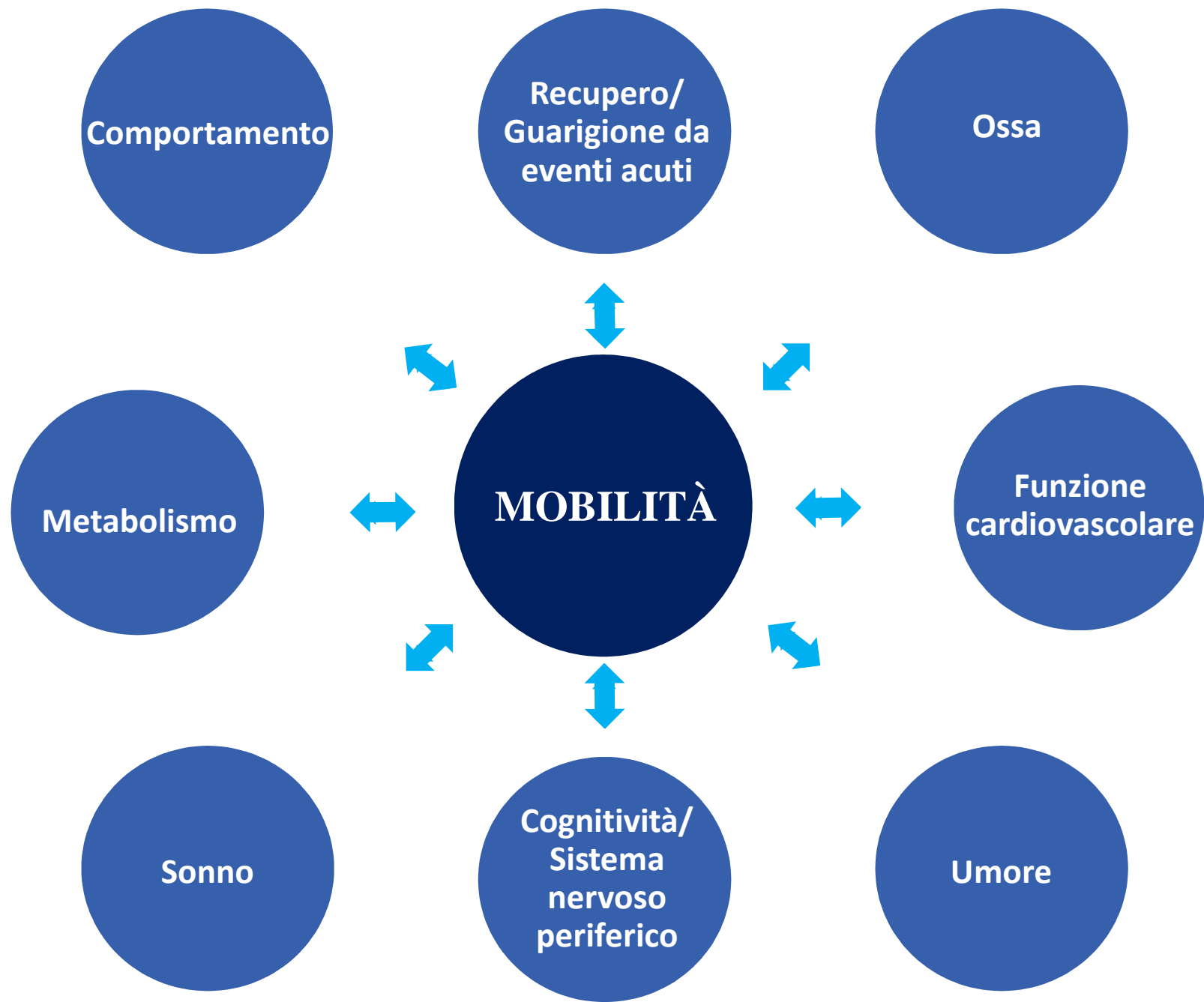
MOBILITÀ

È la capacità di muovere il proprio corpo nello spazio

Richiede forza e sistemi di controllo adeguati per esplorare con la propria massa corporea un ambiente tridimensionale

Camminare rappresenta la funzione fondamentale della mobilità per l'uomo





MOBILITÀ

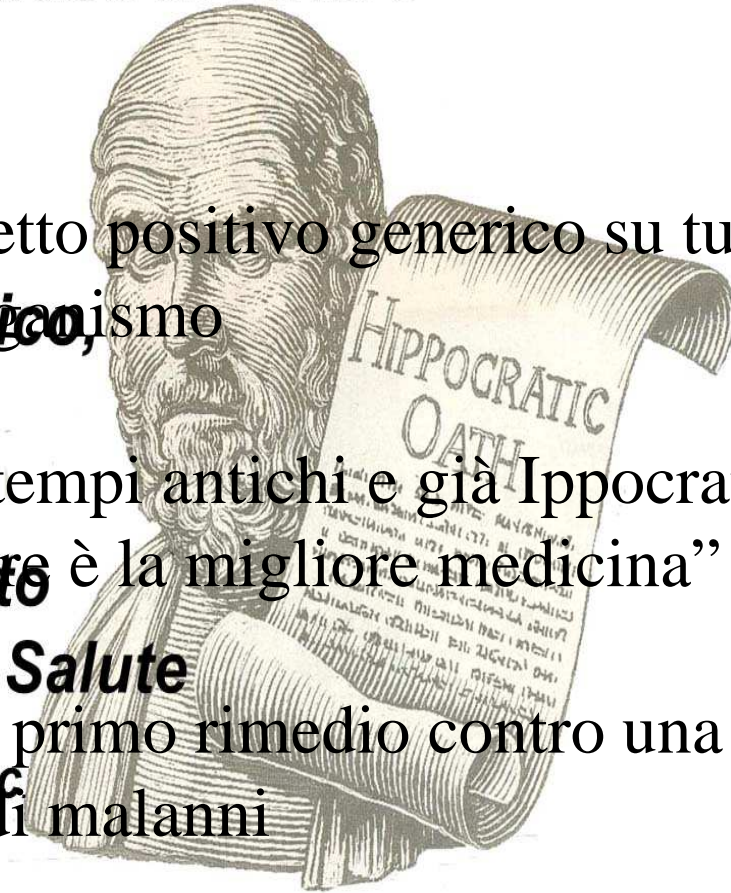
**Se fossimo in grado di fornire
a ciascuno
la giusta dose**

L'attività **di nutrimento** effetto positivo generico su tutto
ed esercizio fisico,ismo
ne' in eccesso

Tutto ciò è noto fin dai tempi antichi e già Ippocrate
ne' in difetto,
sosteneva: "Camminare è la migliore medicina"
avremmo trovato

la strada per la Salute

Una lunga camminata come primo rimedio contro una lunga
Ippocrate, 460-377 a.C.
lista di malanni



MOBILITÀ

Il livello di attività fisica sembra essere inversamente correlato al rischio di mortalità ed è associato ad una maggiore durata di vita media (approssimativamente 2 anni negli studi sugli uomini)

Una correlazione inversa è stata descritta anche tra l'attività fisica e il rischio di sviluppare alcune patologie tra cui quelle cardio e cerebro-vascolari, diabete mellito di tipo 2, osteoporosi, obesità, tumori del seno e del colon, ansia e depressione

*Hazzard's Geriatric Medicine and Gerontology
6th edition McGraw Hill, chapter 113-115*

Leisure Time Physical Activity of Moderate to Vigorous Intensity and Mortality: A Large Pooled Cohort Analysis

Steven C. Moore^{1*}, Alpa V. Patel², Charles E. Matthews¹, Amy Berrington de Gonzalez¹, Yikyung Park¹, Hormuzd A. Katki¹, Martha S. Linet¹, Elisabete Weiderpass^{3,4,5,6}, Kala Visvanathan⁷, Kathy J. Helzlsouer⁷, Michael Thun², Susan M. Gapstur², Patricia Hartge¹, I-Min Lee⁸

Background: Leisure time physical activity reduces the risk of premature mortality, but the years of life expectancy gained at different levels remains unclear. Our objective was to determine the years of life gained after age 40 associated with various levels of physical activity, both overall and according to body mass index (BMI) groups, in a large pooled analysis.

Methods and Findings: We examined the association of leisure time physical activity with mortality during follow-up in pooled data from six prospective cohort studies in the National Cancer Institute Cohort Consortium, comprising 654,827 individuals, 21–90 y of age. Physical activity was categorized by metabolic equivalent hours per week (MET-h/wk). Life expectancies and years of life gained/lost were calculated using direct adjusted survival curves (for participants 40+ years of age), with 95% confidence intervals (CIs) derived by bootstrap. The study includes a median 10 y of follow-up and 82,465 deaths. A physical activity level of 0.1–3.74 MET-h/wk, equivalent to brisk walking for up to 75 min/wk, was associated with a gain of 1.8 (95% CI: 1.6–2.0) y in life expectancy relative to no leisure time activity (0 MET-h/wk). Higher levels of physical activity were associated with greater gains in life expectancy, with a gain of 4.5 (95% CI: 4.3–4.7) y at the highest level (22.5+ MET-h/wk, equivalent to brisk walking for 450+ min/wk). Substantial gains were also observed in each BMI group. In joint analyses, being active (7.5+ MET-h/wk) and normal weight (BMI 18.5–24.9) was associated with a gain of 7.2 (95% CI: 6.5–7.9) y of life compared to being inactive (0 MET-h/wk) and obese (BMI 35.0+). A limitation was that physical activity and BMI were ascertained by self report.

Conclusions: More leisure time physical activity was associated with longer life expectancy across a range of activity levels and BMI groups.

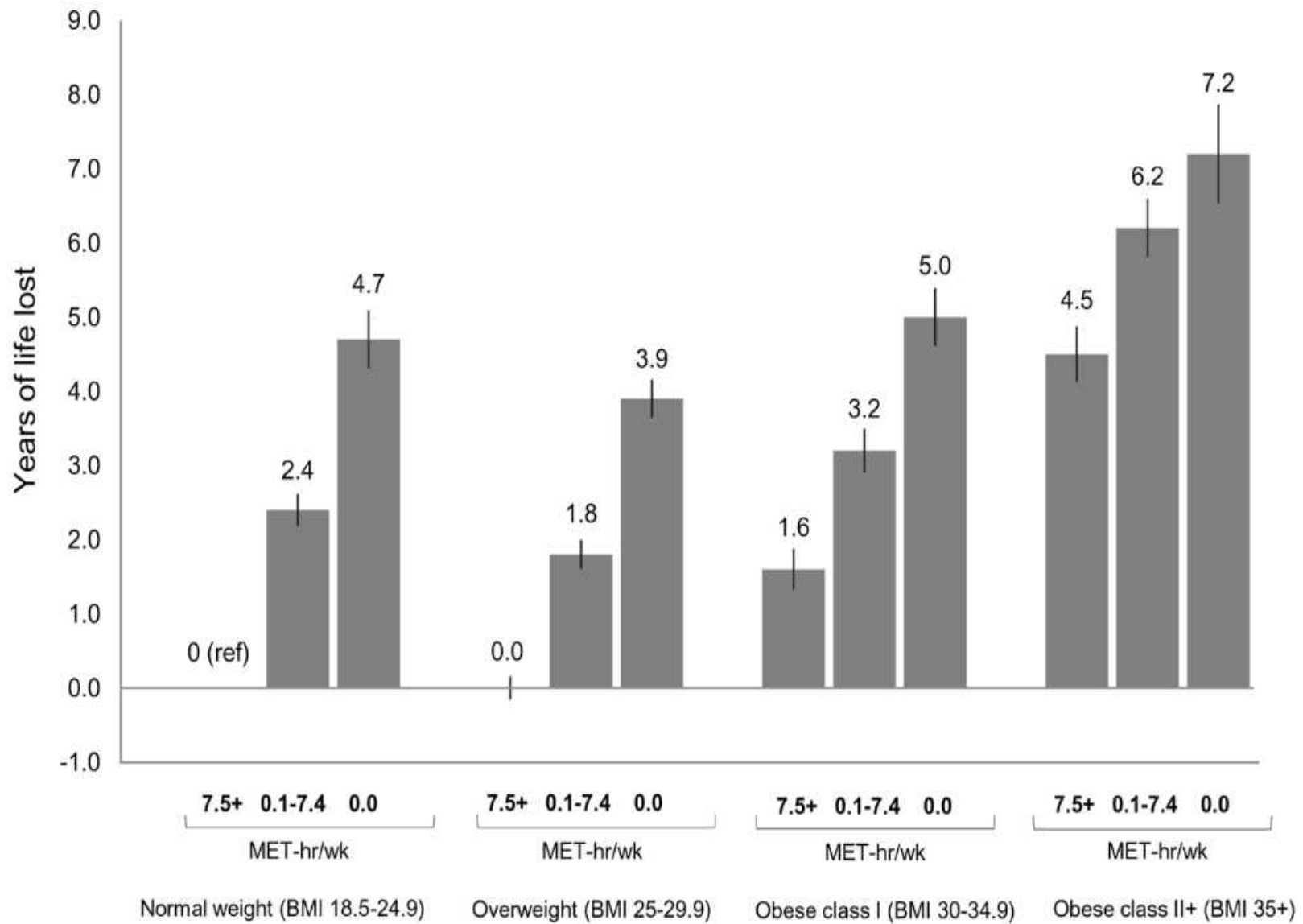


Figure 2. Years of life expectancy lost after age 40 in relation to joint categories of physical activity level and body mass index. T

Moore SC et al. PLoS Med 2012; 9: e1001335



RIDUZIONE VELOCITÀ DEL CAMMINO CON L'ETÀ

Processo progressivo e multifattoriale

Modificazioni età-correlate:

+ rigidità delle articolazioni

- forza muscolare arti inferiori

strategie di conservazione dell'energia

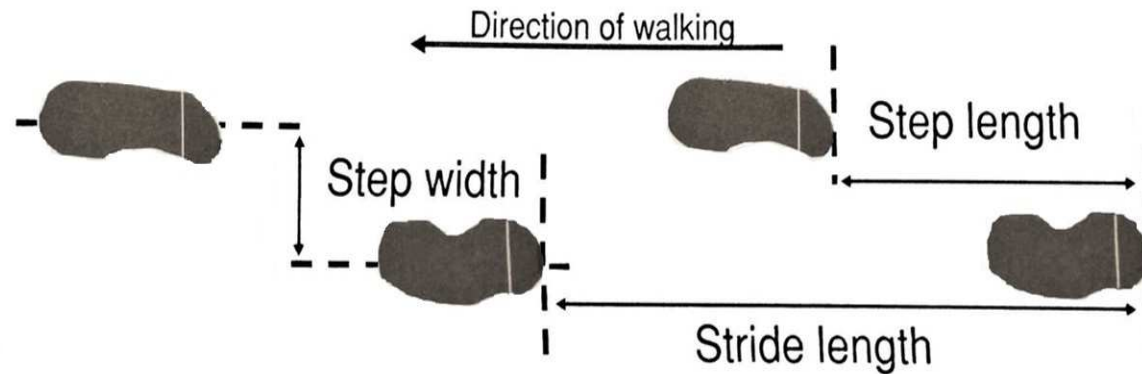


Riduzione lunghezza del passo (step length e stride length)

Aumento del tempo di doppio appoggio

Base d'appoggio allargata





Step length = la distanza tra due passi consecutivi ($dx-sx$)

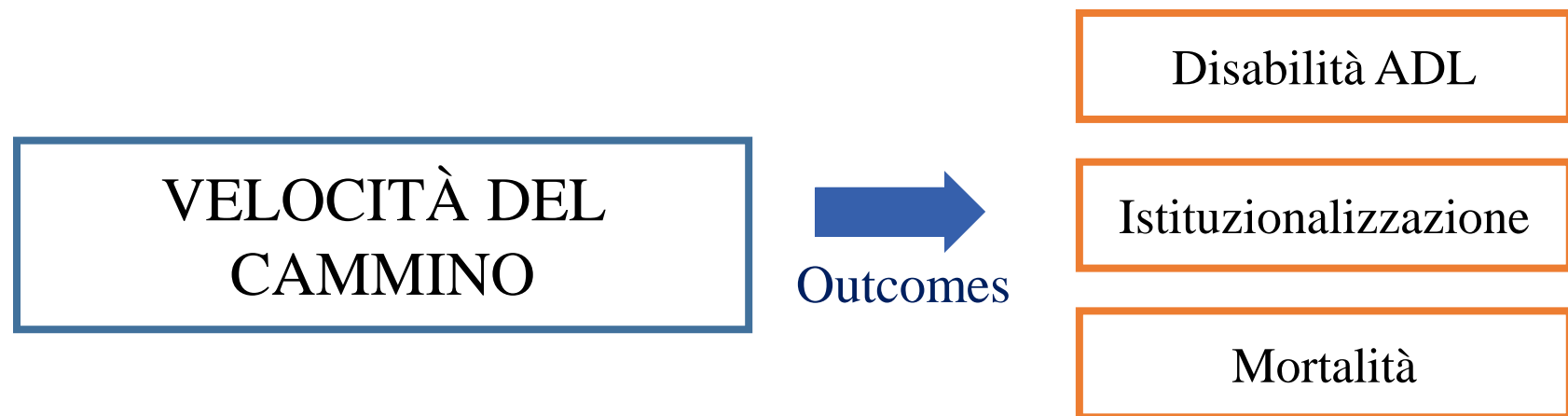
Stride length = la distanza tra due passi $dx-dx$ o $sx-sx$

Step width = la distanza tra i margini più esterni di due passi consecutivi

Stride variability = variabilità nel tempo del passo

Un aumento della variabilità nel tempo del passo è stato associato ad un incremento del rischio di cadute di 5 volte

Nell'invecchiamento la velocità del cammino si riduce in maniera minima fino ai 60 anni, successivamente declina dell'1-2% l'anno fino agli 80 anni



Velocità del cammino **inferiori a 0.8 m/s** sono indicative di elevato rischio di declino funzionale e ospedalizzazione

Gait Speed as an Integrator of Multiple Approaches

Walking speed could be considered a "vital sign" in older adults

Treatments could be aimed at managing the underlying pathological conditions that are causing the impairment (e.g., improving cardiac ejection fraction through treatment of congestive heart failure), treating the impairments themselves (e.g., strength training), or creating compensations and adaptations at the level of functional limitations (such as using a cane)

Research on the link among cardiovascular risk factors, brain structural abnormalities, mobility, cognition, and mood is developing rapidly. In the future, it may be possible to refine these observations into diagnosable and possibly treatable disorders.

*Hazzard's Geriatric Medicine and Gerontology
6th edition McGraw Hill, chapter 113-115*



Tabella 1

Fattori associati a disturbi dell'equilibrio e della marcia nell'anziano

Malattie cardiovascolari	Malattie metaboliche	Alterazioni muscolo scheletriche
<p><i>aritmie</i> <i>scompenso cardiaco</i> <i>cardiopatìa ischemica</i> <i>ipotensione ortostatica</i> <i>malattia trombo embolica</i> <i>arteriopatie periferiche</i></p>	<p><i>diabete mellito</i> <i>encefalopati aepatica</i> <i>distiroidismi</i> <i>obesità</i> <i>malnutrizione</i> <i>gotta</i></p>	<p><i>ipotrofia muscolare</i> <i>artrosi</i> <i>osteoporosi</i> <i>stenosi canale spinale</i> <i>spondilo lisi cervicale</i></p>
Malattie neurologiche	Anormalità sensoriali	Miscellanea
<p><i>morbo di Parkinson e parkinsonismi</i> <i>stroke</i> <i>idrocefalo normoteso</i> <i>disturbi vestibolari</i> <i>alterazioni cerebellari</i> <i>neuropatie</i> <i>demenza</i> <i>delirium</i></p>	<p><i>Ipoacusia</i> <i>ipovisus</i></p>	<p><i>Recente ospedalizzazione</i> <i>Malattia acuta</i> <i>Farmaci (antiaritmici, diuretici, oppioidi, anticonvulsivanti, antidepressivi, benzodiazepine o sedativi)</i> <i>Depressione</i> <i>Insonnia</i> <i>Paura di cadere</i> <i>Abuso di alcolici</i></p>

DISABILITÀ MOTORIA

La disabilità è provocata da processi patologici e declino nella funzione di diversi sistemi dell'organismo. Provoca handicap ponendo dei limiti al ruolo dell'individuo nella società.

La disabilità motoria provoca riduzione dell'attività fisica che, a sua volta, peggiora le limitazioni funzionali causando decondizionamento (debolezza muscolare, ridotta articolarietà e scarsa resistenza cardiovascolare).

Un'alterata mobilità è comune negli anziani, in particolare dopo gli 80 anni. Anche tra i non istituzionalizzati ultraottantenni vi è un'alta percentuale di individui che presentano difficoltà nello svolgimento delle attività della vita quotidiana.



Gli anziani che camminano male tendono a camminare sempre meno. Molti anziani rifiutano l'uso del bastone, delle stampelle o del roller ritirandosi tra le mura domestiche, dove grazie a punti di riferimento e di appoggio noti riescono ancora a mantenere la loro autonomia. La vergogna di mostrarsi disabile spesso limita di più delle effettive difficoltà a muoversi per strada e a superare gli ostacoli e le barriere architettoniche.

A favorire ancora di più il ritiro sociale secondario ai disturbi del cammino è la paura stessa di cadere, fattore che può determinare ulteriore peggioramento del cammino con perdita di autonomia e aumentare il rischio di caduta.

La paura di cadere si associa a disturbi d'ansia e depressione e compromette ulteriormente la qualità della vita. Nei pazienti anziani la prevalenza dei disturbi dell'andatura correlati all'ansia, depressione e paura di cadere, considerando anche le forme lievi, raggiunge l'85%.

*CAP 7. I disturbi del cammino del grande anziano tra sindrome e malattia. Marina Pizzoni, Angelo Bianchetti
Da: Umberto Senin, Luisa Bartorelli, Gianfranco Salvioli EDIZIONE: Carocci Faber 2013*

MOBILITÀ E CADUTE

La più seria conseguenza della ridotta mobilità nell'anziano è la tendenza alle cadute e i possibili danni da esse derivanti



Le cadute sono un evento comune nelle persone anziane.

PREVALENZA ANNUALE CADUTE:

1/3 anziani > 65 anni e 1/2 anziani > 80 anni

I disturbi della marcia rappresentano un fattore predisponente alle cadute soprattutto quando ad essi si aggiungono fattori precipitanti come cambiamenti ambientali, malattie, o effetti avversi ai farmaci.

I fattori che favoriscono le cadute sono: cadute precedenti, forza muscolare ridotta, disturbi visivi, politerapia (assumere più di 4 farmaci), psicofarmaci, vertigini, ipotensione ortostatica, malattie osteoarticolari, incontinenza, disturbi cognitivi, diabete e dolore. Le cadute possono, in alcuni casi, aggravare ancora di più l'incapacità funzionale preesistente con conseguente dipendenza e necessità di aiuto da parte degli altri nelle attività della vita quotidiana, per lunghi periodi o anche fino alla morte.



*CAP 7. I disturbi del cammino del grande anziano tra sindrome e malattia. Marina Pizzoni, Angelo Bianchetti
Da: Umberto Senin, Luisa Bartorelli, Gianfranco Salvioli EDIZIONE: Carocci Faber 2013*

RISERVA MOTORIA

Quando una sufficiente riserva viene persa o un sistema di compenso diventa insufficiente, la disabilità motoria si manifesta.

Per esempio, quando una persona con molti deficit subclinici affronta una richiesta motoria inaspettata, questa potrebbe essere più grande delle capacità motorie residue.

Può essere valutata:

- Chiedendo di eseguire compiti cognitivi e fisici simultanei ("dual task"). I soggetti anziani possono mostrare deterioramento motorio qualora venga richiesto di camminare e parlare o di compiere un contemporaneo calcolo mentale
- Attraverso test di mobilità che prevedano ostacoli
- Attraverso test di variabilità della marcia



**MOBILITÀ
E
STATO COGNITIVO**

Aree corticali e controllo del movimento volontario

Area motoria primaria (4)

M1

Aree motorie secondarie (6)

AMS

area motoria supplementare

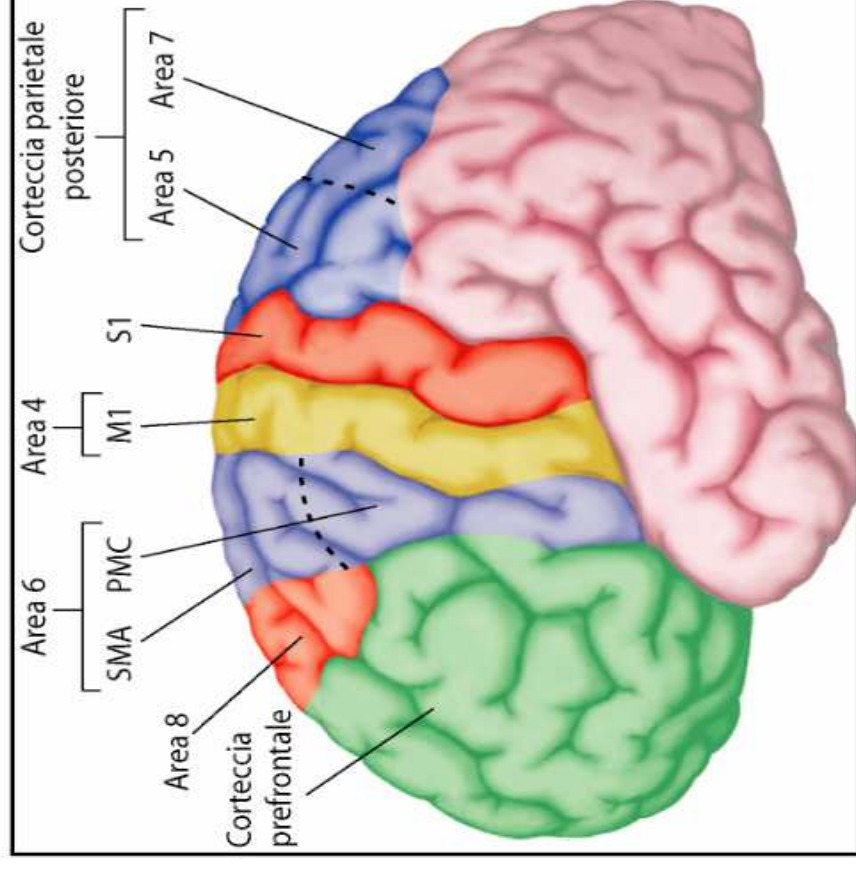
APM

area premotoria

Area associative (8, 5-7)

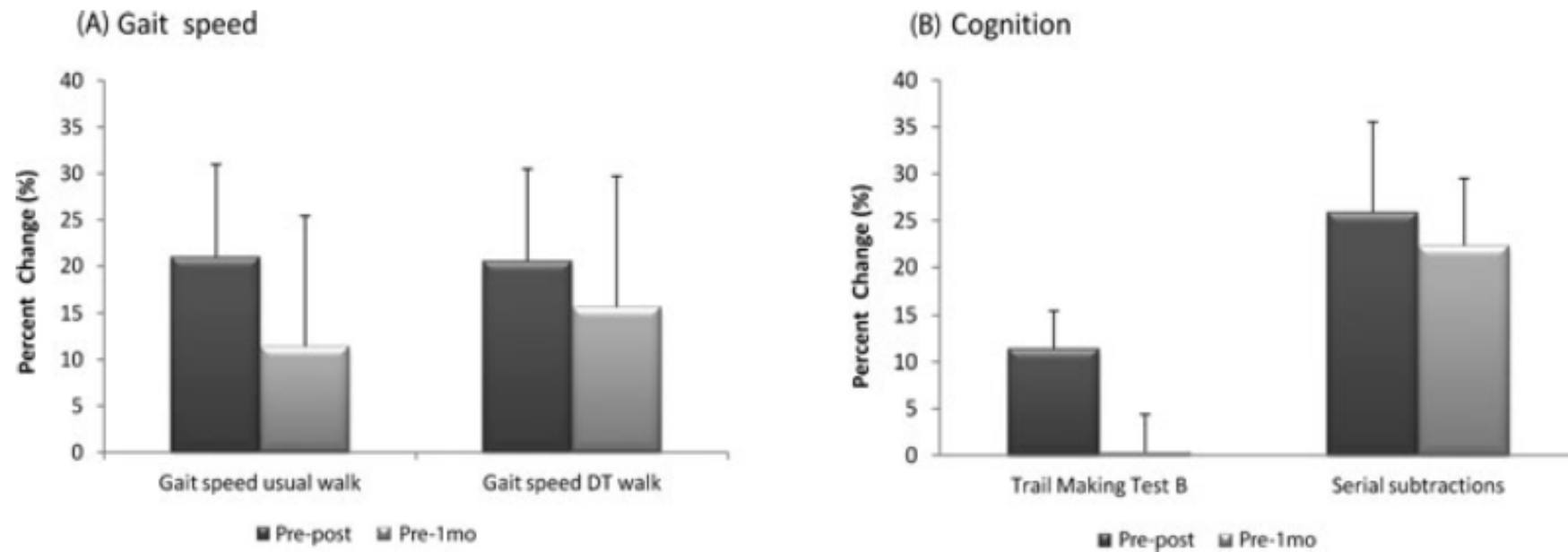
Area prefrontale dorsolaterale

Area parietale posteriore



Dual-Task Training on a Treadmill to Improve Gait and Cognitive Function in Elderly Idiopathic Fallers

Moran Dorfman, MPT, Talia Herman, MPT, Marina Brozgol, PT, Shirley Shema, PT, Aner Weiss, MSc, Jeffrey M. Hausdorff, PhD, and Anat Mirelman, PhD



(A) percent improvement in gait speed overground during usual walking and during DT and (B) percent improvement in cognitive function on the Trail Making Test B and serial subtraction during walking (dual task). Improvements in all measures were maintained at follow-up except in Trail Making Test B, in which time to complete the test returned to baseline.

JNPT 2014 38: 246-53

The Neurocognitive Basis for Impaired Dual-Task Performance in Senior Fallers

Falls are a major health-care concern, and while dual-task performance is widely recognized as being impaired in those at-risk for falls, the underlying neurocognitive mechanisms remain unknown. A better understanding of the underlying mechanisms could lead to the refinement and development of behavioral, cognitive, or neuropharmacological interventions for falls prevention. Therefore, we conducted a cross-sectional study with community-dwelling older adults aged 70–80 years with a history of falls (i.e., two or more falls in the past 12 months) or no history of falls (i.e., zero falls in the past 12 months); $n = 28$ per group. We compared functional activation during cognitive-based dual-task performance between fallers and non-fallers using functional magnetic resonance imaging (fMRI). Executive cognitive functioning was assessed via Stroop, Trail Making, and Digit Span. Mobility was assessed via the Timed Up and Go test (TUG). We found that non-fallers exhibited significantly greater functional activation compared with fallers during dual-task performance in key regions responsible for resolving dual-task interference, including precentral, postcentral, and lingual gyri. Further, we report slower reaction times during dual-task performance in fallers and significant correlations between level of functional activation and independent measures of executive cognitive functioning and mobility. Our study is the first neuroimaging study to examine dual-task performance in fallers, and supports the notion that fallers have reduced functional brain activation compared with non-fallers. Given that dual-task performance—and the underlying neural concomitants—appears to be malleable with relevant training, our study serves as a launching point for promising strategies to reduce falls in the future.

Nagamatsu LS et al. Front Aging Neurosci 2016; 8: 20

The Neurocognitive Basis for Impaired Dual-Task Performance in Senior Fallers

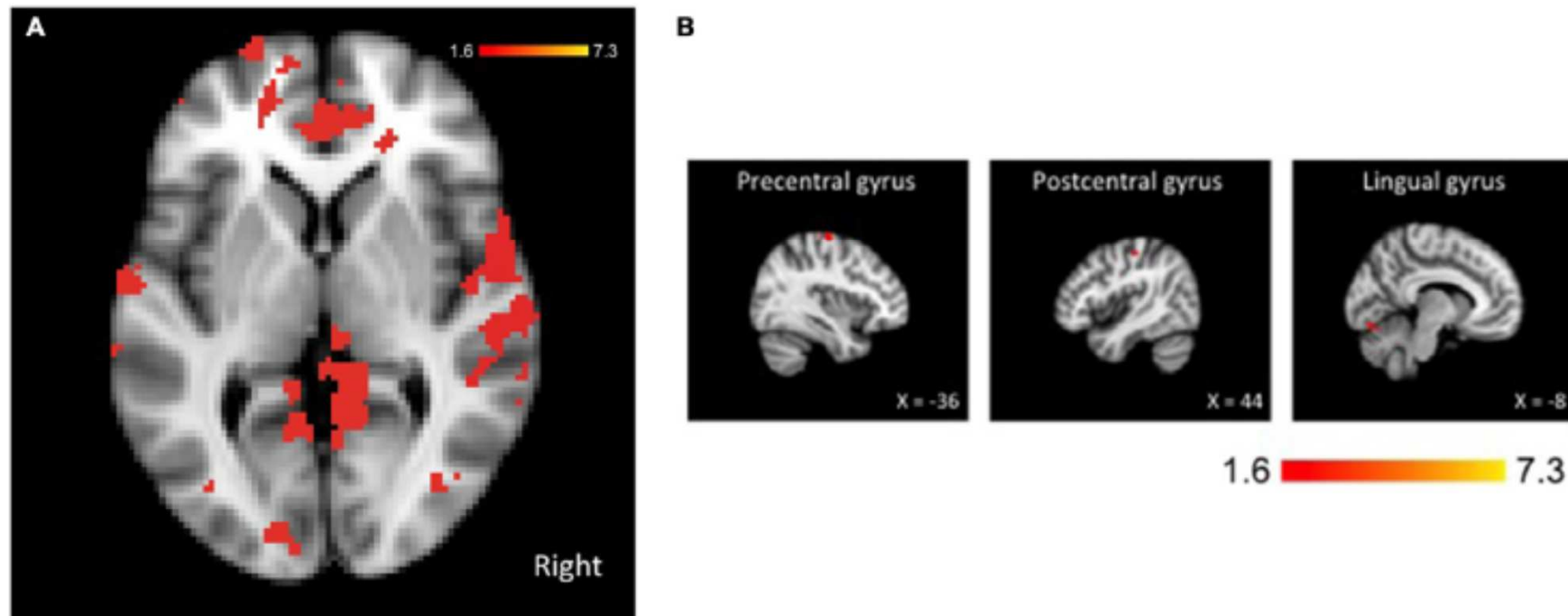


FIGURE 2 | Brain activation for the dual-task > single-task contrast showing greater activation for non-fallers compared with fallers. The threshold was set at $p < 0.05$, presented in neurological orientation. **(A)** Whole brain activation shown at coordinates $x = 0, y = 0, z = 0$. **(B)** Three significant clusters with maxima in precentral, postcentral, and lingual gyri. The threshold was set at $p < 0.05$, presented in neurological orientation.

Il declino cognitivo e la demenza sono comuni conseguenze dell'invecchiamento con un enorme impatto funzionale e sulla qualità della vita. Il riconoscimento precoce di individui ad elevato rischio di sviluppare demenza e l'attuazione di interventi efficaci rappresentano priorità sanitarie.

Una ridotta funzione motoria, come un rallentamento del cammino è fattore di rischio per lo sviluppo di MCI, demenza e un più rapido tasso di declino cognitivo. Allo stesso tempo, una funzione cognitiva ridotta, in particolare nelle funzioni esecutive, rappresenta un fattore di rischio per lo sviluppo di disabilità motoria, in particolar modo cadute e un più rapido tasso di declino motorio e funzionale



Hausdorff JM, Buchman AS. J Gerontol A Biol Sci Med Sci 2013 68: 409–411

MRI brain abnormalities are associated with alterations in central processing and abnormal gait. Small vessel cerebrovascular disease and MRI findings of "white matter disease" or focal grey matter atrophy are associated with slower gait speed, even among high-functioning older adults. These MRI findings predict the onset of mobility disability. **Such brain abnormalities have been found to concurrently affect mobility, cognition, and mood and may suggest a shared underlying cerebrovascular process.**

Subclinical losses of dopaminergic transmission in the aged brain (that may be related to cerebrovascular disease) also could contribute to altered mobility.

Loss of oxygen-carrying capacity because of anemia has been recognized as a potential contributor to mobility limitations, perhaps owing to decreased endurance but also possibly because of chronic subclinical ischemic effects on the brain.

Gait analysis in demented subjects: Interests and perspectives

Olivier Beauchet¹
Gilles Allali²
Gilles Berrut³
Caroline Hommet⁴
Véronique Dubost⁵
Frédéric Assal²

¹Department of Geriatrics, Angers University Hospital, France;

²Department of Neurology, Geneva University Hospital, France;

³Department of Geriatrics, Nantes University Hospital, France;

⁴Department of Internal Medicine and Geriatrics, Tours University Hospital, France;

⁵Department of Geriatrics, Dijon University Hospital, France

Abstract: Gait disorders are more prevalent in dementia than in normal aging and are related to the severity of cognitive decline. Dementia-related gait changes (DRGC) mainly include decrease in walking speed provoked by a decrease in stride length and an increase in support phase. More recently, dual-task related changes in gait were found in Alzheimer's disease (AD) and non-Alzheimer dementia, even at an early stage. An increase in stride-to-stride variability while usual walking and dual-tasking has been shown to be more specific and sensitive than any change in mean value in subjects with dementia. Those data show that DRGC are not only associated to motor disorders but also to problem with central processing of information and highlight that dysfunction of temporal and frontal lobe may in part explain gait impairment among demented subjects. Gait assessment, and more particularly dual-task analysis, is therefore crucial in early diagnosis of dementia and/or related syndromes in the elderly. Moreover, dual-task disturbances could be a specific marker of falling at a pre-dementia stage.

Keywords: gait, prediction of dementia, risk of falling, older adult

The main clinical hallmark of dementia is cognitive decline

Although not as prominent, motor disorders are commonly described in later stages of dementia and include:

- Gait apraxia
- Bradykinesia
- Extrapyrarnidal rigidity
- Resting tremor
- Various gait disorders such as cautious gait or gait slowing



...motor disorders, and specifically gait disorders, may be present at an early stage of dementia.

Dementia-related gait changes could be used to improve early diagnosis and better understand risk of falling in subjects with dementia or even at a pre-dementia stage.

The Motor Signature of Mild Cognitive Impairment: Results From the Gait and Brain Study

Manuel Montero-Odasso,^{1,2,3} Afua Oteng-Amoako,¹ Mark Speechley,^{1,2,3} Karen Gopaul,¹ Olivier Beauchet,⁴ Cedric Annweiler,⁴ and Susan W. Muir-Hunter^{1,2}

¹Gait and Brain Lab, Parkwood Hospital, Lawson Health Research Institute,

²Schulich School of Medicine and Dentistry, Department of Medicine and Division of Geriatric Medicine and

³Department of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario, Canada.

⁴Department of Neuroscience, Division of Geriatric Medicine, Angers University Hospital, Angers, France.

Address correspondence to Manuel Montero-Odasso, MD, PhD, AGSF, FRCPC, 801 Commissioners Road, E. Rm A-280, London, ON N6C 5J1, Canada. Email: mmontero@uwo.ca

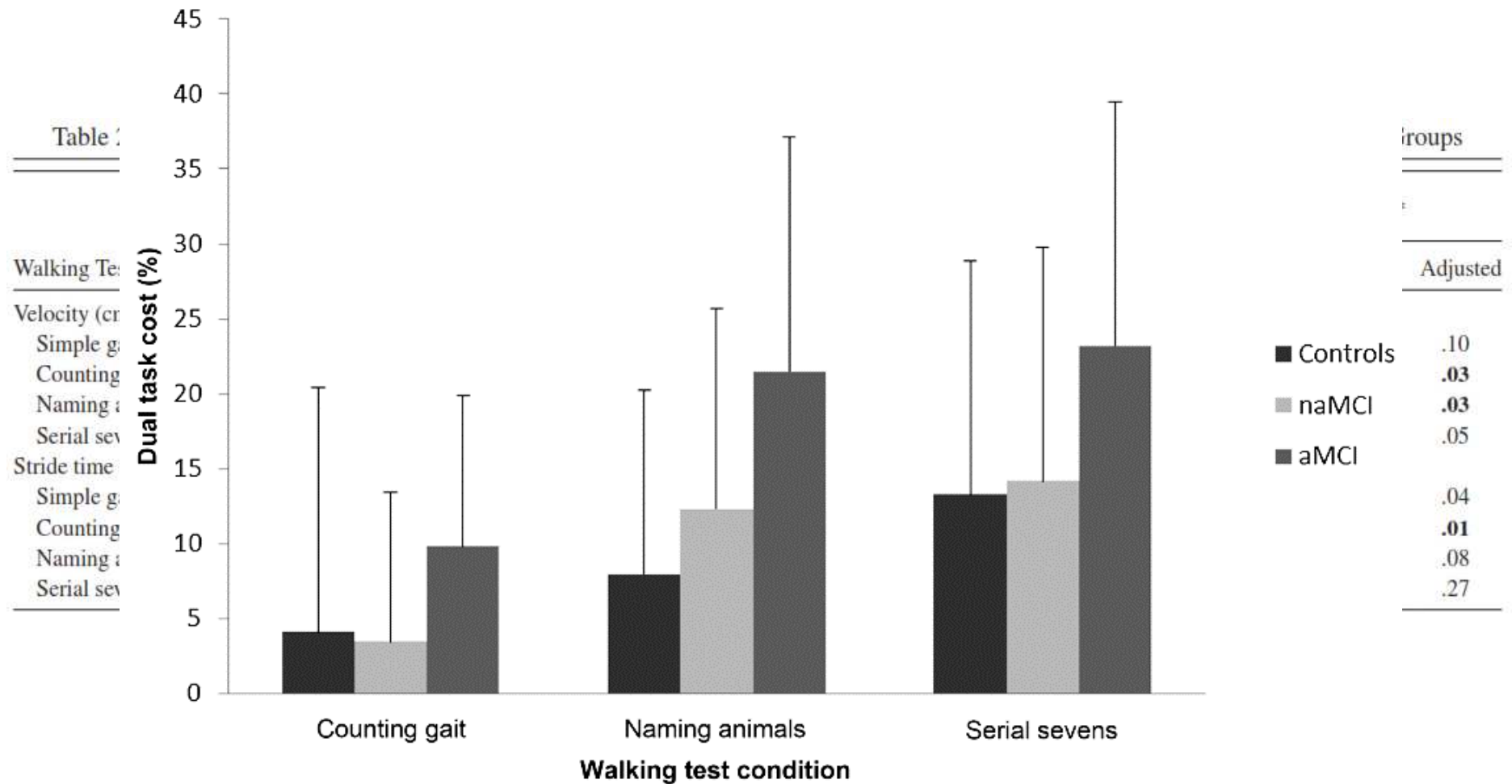
Background. Early motor changes associated with aging predict cognitive decline, which suggests that a “motor signature” can be detected in predementia states. In line with previous research, we aim to demonstrate that individuals with mild cognitive impairment (MCI) have a distinct motor signature, and specifically, that dual-task gait can be a tool to distinguish amnesic (a-MCI) from nonamnesic MCI.

Methods. Older adults with MCI and controls from the “Gait and Brain Study” were assessed with neurocognitive tests to assess cognitive performance and with an electronic gait mat to record temporal and spatial gait parameters. Mean gait velocity and stride time variability were evaluated under simple and three separate dual-task conditions. The relationship between cognitive groups (a-MCI vs nonamnesic MCI) and gait parameters was evaluated with linear regression models and adjusted for confounders.

Results. Ninety-nine older participants, 64 MCI (mean age 76.3 ± 7.1 years; 50% female), and 35 controls (mean age 70.4 ± 3.9 years; 82.9% female) were included. Forty-two participants were a-MCI and 22 were nonamnesic MCI. Multivariable linear regression (adjusted for age, sex, physical activity level, comorbidities, and executive function) showed that a-MCI was significantly associated with slower gait and higher dual-task cost under dual-task conditions.

Conclusion. Participants with a-MCI, specifically with episodic memory impairment, had poor gait performance, particularly under dual tasking. Our findings suggest that dual-task assessment can help to differentiate MCI subtyping, revealing a motor signature in MCI.

The Motor Signature of Mild Cognitive Impairment: Results From the Gait and Brain Study



Cognitive function and gait speed under normal and dual-task walking among older adults with mild cognitive impairment

Takehiko Doi^{1,2,3*}, Hiroyuki Shimada¹, Hyuma Makizako^{1,2,3}, Kota Tsutsumimoto¹, Kazuki Uemura^{1,2}, Yuya Anan¹ and Takao Suzuki³

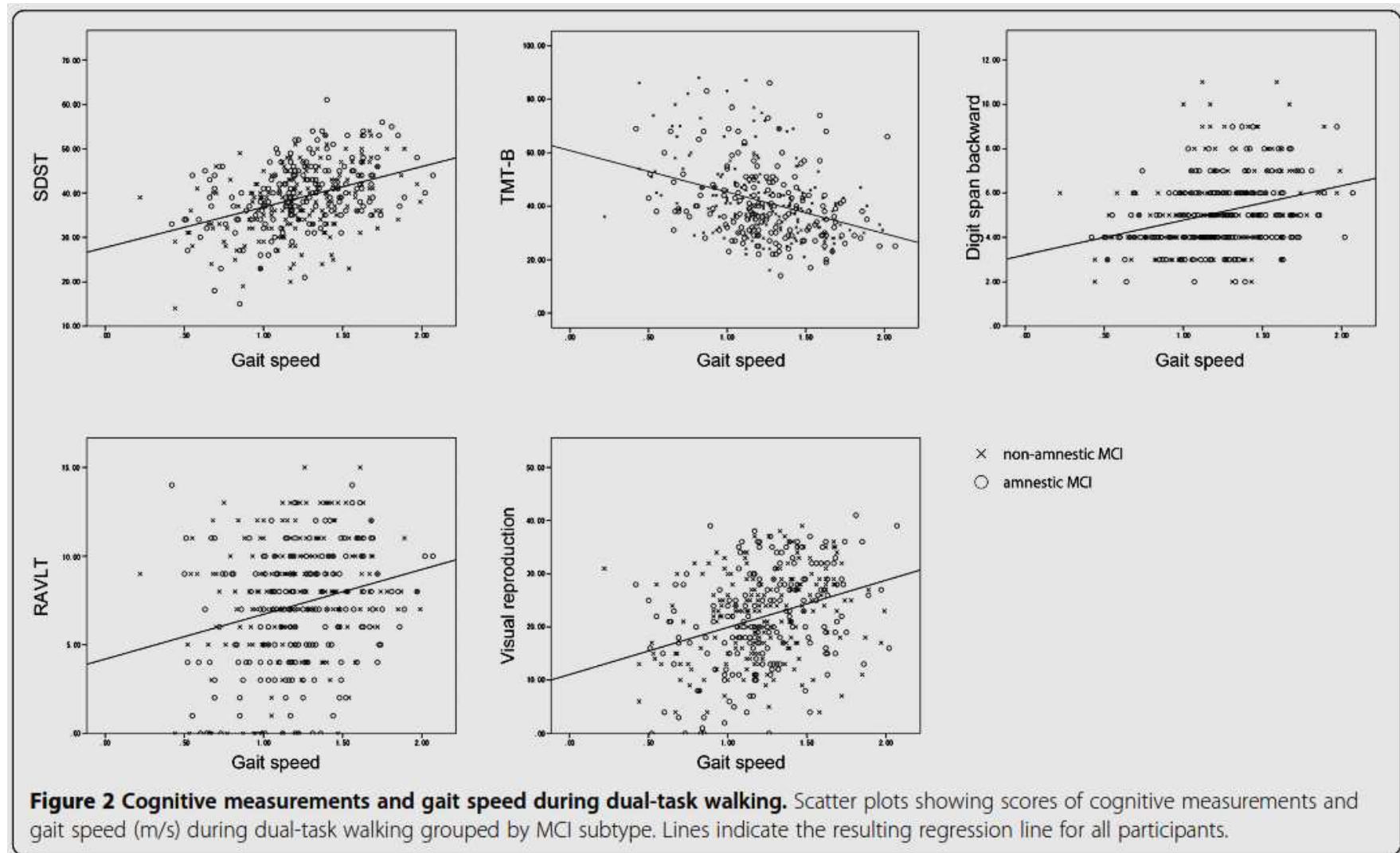
Abstract

Background: Gait ability and cognitive function are interrelated during both normal walking (NW) and dual-task walking (DTW), and gait ability is thus adversely affected by cognitive impairment in both situations. However, this association is insufficiently understood in people with mild cognitive impairment (MCI). Here, we conducted a study with MCI participants, to examine whether the association depends on walking conditions and MCI subtypes.

Methods: We classified 389 elderly adults into amnesic MCI (n = 191) and non-amnesic MCI (n = 198), assessed their cognitive functions, and administered gait experiments under NW and DTW conditions. Gait ability was defined as gait speed. Five aspects of cognitive function were assessed: processing speed, executive function, working memory, verbal memory, and visual memory.

Results: Regression analysis adjusted for covariates showed a significant association between cognitive functions and gait speed. Processing speed and executive function correlated with gait speed during both NW and DTW ($p < .05$). Gait speed during DTW was also significantly associated with working memory ($p < .001$). Visual memory was associated during NW and DTW, particularly for amnesic MCI participants ($p < .05$).

Conclusions: Our findings support the idea that the association between gait speed and cognitive function depends on walking condition and MCI subtypes. Additional studies are necessary to determine the neural basis for the disruption in gait control in older adults with MCI.



Cognitive measurements and gait speed during dual-task walking. Scatter plots showing scores of cognitive measurements and gait speed (m/s) during dual-task walking grouped by MCI subtype. Lines indicate the resulting regression line for all participants.

Episodic memory and executive function impairments in non-demented older adults: which are the respective and combined effects on gait performances?

Abstract Gait control depends in part on cognition. This study aims to examine the separate and combined effects of episodic memory and executive function impairments on the mean value and the coefficient of variation (CoV) of stride time among non-demented older community dwellers. Based on a cross-sectional design, 1458 older community dwellers without dementia (70.6 ± 4.9 years; 49.2 % female) were recruited and separated into cognitively healthy individuals (CHI) and individuals with cognitive impairment. A score $\leq 5/6$ on the Short Mini-Mental State Examination defined episodic memory impairment. Impaired executive function was defined by errors on the clock-drawing test. Mean value and CoV of

stride time were measured by the GAITRite[®] system. A total of 517 participants (35.5 %) had cognitive impairment in at least one cognitive domain. Participants with memory impairment ($P = 0.006$) and those with combined cognitive impairments ($P < 0.001$) had greater (i.e., worse gait performance) mean value of stride time ($P = 0.006$) compared to CHI. Participants with combined cognitive impairment had a greater CoV of stride time (i.e., worse gait performance) compared to CHI ($P = 0.004$) and to those with separate memory impairment ($P = 0.037$). Among participants with combined cognitive impairments, mean value and CoV of stride time had the highest effect size (respectively, effect size = 0.49 [95 % confidence interval (CI) 0.27;0.71] and effect size = 0.40 [95 %CI 0.18;0.62]). Participants with episodic memory or executive impairments had a greater mean value and CoV of stride time compared to those with no cognitive impairment. Combined episodic memory and executive impairments exceeded the sum of separate impairments on gait performances, suggesting a complex interplay going beyond a simple additive effect.

O. Beauchet (✉) · C. P. Launay · B. Fantino · C. Annweiler
Department of Neuroscience, Division of Geriatric Medicine,
UPRES EA 4638, UNAM, Angers University Hospital,
49933 Angers cedex 9, France
e-mail: olbeauchet@chu-angers.fr

O. Beauchet
Department of Medicine, Division of Geriatrics, McGill
University, Montréal, QC, Canada

Episodic memory and executive function impairments in non-demented older adults: which are the respective and combined effects on gait performances?

Table 1 Comparisons of the participants' characteristics separated into four groups based on cognitive status ($n = 1458$)

	Total population ($n = 1458$)	CHI ($n = 941$)	Individuals with			<i>P</i> value ^a						
			MI ($n = 244$)	EFI ($n = 189$)	MI and EFI ($n = 84$)	Overall	CHI vs. MI	CHI vs. EFI	CHI vs. MI and EFI	MI vs. EFI	MI vs. MI and EFI	EI vs MI and EFI
Age (years), mean \pm SD	70.6 \pm 4.9	70.1 \pm 4.5	70.8 \pm 5.1	71.9 \pm 5.6	72.6 \pm 5.9	<i><0.001</i>	0.308	<i><0.001</i>	<i><0.001</i>	0.118	<i>0.022</i>	1.000
Female gender, n (%)	717 (49.2)	485 (51.5)	103 (42.2)	92 (48.7)	37 (44.0)	0.052	–	–	–	–	–	–
Number of drugs taken per day, mean \pm SD	2.9 \pm 2.5	2.8 \pm 2.5	3.0 \pm 2.6	3.2 \pm 2.6	3.5 \pm 2.6	<i>0.020</i>	0.927	0.178	0.109	1.000	1.000	1.000
Use of psychoactive drugs ^b , n (%)	268 (18.4)	153 (16.3)	57 (23.4)	39 (20.6)	19 (22.6)	<i>0.045</i>	0.019	0.064	0.293	0.344	0.929	0.682
Depression symptoms ^c , n (%)	345 (23.7)	190 (20.2)	71 (29.1)	52 (27.5)	32 (38.1)	<i><0.001</i>	<i><0.001</i>	<i>0.002</i>	<i><0.001</i>	0.679	0.125	0.080
Body mass index (kg/m ²), mean \pm SD	26.3 \pm 4.2	26.1 \pm 4.1	26.8 \pm 4.4	26.6 \pm 4.2	27.3 \pm 5.2	<i>0.008</i>	0.080	0.831	0.063	1.000	1.000	1.000
Handgrip strength ^e (N m ⁻²), mean \pm SD	30.9 \pm 10.5	31.1 \pm 10.6	32.0 \pm 10.8	29.8 \pm 9.8	27.8 \pm 9.9	<i>0.006</i>	1.000	0.678	<i>0.034</i>	0.169	<i>0.009</i>	0.893
Lower-limb proprioception ^e (/8), mean \pm SD	6.3 \pm 1.7	6.4 \pm 1.7	6.1 \pm 1.7	6.2 \pm 1.7	5.7 \pm 1.9	<i>0.001</i>	0.116	1.000	<i>0.003</i>	1.000	0.401	0.131
Distance visual acuity ^f (/10), mean \pm SD	7.1 \pm 2.1	7.3 \pm 2.1	7.1 \pm 2.0	6.6 \pm 2.2	6.0 \pm 2.3	<i><0.001</i>	1.000	<i>0.001</i>	<i><0.001</i>	0.078	<i><0.001</i>	0.083
Fear of falling ^g , n (%)	303 (20.8)	180 (19.1)	56 (23.0)	41 (21.7)	26 (31.0)	0.054	–	–	–	–	–	–
History of falls in the past year, n (%)	460 (31.6)	290 (30.8)	80 (32.8)	57 (30.2)	33 (39.3)	0.407	–	–	–	–	–	–
Stride time												
Mean value (ms), mean \pm SD	1152.6 \pm 134.5	1140.9 \pm 127.7	1172.7 \pm 136.5	1161.7 \pm 140.8	1205.0 \pm 165.6	<i><0.001</i>	<i>0.006</i>	0.301	<i><0.001</i>	1.000	0.333	0.080
Coefficient of variation (%), mean \pm SD	2.1 \pm 1.4	2.0 \pm 1.4	2.1 \pm 1.4	2.2 \pm 1.5	2.6 \pm 1.8	<i>0.004</i>	1.000	0.450	<i>0.004</i>	1.000	<i>0.037</i>	0.359

Significant *P* value (i.e., $P < 0.05$) indicated in italics

Gait phenotype from mild cognitive impairment to moderate dementia: results from the GOOD initiative

G. Allali^{a,b}, C. Annweiler^{c,d}, H. M. Blumen^a, M. L. Callisaya^{e,f}, A.-M. De Cock^{g,h,i}, R. W. Kressig^j, V. Srikanth^{e,f}, J.-P. Steinmetz^k, J. Verghese^a and O. Beauchet^{c,l,m,n}

Background. The differences in gait abnormalities from the earliest to the later stages of dementia and in the different subtypes of dementia have not been fully examined

Purpose. To compare spatiotemporal gait parameters in:

- cognitively healthy individuals
- amnesic mild cognitive impairment (MCI)
- non-amnesic MCI
- mild and moderate stages of Alzheimer's disease (AD)
- Mild and moderate stages non-Alzheimer's disease (non-AD)

Gait phenotype from mild cognitive impairment to moderate dementia: results from the GOOD initiative

G. Allali^{a,b}, C. Annweiler^{c,d}, H. M. Blumen^a, M. L. Callisaya^{e,f}, A.-M. De Cock^{g,h,i}, R. W. Kressig^j, V. Srikanth^{e,f}, J.-P. Steinmetz^k, J. Verghese^a and O. Beauchet^{c,l,m,n}

Nr participants: 1719 (77.4±7.3 years, 53.9% female)

Countries participating in the Gait, Cognition and Decline (GOOD) initiative: Australia, Belgium, France, India, Luxembourg, Switzerland and the USA

Mean values and coefficients of variation of spatiotemporal gait parameters were measured during normal pace walking with the GAITRite system

	MCI				Dementia					
	CHI (n = 735)	Amnestic		P value ^a (P value ^b)	Mild			Moderate		
		(n = 108)	Non-amnestic (n = 286)		AD (n = 196)	Non-AD (n = 126)	P value ^a (P value ^c)	AD (n = 177)	Non-AD (n = 91)	P value ^a (P value ^d)
Age (years), mean ± SD	73.9 ± 6.3	76.7 ± 7.9	75.5 ± 6.6	0.117	82.5 ± 5.1	81.9 ± 5.1	0.280	83.9 ± 5.6	83.3 ± 5.2	0.411
Female gender, n (%)	374 (50.9)	40 (37.0)	134 (46.9)	0.080	134 (68.4)	71 (56.3)	0.029	121 (68.4)	52 (57.1)	0.069
Number of drugs taken per day, mean ± SD	1.2 ± 1.4	0.7 ± 1.0	0.8 ± 1.0	0.322	4.2 ± 2.3	4.6 ± 2.5	0.330	4.6 ± 2.6	4.4 ± 2.3	0.147
Body mass index (kg/m ²), mean ± SD	27.5 ± 5.3	26.4 ± 4.8	27.7 ± 5.1	0.020	26.2 ± 4.4	27.2 ± 4.9	0.054	25.8 ± 4.6	26.2 ± 3.8	0.069
Use of psychoactive drugs ^e , n (%)	93 (12.7)	24 (22.2)	70 (24.5)	0.640	85 (43.4)	60 (47.6)	0.454	79 (44.6)	46 (50.5)	0.358
Depression symptoms ^f , n (%)	134 (18.2)	30 (27.8)	98 (34.3)	0.220	105 (53.6)	58 (46.0)	0.187	93 (52.5)	50 (54.9)	0.709
History of falls ^g , n (%)	178 (24.2)	34 (32.4)	84 (29.4)	0.558	93 (47.4)	71 (56.3)	0.119	86 (48.6)	61 (67.0)	0.004
Walking speed (cm/s), mean ± SD	104.7 ± 22.2	96.7 ± 26.2	92.4 ± 25.9	0.138 (0.089)	74.1 ± 18.9	71.6 ± 20.4	0.245 (0.107)	68.1 ± 20.6	61.7 ± 20.3	0.015 (0.005)
Stride length										
Mean value (cm)	121.9 ± 20.2	116.4 ± 23.8	111.3 ± 24.7	0.067 (0.016)	93.0 ± 19.5	90.6 ± 21.7	0.298 (0.063)	85.3 ± 21.6	79.6 ± 20.3	0.038 (0.008)
CoV (%)	2.8 ± 1.7	3.5 ± 2.3	3.8 ± 3.2	0.265 (0.031)	5.4 ± 3.6	6.3 ± 3.7	0.025 (0.015)	6.8 ± 4.2	7.1 ± 4.0	0.587 (0.992)
Stride time										
Mean value (ms)	1175.6 ± 135.2	1224.5 ± 153.1	1225.1 ± 159.1	0.976 (0.818)	1270.1 ± 163.7	1282.6 ± 173.3	0.515 (0.793)	1273.9 ± 187.6	1321.1 ± 189.2	0.053 (0.058)
CoV (%)	2.6 ± 1.4	3.2 ± 1.9	3.6 ± 2.8	0.196 (0.076)	4.5 ± 3.5	4.7 ± 4.3	0.641 (0.313)	5.3 ± 3.4	5.7 ± 4.1	0.486 (0.952)
Swing time										
Mean value (ms)	411.7 ± 45.4	422.8 ± 41.8	416.3 ± 51.7	0.242 (0.382)	414.1 ± 49.4	407.3 ± 57.3	0.260 (0.465)	401.3 ± 60.7	406.5 ± 55.0	0.489 (0.271)
CoV (%)	4.4 ± 2.7	5.4 ± 3.9	5.8 ± 6.0	0.540 (0.182)	8.3 ± 8.7	7.9 ± 4.6	0.677 (0.290)	10.2 ± 10.1	10.6 ± 9.9	0.742 (0.782)
Stance time										
Mean value (ms)	764.0 ± 103.8	801.8 ± 128.9	808.8 ± 131.1	0.633 (0.970)	856.1 ± 135.1	875.3 ± 145.0	0.227 (0.841)	872.6 ± 156.8	914.6 ± 159.1	0.040 (0.043)
CoV (%)	3.3 ± 1.7	4.1 ± 2.4	4.6 ± 3.5	0.229 (0.135)	5.3 ± 3.0	5.8 ± 5.5	0.327 (0.222)	5.9 ± 2.5	6.8 ± 4.4	0.040 (0.458)

	MCI				Dementia					
	CHI (n = 735)			P value ^a (P value ^b)	Mild			Moderate		
		Amnestic (n = 108)	Non-amnestic (n = 286)		AD (n = 196)	Non-AD (n = 126)	P value ^a (P value ^c)	AD (n = 177)	Non-AD (n = 91)	P value ^a (P value ^d)
Single support time										
Mean	411.7 ± 45.4	423.0 ± 41.2	416.4 ± 51.4	0.229 (0.367)	414.1 ± 49.2	407.3 ± 57.3	0.255 (0.464)	401.9 ± 59.8	407.2 ± 54.6	0.483 (0.357)
value (ms)										
CoV (%)	4.4 ± 2.7	5.3 ± 3.8	5.8 ± 5.9	0.503 (0.165)	8.3 ± 8.7	7.9 ± 4.6	0.644 (0.299)	10.0 ± 9.9	10.5 ± 9.6	0.692 (0.923)
Double support time										
Mean	350.7 ± 85.1	378.6 ± 116.8	392.1 ± 121.4	0.319 (0.604)	447.3 ± 121.1	468.9 ± 134.9	0.137 (0.708)	477.7 ± 150.7	512.3 ± 148.7	0.075 (0.075)
value (ms)										
CoV (%)	6.2 ± 2.9	7.1 ± 4.2	7.8 ± 5.3	0.801 (0.059)	9.5 ± 5.2	9.2 ± 4.7	0.644 (0.754)	10.7 ± 8.4	10.3 ± 5.4	0.749 (0.385)
Stride width										
Mean	9.3 ± 3.3	9.8 ± 3.6	9.9 ± 3.7	0.775 (0.175)	10.3 ± 3.4	11.8 ± 3.6	<0.001 (0.003)	11.3 ± 3.7	12.3 ± 3.8	0.031 (0.070)
value (cm)										
CoV (%)	27.7 ± 16.1	27.4 ± 17.9	26.2 ± 15.2	0.551 (0.026)	25.7 ± 14.2	21.5 ± 13.0	0.007 (0.424)	23.3 ± 14.4	19.9 ± 13.0	0.065 (0.422)
Stride velocity										
Mean	105.5 ± 22.4	97.7 ± 26.4	93.2 ± 26.1	0.137 (0.088)	74.9 ± 19.0	72.4 ± 20.5	0.254 (0.110)	68.9 ± 20.8	62.4 ± 20.4	0.015 (0.005)
value (cm/s)										
CoV (%)	4.0 ± 2.1	5.1 ± 2.9	5.4 ± 3.4	0.288 (0.055)	6.9 ± 3.2	7.9 ± 4.4	0.022 (0.010)	8.2 ± 3.9	8.7 ± 4.4	0.257 (0.204)

Gait phenotype from mild cognitive impairment to moderate dementia: results from the GOOD initiative

G. Allali^{a,b}, C. Annweiler^{c,d}, H. M. Blumen^a, M. L. Callisaya^{e,f}, A.-M. De Cock^{g,h,i}, R. W. Kressig^j, V. Srikanth^{e,f}, J.-P. Steinmetz^k, J. Verghese^a and O. Beauchet^{c,l,m,n}

Results. Performance of spatiotemporal gait parameters declined in parallel with the stage of cognitive decline from MCI status to moderate dementia.

Conclusions. Spatiotemporal gait parameters were more disturbed in the advanced stages of dementia, and more affected in the non-AD subtypes than in AD.

These findings suggest that quantitative gait parameters could be used as a surrogate marker for improving the diagnosis of dementia.

**“MOTORIC COGNITIVE RISK
SYNDROME”**

Motoric Cognitive Risk Syndrome and the Risk of Dementia

Joe Verghese,¹ Cuiling Wang,² Richard B. Lipton,^{1,2} and Roe Holtzer^{1,3}

Background. Despite growing evidence of links between gait and cognition in aging, cognitive risk assessments that incorporate motoric signs have not been examined. We sought to validate a new Motoric Cognitive Risk (MCR) syndrome to identify individuals at high risk of developing dementia.

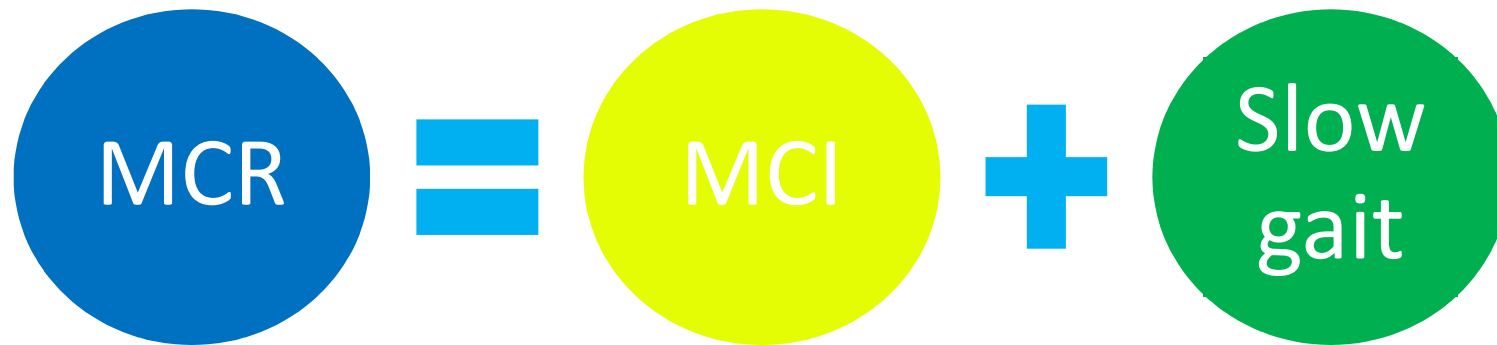
Methods. We evaluated 997 community residing individuals aged 70 and older participating in the Einstein Aging Study over a median follow-up time of 36.9 months. MCR syndrome was defined as presence of cognitive complaints and slow gait (one standard deviation below age- and sex-specific gait speed means) in nondemented individuals. Cox models were used to evaluate the effect of MCR syndrome on the risk of developing dementia and subtypes.

Results. Fifty-two participants met criteria for MCR syndrome at baseline with a prevalence of 7% (95% CI: 5–9%). Prevalence of MCR increased with age. Participants with MCR were at higher risk of developing dementia (hazard ratio [HR] adjusted for age, sex, and education: 3.27, 95% CI: 1.55–6.90) and vascular dementia (adjusted HR: 12.81, 95% CI: 4.98–32.97). The association of MCR with risk of dementia or vascular dementia remained significant even after accounting for other confounders and diagnostic overlap with “cognitive” mild cognitive impairment syndrome subtypes.

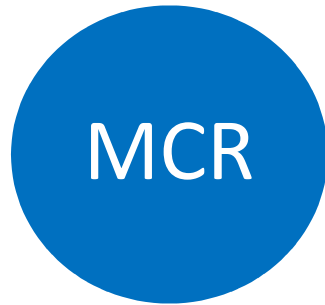
Conclusions. A motor-based MCR syndrome provides a clinical approach to identify individuals at high risk for dementia, especially vascular dementia, to target for further investigations and who may benefit from preventive interventions.

Motoric Cognitive Risk Syndrome and the Risk of Dementia

Identificare individui ad alto rischio di sviluppare demenza attraverso un assessment del rischio cognitivo che incorpori anche segni "motori"



(≤ 1 DS rispetto ad individui di uguale età o sesso)



1. Cognitive complaints
2. Slow gait (defined as gait speed one standard deviation or more below age- and sex-specific mean values established within the same cohort)
3. Preserved ADL (ability to ambulate)
4. Absence of dementia

Motoric Cognitive Risk Syndrome and the Risk of Dementia

52 partecipanti MCR al basale (età media 79,9 anni).
21 uomini (40%) e 31 donne (60%) con MCR.

Non c'erano differenze tra i gruppi per quanto riguardava età, sesso, e istruzione. I partecipanti MCR presentavano maggiore proporzione di etnia nera, punteggi CDR $\geq 0,5$ e anomalie dell'andatura. E anche maggiori comorbilità vascolari e artrite.

La velocità di andatura, i punteggi dei test cognitivi e i sintomi depressivi erano peggiori nei soggetti con MCR.

Prevalenza MCR basale: 7%

Follow-up: 70 hanno sviluppato demenza (41 AD, 21 VaD, e 8 altro tipo di demenza)



8 MCR (15%) e 62 non MCR (9%)



AD (1) VaD (7)

I partecipanti MCR hanno mostrato un aumentato rischio di demenza.

Incidenza: 66 per 1000-anno in MCR e 24 per 1000-anno in non-MCR

MCR non correla in maniera significativa con AD ma è forte predittore di VaD

Gli anziani che presentano criteri per MCR sembra abbiano un rischio aumentato di più di tre volte di sviluppare demenza e più di 12 volte di andare incontro a VaD

La MCR syndrome ha un valore maggiore rispetto alla semplice somma degli effetti dei suoi componenti singolarmente considerati

Joe Verghese, MBBS
 Cedric Annweiler, MD
 Emmeline Ayers, MPH
 Nir Barzilai, MD
 Olivier Beauchet, MD,
 PhD
 David A. Bennett, MD
 Stephanie A.
 Bridenbaugh, MD
 Aron S. Buchman, MD
 Michele L. Callisaya, PhD
 Richard Camicioli, MD
 Benjamin Capistrant, ScD
 Somnath Chatterji, PhD
 Anne-Marie De Cock,
 MD
 Luigi Ferrucci, MD
 Nir Giladi, MD
 Jack M. Guralnik, MD
 Jeffrey M. Hausdorff,
 PhD
 Roce Holtzer, PhD
 Ki Woong Kim, MD
 Paul Kowal, MD
 Reto W. Kressig, MD
 Jae-Young Lim, MD
 Susan Lord, PhD
 Kenichi Meguro, MD
 Manuel Montero-Odasso,
 MD, PhD
 Susan W. Muir-Hunter,
 PhD
 Mohan L. Noone, DM
 Lynn Rochester, PhD
 Velandai Srikanth, PhD
 Cuiling Wang, PhD

Motoric cognitive risk syndrome

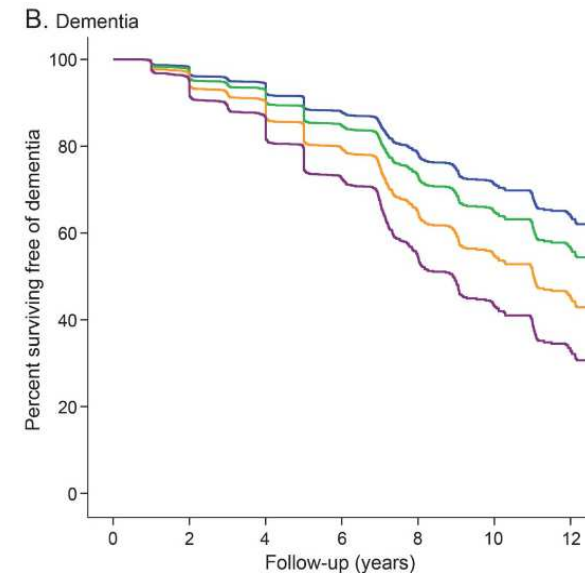
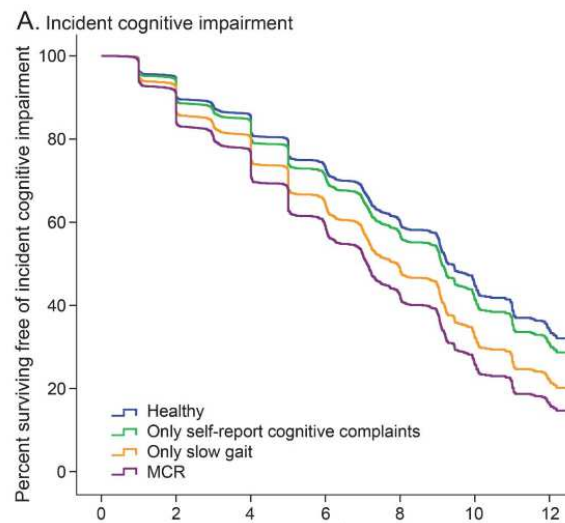
Multicountry prevalence and dementia risk

Table 3 Motoric cognitive risk syndrome and risk of cognitive impairment

Country (study)	Eligible sample, n	Follow-up, y, mean ± SD	Incident cases, n	Cognitive impairment	
				Unadjusted HR (95% CI), p value	Adjusted HR (95% CI), p value
United States (H-EPESE)	1,562	6.04 ± 2.06	826	1.65 (1.30-2.10), <0.001	1.48 (1.16-1.88), 0.002
United States (MAP)	1,280	5.08 ± 3.61	377	1.61 (1.17-2.21), 0.003	1.49 (1.08-2.07), 0.015
United States (ROS)	1,013	9.28 ± 5.38	374	2.19 (1.67-2.88), <0.001	1.90 (1.44-2.51), <0.001
Italy (InCHIANTI)	700	7.23 ± 3.21	180	3.54 (2.05-6.12), <0.001	2.74 (1.54-4.86), 0.001

Abbreviations: CI = confidence interval; H-EPESE = Hispanic Established Populations for Epidemiologic Studies of the Elderly; HR = hazard ratio; InCHIANTI = Invecchiare in Chianti; MAP = Memory and Aging Project; ROS = Religious Orders Study. Associations are reported as HRs with 95% CIs unadjusted as well as adjusted for age, sex, education, baseline Mini-Mental State Examination scores, and presence of vascular disease. Cognitive impairment was defined as a 4-point or more change in Mini-Mental State Examination scores over follow-up.

Figure 2 MCR and risk of incident cognitive impairment (A) and dementia (B)



Review Article

Poor Gait Performance and Prediction of Dementia: Results From a Meta-Analysis

Olivier Beauchet MD, PhD^{a,b,c,*}, Cédric Annweiler MD, PhD^d,
Michele L. Callisaya PhD^{e,f}, Anne-Marie De Cock MD^g, Jorunn L. Helbostad PhD^h,
Reto W. Kressig MDⁱ, Velandai Srikanth PhD^f, Jean-Paul Steinmetz PhD^j,
Helena M. Blumen PhD^k, Joe Verghese MD, MBBS^k, Gilles Allali MD, PhD^{k,l}

Gait control depends largely on cognition^b; disturbed cognitive performance is responsible for poorer gait performance and greater instability in patients with dementia or pre-dementia stages such as MCI or MCR, but also in cognitively healthy individuals.^{1,5–7,39} In particular, episodic memory and executive function have been separately associated with gait performance in the 2 latter categories of *nondemented individuals*.^{40–42} Thus, we suggest that, in the recruited samples composed of participants free of dementia, **those with poor gait performance were those with most altered brain health and, thus, who were most exposed to dementia.** Therefore, measures of gait performance could be a simple and accessible way to predict dementia in large populations compared with psychometric assessment, and morphologic and biologic biomarkers,^{15,16} which is especially relevant for the early diagnosis of dementia in primary care or developing countries.

Research Article

Association of Motoric Cognitive Risk Syndrome With Brain Volumes: Results From the GAIT Study

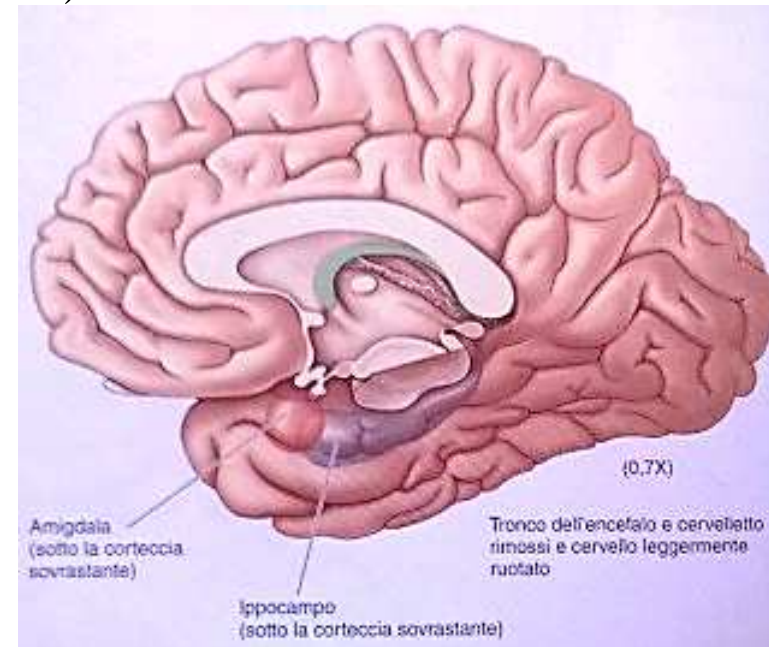
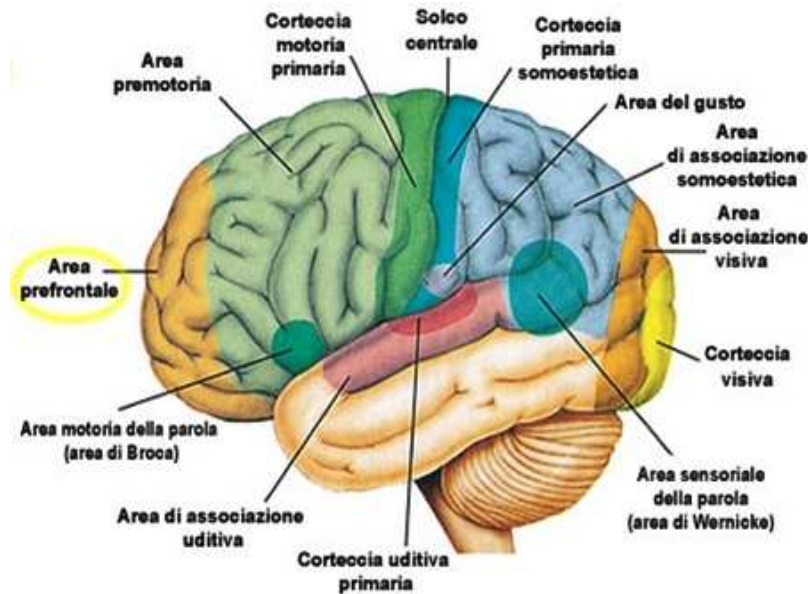
Olivier Beauchet,^{1,2,3} Gilles Allali,^{4,5} Cédric Annweiler,^{6,7} and Joe Verghese⁵

Background: Do individuals with MCR syndrome have lower brain volumes compared with non-MCR individuals? This study aims to compare the cognitive profile of nondemented older community-dwellers with and without MCR syndrome and to examine association of global and regional brain volumes with MCR syndrome.

Methods: A total of 171 individuals (28 MCR and 143 non-MCR) were included in this cross-sectional study. Total white matter abnormalities, total white matter, total cortical and subcortical gray matters, hippocampus, motor cortex, premotor cortex, and prefrontal cortex were examined. Brain volumes were quantified from a three-dimensional T1-weighted magnetic resonance imaging using semi-automated software. Age, gender, education level, number of drugs taken daily, use of psychoactive drugs, and cognitive profile were also measured.

In precedenti studi TRE REGIONI chiave per la correlazione tra cognitiv  e cammino:

- Corteccia motoria (il suo volume correla positivamente con gait speed)
- Ippocampo (ridotto volume correlato sia a deficit di memoria che a disordini della marcia)
- Corteccia prefrontale (funzioni esecutive)



Partendo da queste nozioni, come differisce il volume di queste aree tra i pazienti con MCR e quelli che non lo sono?

Table 2. Multiple Logistic Regression Models Showing the Association Between Motoric Cognitive Risk Syndrome (Dependent Variable) and Brain Structure Volumes in cm³ (Independent Variable) Adjusted for Clinical and Brain Characteristics Among Participants (*n* = 171)

	Model 1		Model 2	
	OR (95% CI)	<i>p</i> Value	OR (95% CI)	<i>p</i> Value
Total white matter abnormalities*	1.135 (0.995; 1.294)	.060	1.079 (0.911; 1.277)	.377
Total white matter	0.994 (0.983; 1.006)	.330	0.991 (0.978; 1.005)	.200
Total gray matter	0.981 (0.968; 0.993)	.002	0.981 (0.965; 0.996)	.016
Total cortical gray matter	0.973 (0.958; 0.989)	.001	0.974 (0.954; 0.994)	.010
Total subcortical gray matter	0.996 (0.989; 1.003)	.267	0.995 (0.988; 1.003)	.213
Hippocampus	0.733 (0.472; 1.139)	.167	0.765 (0.464; 1.263)	.295
Motor cortex	0.563 (0.371; 0.854)	.007	0.641 (0.389; 1.055)	.080
Premotor cortex	0.822 (0.729; 0.927)	.001	0.838 (0.725; 0.970)	.018
Prefrontal cortex†	0.865 (0.789; 0.949)	.002	0.875 (0.778; 0.984)	.026
Dorsolateral segment	0.849 (0.757; 0.952)	.005	0.858 (0.746; 0.987)	.032
Orbital segment	0.612 (0.395; 0.947)	.028	0.709 (0.422; 1.190)	.193
Ventromedial segment	0.525 (0.311; 0.887)	.016	0.742 (0.403; 1.366)	.337

Notes: CI = confidence interval; FAB = Frontal Assessment Battery; OR = odds ratio; TMT-A = Trail Making Test part A; TMT-B = Trail Making Test part B. Model 1: adjusted on total cranial volume. Model 2: model 1 + adjusted on clinical characteristics significantly (ie, *p* value < .05) or with a high tendency to be significantly (*p* value < .100; number of drugs taken daily, FAB score, ratio score TMT-B/TMT-A, and use of psychoactive drugs) different between participants with and without motoric cognitive risk and total white matter abnormalities.

*Defined as MRI signal abnormalities (T1 hypointensities) and measured using FreeSurfer.

†Dorsolateral + orbito + ventromedial prefrontal cortex segments; *p* value significant (<.05) indicated in bold.

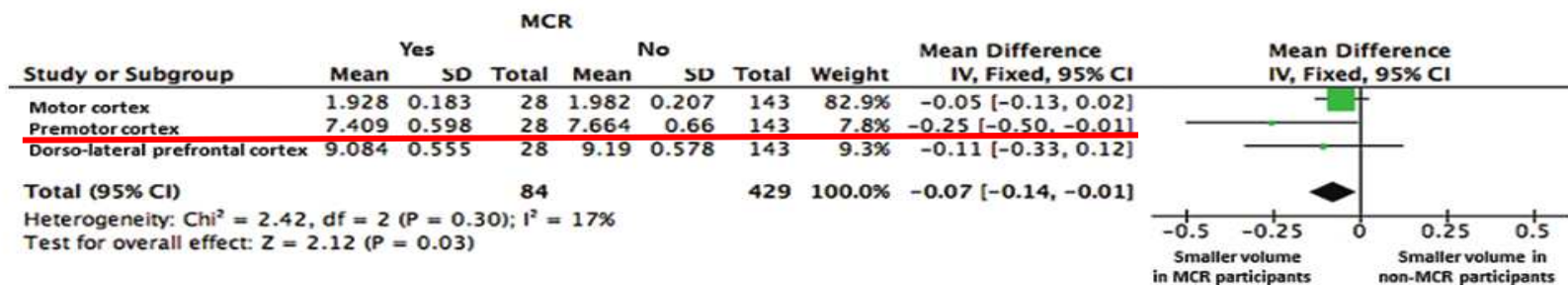


Figure 1. Mean difference in cm³ of cortical volumes between participants with and without motoric cognitive risk (*n* = 171). MCR = motoric cognitive risk syndrome.

Research Article

Association of Motoric Cognitive Risk Syndrome With Brain Volumes: Results From the GAIT Study

Olivier Beauchet,^{1,2,3} Gilles Allali,^{4,5} Cédric Annweiler,^{6,7} and Joe Verghese⁵

Results: The distribution of cognitively healthy individuals and those with mild cognitive impairment was not different in participants with and without MCR. Multiple logistic regression models showed that smaller volumes of total gray matter ($p = .016$), total cortical gray matter ($p = .010$), premotor cortex ($p = .018$), prefrontal cortex ($p = .026$), and dorsolateral segment of prefrontal cortex ($p = .032$) were associated with MCR status. The premotor cortex presented the highest mean difference for brain regional volume between MCR and non-MCR participants ($p = .03$).

Conclusions: The findings revealed similar cognitive profile in MCR and non-MCR participants, and MCR-related smaller global and regional gray matter volumes involving premotor and prefrontal cortices, suggesting that the MCR syndrome may predict cortical neurodegenerative dementia more than subcortical dementia.

Motoric cognitive risk syndrome and risk of mortality in older adults

Emmeline Ayers^{a,*}, Joe Verghese^{a,b}

^aDepartment of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA

^bDepartment of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA

Introduction: Cognitive impairment is associated with increased mortality. We examined the association between motoric cognitive risk (MCR) syndrome, a predementia syndrome characterized by slow gait and cognitive complaints, and survival.

Methods: A total of 11,867 nondemented participants aged >65 years from three established cohort studies in the United States and Europe were screened for MCR. Mortality risk of MCR was assessed with Cox and logistic regression models.

Results: At baseline, 836 (7.0%) participants had MCR. Over a median follow-up of 28 months, 1603 participants died (758 in first 2 years). MCR was associated with increased mortality overall (adjusted hazard ratio, 1.69; 95% confidence interval [CI], 1.46–1.96) and 2-year mortality (adjusted odds ratio, 1.89; 95% CI, 1.50–2.38). The association remained after accounting for established mortality risk factors as well as baseline gait speed and memory performance.

Discussion: MCR is associated with increased mortality. Older adults should be screened for MCR to identify at-risk individuals for dementia and death.

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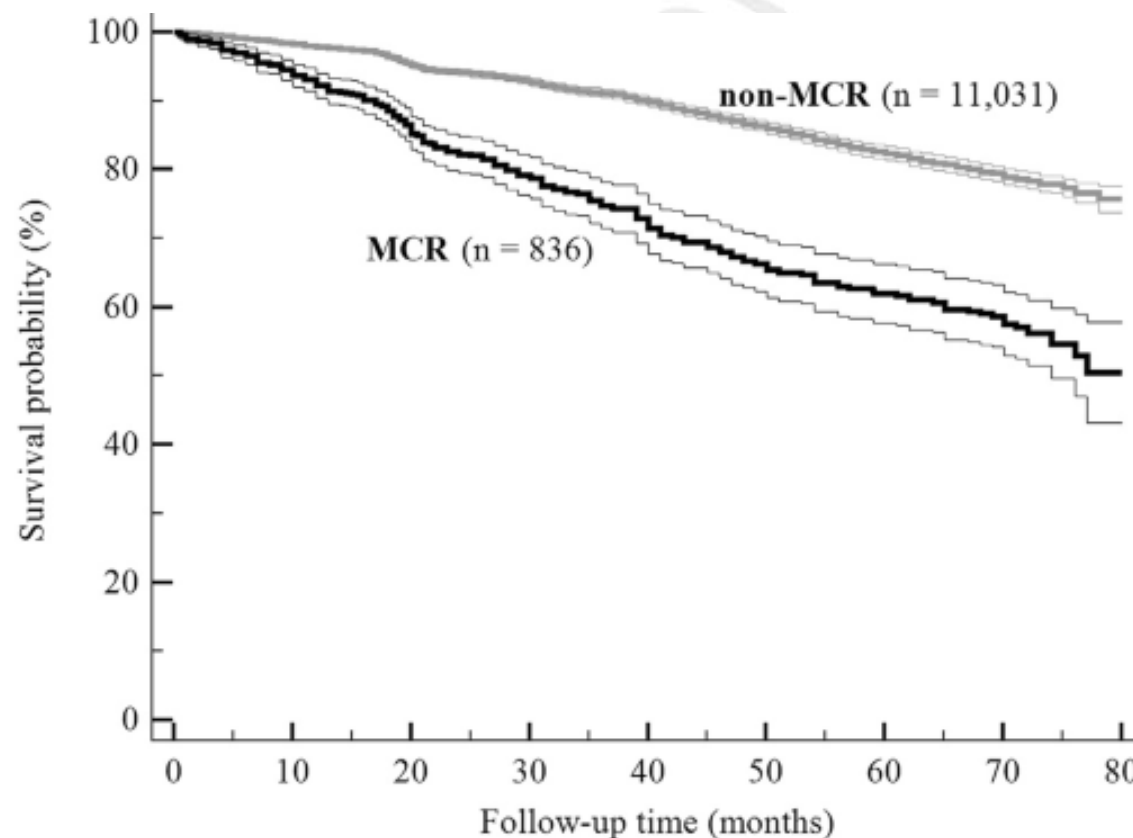
^aDepartment of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA

^bDepartment of Medicine, Albert Einstein College of Medicine, Bronx, NY, USA

The association of MCR with mortality was similar in magnitude to the mortality risk reported with other predementia syndromes.

Slightly higher mortality rate for men despite a lower prevalence of MCR.

The combination of MCR symptoms have incremental predictive validity for mortality over its individual components.



CONCLUSIONI

Should tests for dementia risk now include gait speed?

Aumentare gli sforzi per identificare gli anziani a rischio di sviluppare la demenza.

L'accumulo di patologia cerebrale causa di deficit cognitivi e non che si manifestano prima di una chiara diagnosi clinica di demenza.

Velocità del cammino può rappresentare funzione non cognitiva affetta da patologia cerebrale.

CONCLUSIONI

Should tests for dementia risk now include gait speed?

Il valore predittivo per demenza di un fenotipo motorio basato sull'andatura ne supporta l'utilizzo per identificare i soggetti ad alto rischio, integrando la definizione di MCI.

Prospettive Future... solo gli studi longitudinali potranno chiarirci verso che tipo di patologia cerebrale può evolvere la MCR syndrome.

CONCLUSIONI

Identificare cause di MCR → Modifica dello stile di vita,
trattamenti che riducano il rischio
di sviluppare demenza



Adeguate controllo vari fattori di rischio per declino cognitivo e motorio
(controllo pressorio, glicemico, anemia, carico anticolinergico)

Non perdere la voglia di camminare: io, camminando ogni giorno, raggiungo uno stato di benessere e mi lascio alle spalle ogni malanno; i pensieri migliori li ho avuti mentre camminavo, e non conosco pensiero così gravoso da non poter essere lasciato alle spalle con una camminata... ma stando fermi si arriva sempre più vicini a sentirsi malati... Perciò basta continuare a camminare, e andrà tutto bene.

Bruce Chatwin





