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SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Carenza di nutrienti e fragilità cognitiva: ruolo dell'associazione di colina e vitamina B12

Andrea Ungar
Università di Firenze

Outline

- «Fragilità cognitiva»
- Il perché di questa definizione
- Delirium: cosa è e perché potrebbe essere un marcatore affidabile di «fragilità cognitiva»
- Quali terapie possibili e quali passi ulteriori per il futuro

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Criteri di Mild Cognitive Impairment (MCI)

(National Institute on Aging and Alzheimer's Association workgroup, 2011)

- **Preoccupazione** (“concern”) per un deficit cognitivo: soggettivo / riferito da caregiver/ osservato da un clinico esperto
- **Lieve deficit oggettivo** di una o più aree cognitive (memoria, attenzione, funzioni esecutive, linguaggio, capacità visuo-spaziali) ai test neuropsicologici
- **Mantenimento dell'autonomia, malgrado difficoltà** nello svolgimento degli atti della vita quotidiana
- **No demenza** conclamata

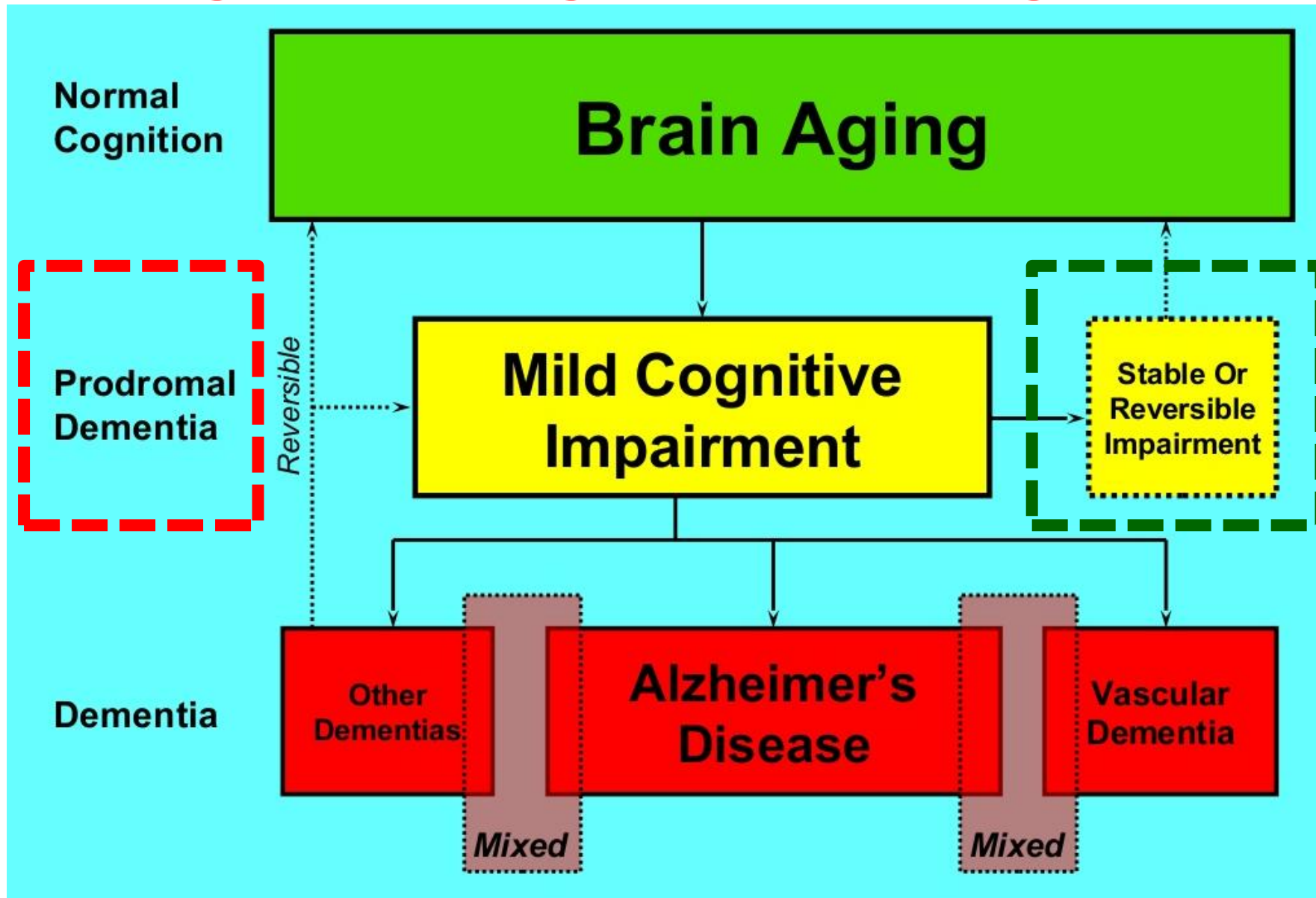
NON È UNA MALATTIA (*Disorder?*)



Disturbo neurocognitivo minore (DSM-V) vs. MCI

- ***Disorder*** = sindrome clinica legata ad un'alterazione del sistema nervoso centrale (**neuro**cognitivo)
- ***Impairment*** = variazione quali-quantitativa di una funzione rispetto alla norma, non necessariamente di significato patologico
- Classificazione delle cause
- Nessun riferimento al profilo neuropsicologico
- Esclusione della patologia psichiatrica dalle possibili cause

Declino cognitivo lieve nell'anziano: eterogeneità diagnostica e prognostica



Secondo il paradigma eziologico e in vista della prognosi

- MCI non associato a patologia neurodegenerativa
- MCI come prodromo di malattia neurodegenerativa

Ruolo chiave dei biomarcatori!

Sarà l'approccio dominante quando avremo a disposizione

- *biomarcatori facilmente accessibili*
- *trattamenti in grado di modificare la storia naturale delle malattie neurodegenerative*

Cognitive frailty: Predementia syndrome and vascular risk factors

Francesco Panza^{a,*}, Alessia D'Introno^a, Anna Maria Colacicco^a, Cristiano Capurso^b,
Angelo Del Parigi^c, Sabrina A. Capurso^a, Richard J. Caselli^d, Alberto Pilotto^e,
Emanuele Scafato^f, Antonio Capurso^a, Vincenzo Solfrizzi^a

Abstract

With increasing emphasis on early diagnosis of Alzheimer disease (AD), clinical research has focused on the identification of risk factors that may be modified at a preclinical and early clinical stage of dementing disorders. Prevalence and incidence of different predementia syndromes vary as a result of different diagnostic criteria, as well as different sampling and assessment procedures. Particular interest in mild cognitive impairment (MCI) arises from the fact that MCI is thought to be a prodromal phase and therefore highly predictive of subsequent AD. Furthermore, many of the risk factors for cerebrovascular disease (CVD) and vascular dementia (VaD), including serum total cholesterol, hypertension, atherosclerosis, and apolipoprotein E (APOE) genotype have also been shown to increase the risk of AD. Both vascular factors and APOE ϵ 4 allele have been associated with higher risk of AD. Some recent studies suggested further that CVD or vascular factors increased the risk of conversion of MCI to dementia. This review will focus on the possible role of vascular risk factors in modulating the risk of age-related cognitive decline, and the progression of predementia syndrome such as MCI to dementia.

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COGNITIVE FRAILTY: RATIONAL AND DEFINITION FROM AN (I.A.N.A./I.A.G.G.) INTERNATIONAL CONSENSUS GROUP

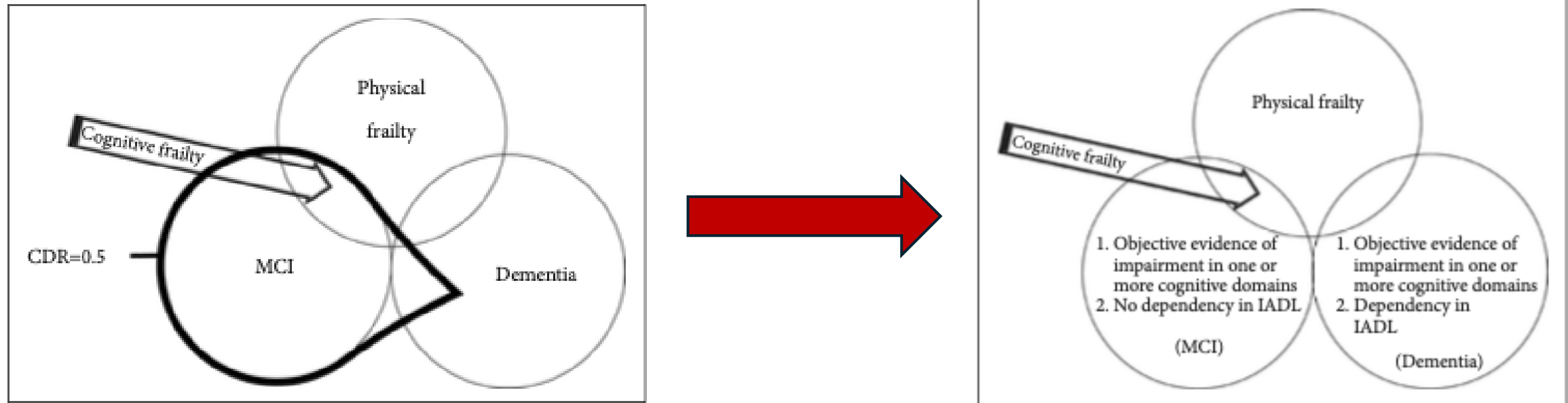
E. KELAIDITI¹, M. CESARI^{1,2,3}, M. CANEVELLI^{1,4}, G. ABELLAN VAN KAN^{1,2}, P.-J. OUSSET¹,
S. GILLETTE-GUYONNET^{1,2}, P. RITZ^{2,5}, F. DUVEAU⁶, M.E. SOTO^{1,2}, V. PROVENCHER⁷,
F. NOURHASHEMI^{1,2}, A. SALVA⁸, P. ROBERT⁹, S. ANDRIEU^{1,2,3,10}, Y. ROLLAND^{1,2}, J. TOUCHON¹¹,
J.L. FITTEN¹², B. VELLAS^{1,2,3}

3 diagnostic criteria:

- i) physical frailty, defined by Fried's phenotype,
- ii) ii) cognitive impairment (CI) with a clinical dementia rating (CDR) of 0.5, i.e. MCI [4],
- iii) no Alzheimer's or other dementias

Modified Criteria for Diagnosing “Cognitive Frailty”










Chang Won Won¹, Yunhwan Lee², Sunyoung Kim³, Jinho Yoo³, Miji Kim⁴,
 Tze-Pin Ng⁵, Haena Kim⁶, and Sang Joon Son⁶ ✉



Any cognitive function test < -1.5 SD of the age-, gender-, and education-adjusted norms mean MCI or Dementia. Dependency in IADL encompasses dementia. The newly suggested definition of cognitive frailty (arrow) is physical frailty and any cognitive function test < -1.5 SD of the age-, gender-, and education-adjusted norm and no dependency in IADL. MCI: mild cognitive impairment, IADL: instrumental activities of daily living.

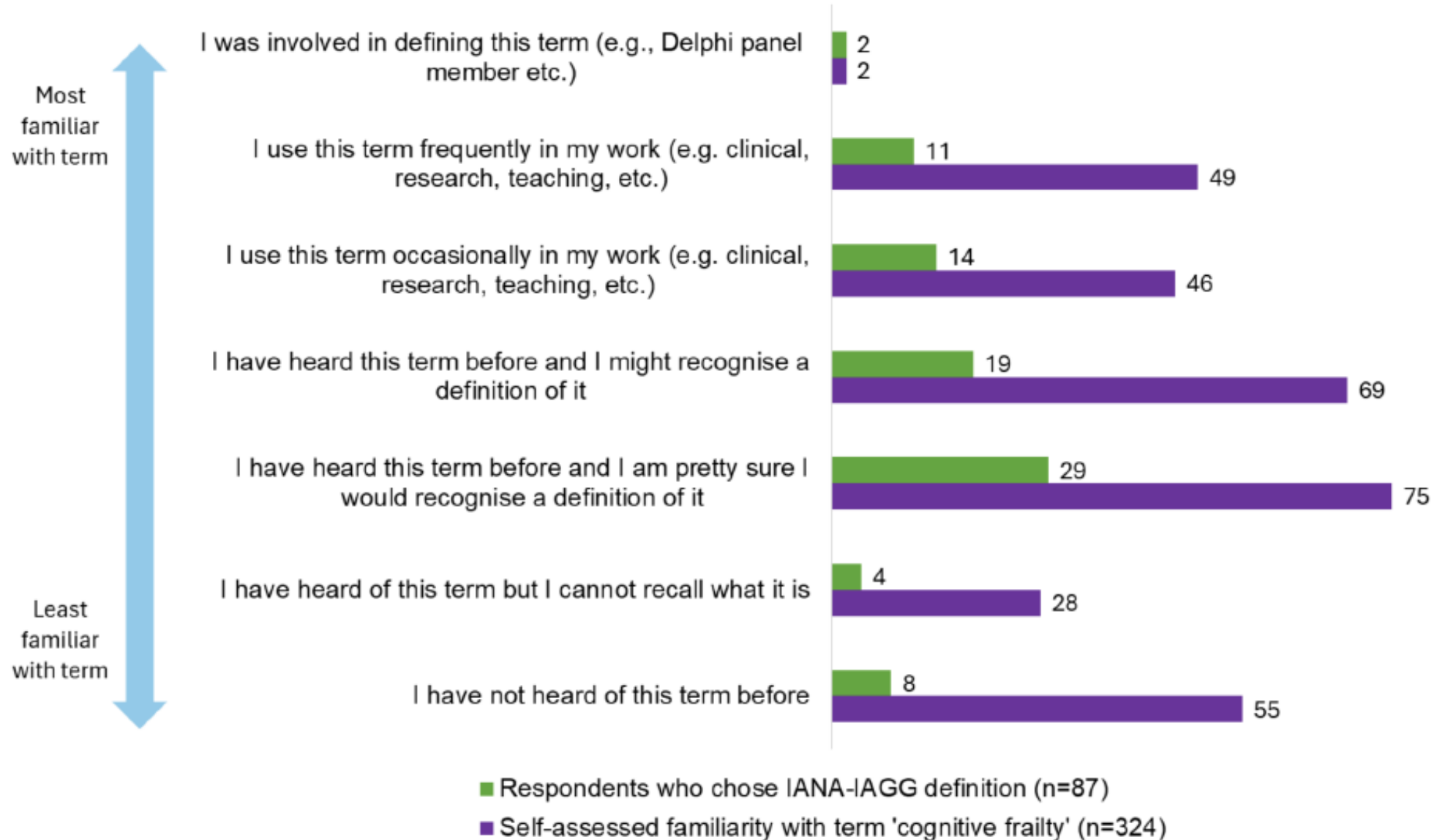
Cognitive frailty: a useful concept or a source of confusion? Insights from a survey of European geriatricians



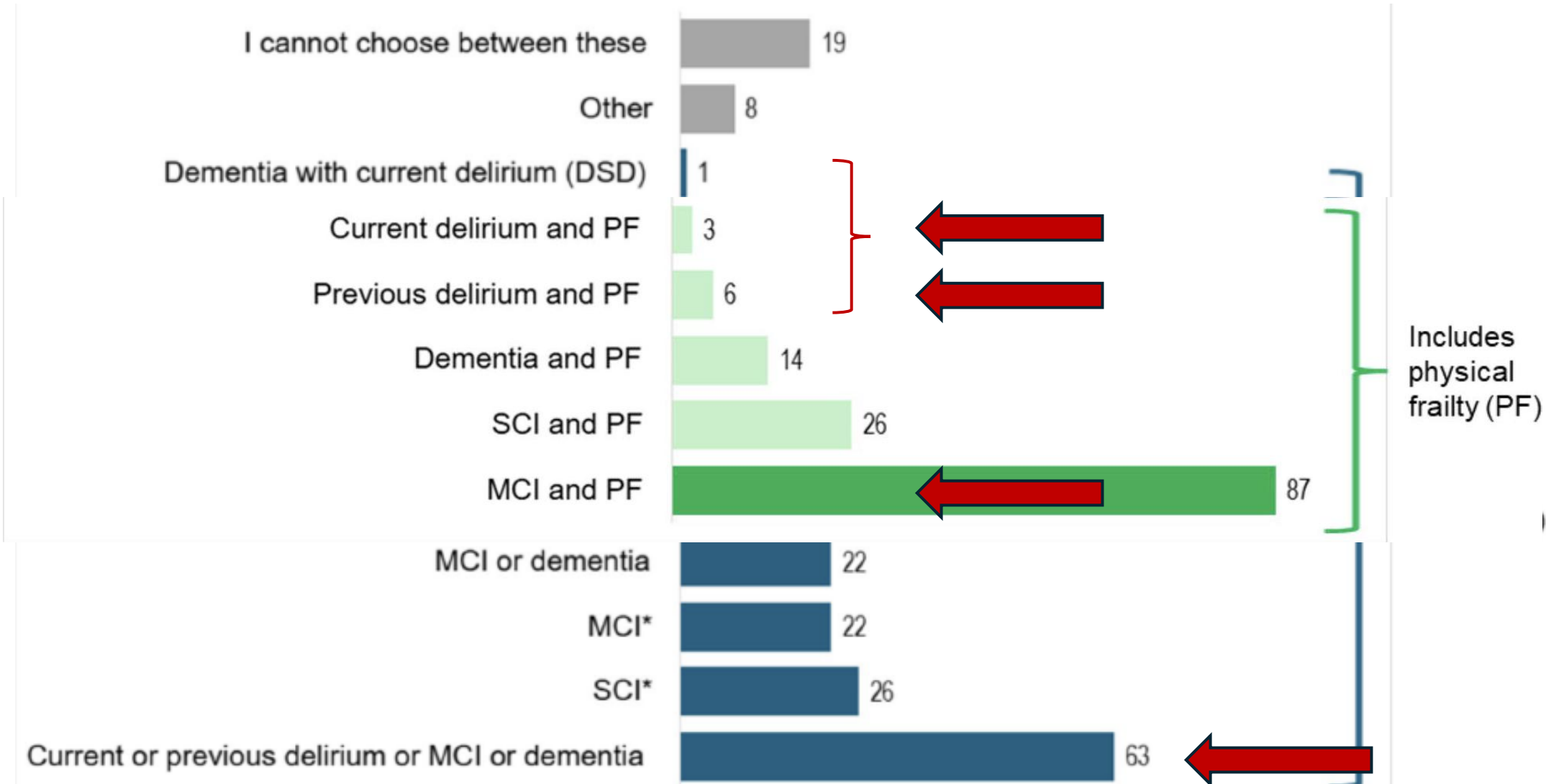
Suzanne Timmons¹ , Mary Faherty^{1*} , Catriona Curtin², Maria Cristina Ferrara³ , Giuseppe Bellelli^{3,4} , Enrico Brunetti^{5,6} , Mario Bo⁷ , Alessandro Morandi^{8,9,10} , Antonio Cherubini^{11,12}, Massimiliano Fedecostante¹¹, Alessandra Coin¹³, Susan D. Shenkin¹⁴  and Pinar Soysal¹⁵ 

- Sondaggio online sulle relazioni e i percorsi relativi a delirio, demenza e fragilità, distribuito in tutta Europa attraverso gruppi professionali appropriati.
- I partecipanti idonei erano geriatri o tirocinanti negli ultimi due anni di formazione specialistica in geriatria, in un paese europeo.
- In totale, 440 persone hanno risposto al sondaggio, di cui 324 hanno risposto alla sezione sulla fragilità cognitiva.

Self-assessed familiarity with 'cognitive frailty' (purple bar) and respondents' selection of IANA-IAGG definition (green bar)



Perceived definition of 'cognitive frailty' (324 respondents)



* regardless of physical status

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journal homepage: www.jamda.com

Special Article

Frailty Consensus: A Call to Action

John E. Morley MB, BCh^{a,*}, Bruno Vellas MD^{b,c}, G. Abellan van Kan MD^{b,c}, Stefan D. Anker MD, PhD^{d,e}, Juergen M. Bauer MD, PhD^f, Roberto Bernabei MD^g, Matteo Cesari MD, PhD^{b,c}, W.C. Chumlea PhD^h, Wolfram Doehner MD, PhD^{d,i}, Jonathan Evans MD^j, Linda P. Fried MD, MPH^k, Jack M. Guralnik MD, PhD^l, Paul R. Katz MD, CMD^m, Theodore K. Malmstrom PhD^{a,n}, Roger J. McCarter PhD^o, Luis M. Gutierrez Robledo MD, PhD^p, Ken Rockwood MD^q, Stephan von Haehling MD, PhD^r, Maurits F. Vandewoude MD, PhD^s, Jeremy Walston MD^t

“...A clinical condition with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability for developing increased dependency and/or death...”

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

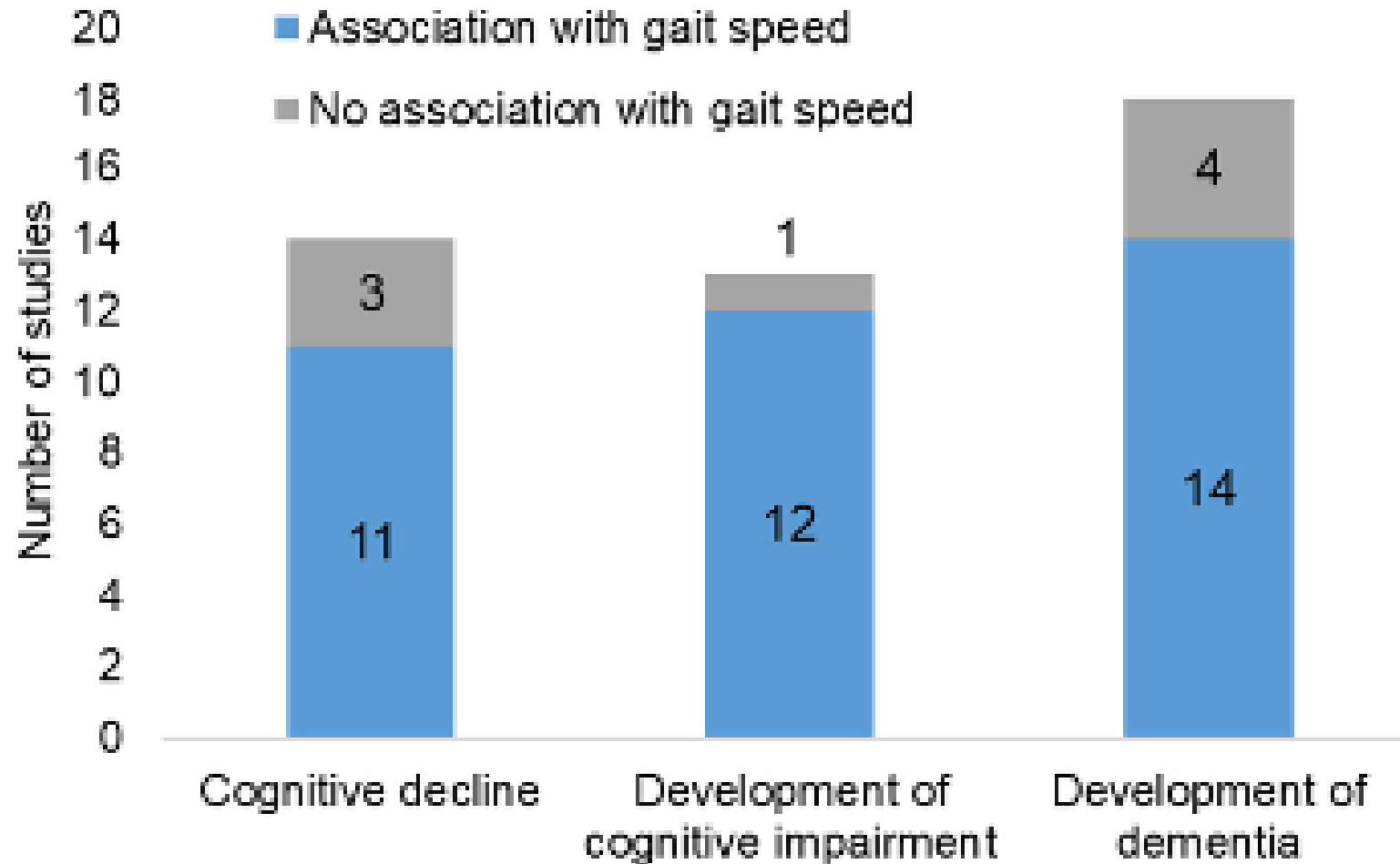
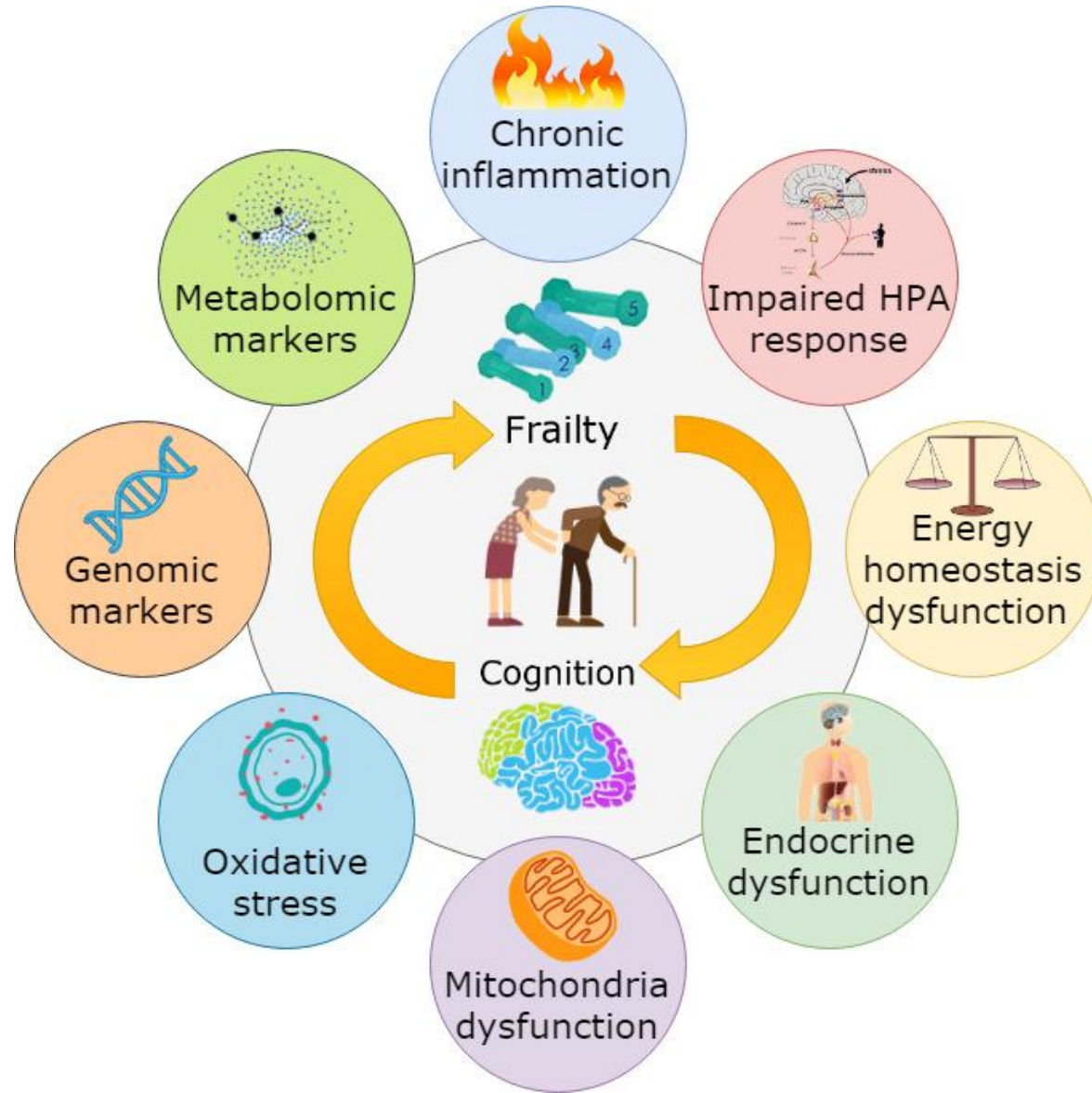


Table 2. Cognitive Profile of Participants According to Frailty Status: The Three-City Study

Variable	All N = 6,030	Nonfrail n = 2,738 (45.4%)	Prefrail n = 2,871 (47.6%)	Frail n = 421 (7.0%)	P-Value
Age, mean ± SD	74.1 (5.2)	73.5 (5.1) ^a	74.4 (5.2) ^b	76.6 (5.5) ^c	<.001
Center for Epidemiological Studies Depression Scale score, mean ± SD*	8.05 (7.4)	5.20 (5.2) ^a	9.25 (7.83) ^b	15.67 (9.3) ^c	<.001
MMSE score, mean ± SD (range 0–30) [†]	27.4 (1.9)	27.5 (1.9) ^a	27.4 (1.9) ^b	26.9 (2.0) ^c	<.001
Isaac Set Test score, mean ± SD	47.9 (10.6)	48.3 (10.4) ^a	48.1 (10.7) ^b	44.8 (10.9) ^b	<.001
Cognitively impaired, % [‡]	711 (11.8)	274 (10.0)	345 (12.0)	92 (21.9)	<.001
Poor self-reported health, %	4.4	1.1	5.0	21.9	<.001
Cognitive complaints, %					
Forgetfulness	46.4	41.1	49.9	60.0	<.001
Short-term memory impairment	37.7	32.2	41.0	54.2	<.001
Long-term memory impairment	9.0	7.6	9.7	14.4	.007
Calculation	16.3	12.4	18.7	27.7	<.001
Language	58.6	52.5	62.2	76.2	<.001
Orientation	6.8	4.9	8.0	12.0	<.001
Complaint with the doctor	18.4	21.8	27.6	36.9	<.001
Apolipoprotein E ε4 allele, %	19.6	20.4	20.9	22.6	.59

Understanding the Physiological Links Between Physical Frailty and Cognitive Decline



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Delirium

- Il delirium è una sindrome neuropsichiatrica caratterizzata da un cambiamento acuto delle performances cognitive (con particolare riferimento alle capacità attentive e alla consapevolezza di se nell'ambiente), un alterato «arousal» e una tendenza alla fluttuazione dei sintomi
- Ampio range di cause potenziali (spesso multiple)
- Tre sottotipi: ipercinetico, ipocinetico e misto

Comparison of Frailty and Delirium: Definition, Time Course, and Features

	Frailty	Delirium
Definition	Vulnerability in multiple physiologic systems	Acute change in attention and cognition
Time course	Chronic Acute change with stressors (potentially) Reversible	Acute with fluctuation Reversible in most cases Persistent in some cases
Features	Sarcopenia Reduced energy expenditure Nutritional deficiency Weight loss Decreased physical activity	Inattention Thought disorders Altered consciousness

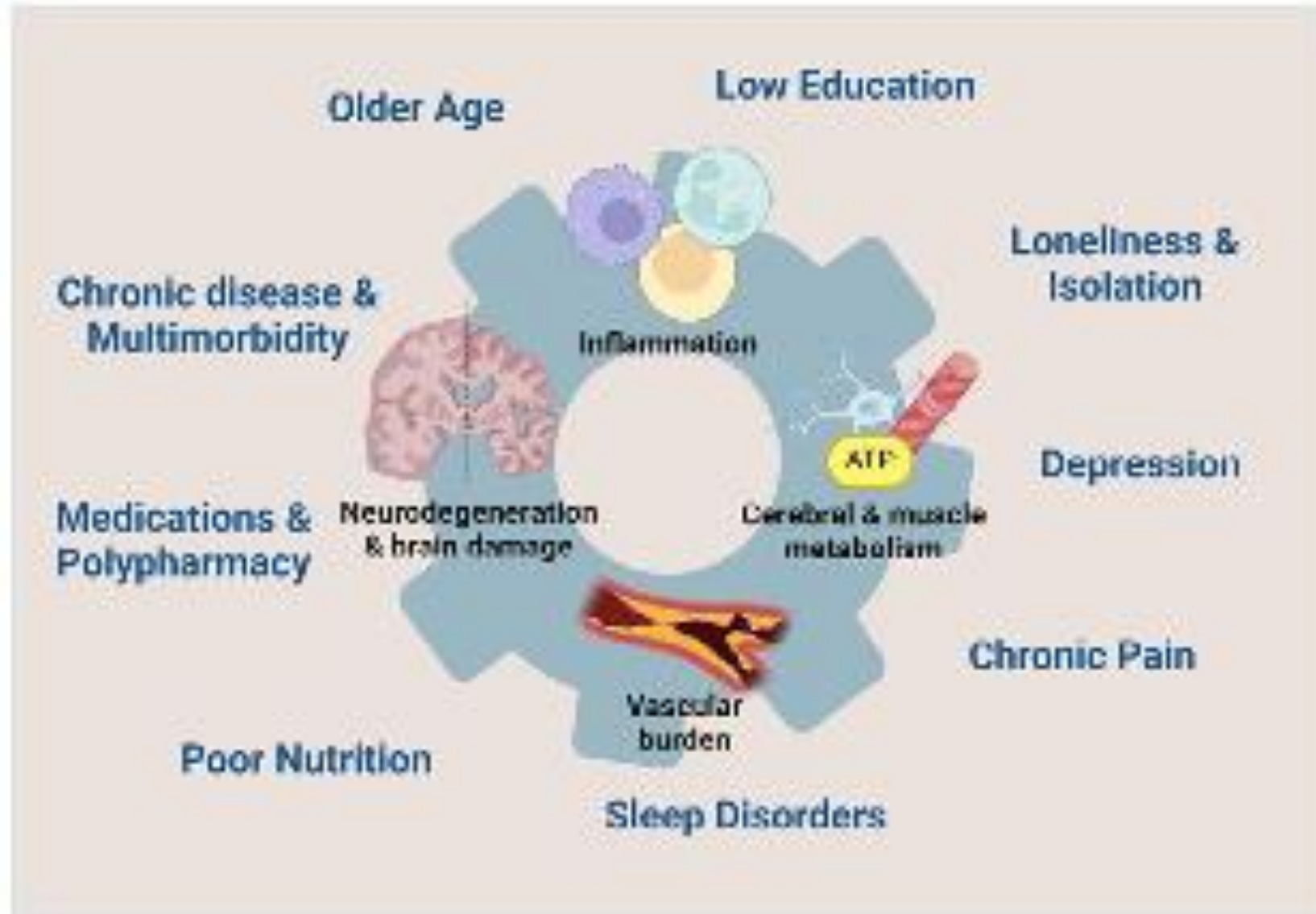
Delirium and frailty in older adults: Clinical overlap and biological underpinnings

■ Giuseppe Bellelli^{1,2} , Federico Triolo³ , Maria Cristina Ferrara¹ , Stacie G. Deiner⁴,
Alessandro Morandi^{5,6}, Matteo Cesari⁷, Daniel Davis⁸, Alessandra Marengoni⁹, Marco Inzitari^{6,10},
Leiv Otto Watne^{11,12}, Kenneth Rockwood¹³ & Davide Liborio Vetrano^{3,14}

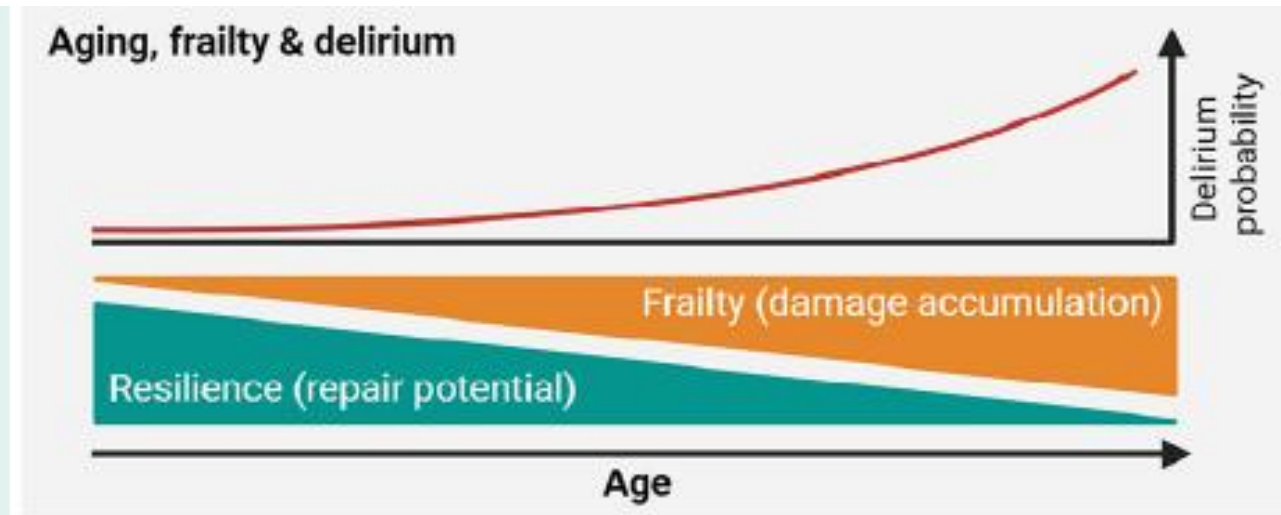
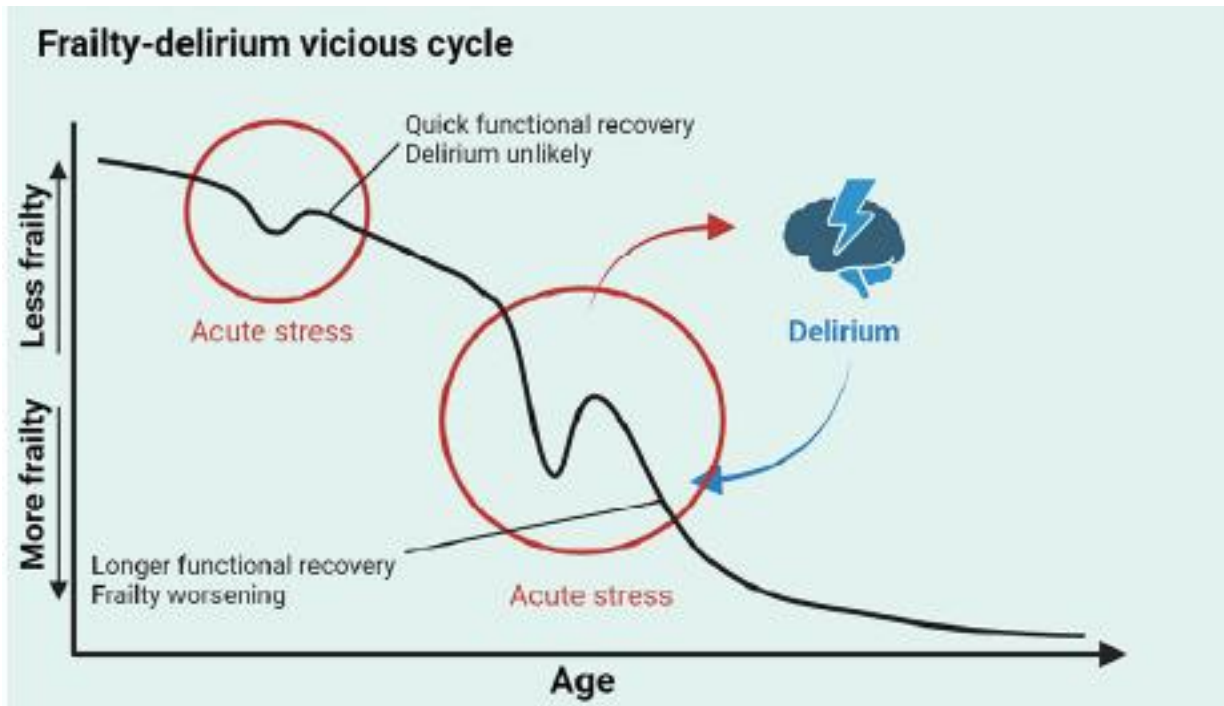
Table 1. Overview of diagnostic clinical signs and symptoms of delirium and frailty, highlighting commonalities between the two conditions.

Delirium ^a	Frailty ^b
Affective domain <ul style="list-style-type: none">• Possible disturbance of emotion, including anxiety symptoms, depressed mood, irritability, fear, anger, euphoria, or apathy [60–62]	<ul style="list-style-type: none">• Feeling down [66, 67]/sad or depressed [67, 69]/lack of joy or fulfillment in daily life [71]• Feeling nervous or anxious [66, 67]
Other domains (sleep–wake cycle, functional independence, nutrition, sensory deficits, social support) <ul style="list-style-type: none">• Possible disturbance of the sleep–wake cycle (e.g., reduced arousal of acute onset or total sleep loss followed by reversal of the sleep–wake cycle) [60–62]	<ul style="list-style-type: none">• Requiring help in basic or complex activities of daily living [65, 67, 69–72]• Unexplained weight loss [22, 63, 64, 67, 69–72]/poor nutrition or eating [67, 70, 71]/experiencing dry mouth [71]• Poor hearing/poor vision [66, 67]• Poor social interactions (feeling alone, feeling helpless) [65–67, 69, 71]

Common risk factors and pathophysiological pathways linking frailty and delirium

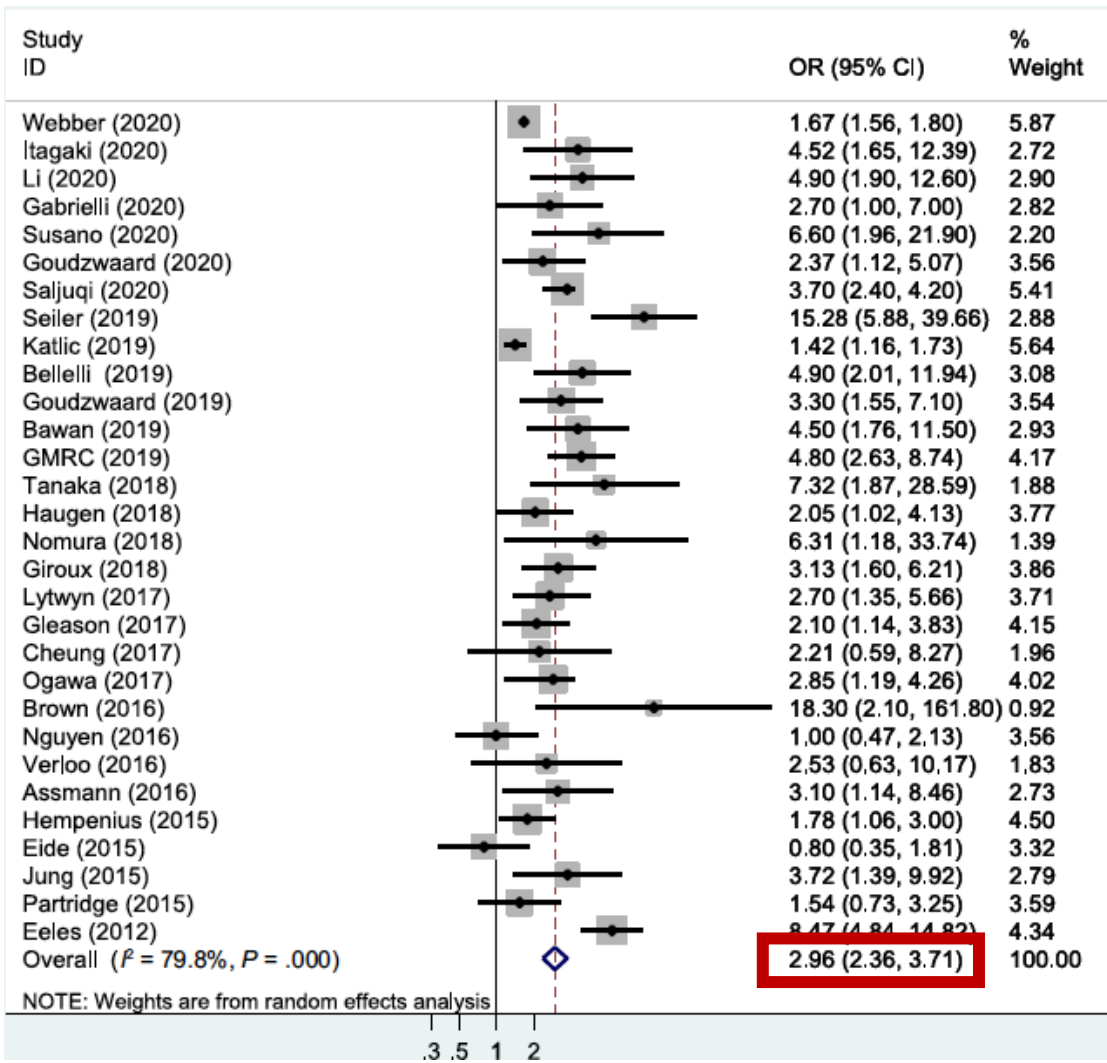


Unifying framework of the interplay between frailty & delirium



The Association Between Frailty and Delirium Among Hospitalized Patients: An Updated Meta-Analysis

Xiao-Ming Zhang PhD^a, Jing Jiao MSN^a, Xiao-Hua Xie MPH^b, Xin-Juan Wu MSN^{a,*}




30 articles, (N=217,623) eligible for meta-analysis; Frailty prevalence ranged from 16.20% to 78%.

Different frailty assessment tools had different OR:

- CFS =OR 4.07, 95% CI 2.71-6.11)
- FRAIL =OR 2.83, 95% CI 1.56-5.13)
- FI= OR 6.15, 95% CI 3.75-10.07)
- Frailty phenotype =OR 2.30, 95%CI 1.35-5.66)
- Erasmus Frailty Score= OR 2.79, 95% CI 1.63-4.77
- Edmonton Frail Scale = OR 1.45, 95% CI 0.91-2.30.

Does delirium predispose to frailty?

Frailty and post-operative delirium influence on functional status in patients with hip fracture: the GIOG 2.0 study

Chiara Maria Gandossi¹ · Antonella Zambon^{2,3} · Maria Cristina Ferrara⁴ · Elena Tassistro⁵ · Giuseppe Castoldi⁶ ·
Francesca Colombo⁶ · Chiara Mussi⁷ · Emilio Martini⁷ · Giuseppe Sergi⁸ · Alessandra Coln⁸ · Giovanni Zatti^{1,9} ·
Caterina Trevisan^{10,11} · Stefano Volpato^{10,11} · Andrea Ungar¹² · Giuseppe Bellelli^{1,13}  on behalf of GIOG 2.0 Study
Group, Società Italiana di Gerontologia e Geriatria (SIGG)

Aging Clinical and Experimental Research

<https://doi.org/10.1007/s40520-023-02522-8>

Delirium and Delirium Severity Predict the Trajectory of the Hierarchical Assessment of Balance and Mobility in Hospitalized Older People: Findings From the DECIDE Study

Sarah Richardson, MBBS,^{1,2,◉} James Murray, MSc,^{1,2} Daniel Davis, PhD,^{3,◉}
Blossom C. M. Stephan, PhD,^{4,◉} Louise Robinson, PhD,⁵ Carol Brayne, MD,^{6,◉}
Linda Barnes,⁶ Stuart Parker, MD,⁵ Avan A. Sayer, PhD,^{1,2} Richard M. Dodds, PhD,^{1,2,*†,◉}
and Louise Allan, PhD^{7,†,◉}

Impact of delirium on postoperative frailty and long term cardiovascular events after cardiac surgery

Masato Ogawa^{1,2}, Kazuhiro P. Izawa^{2*}, Seimi Satomi-Kobayashi³, Yasunori Tsuboi¹, Kodai Komaki¹, Yasuko Gotake⁴, Yoshitada Sakai⁵, Hiroshi Tanaka⁴, Yutaka Okita⁴

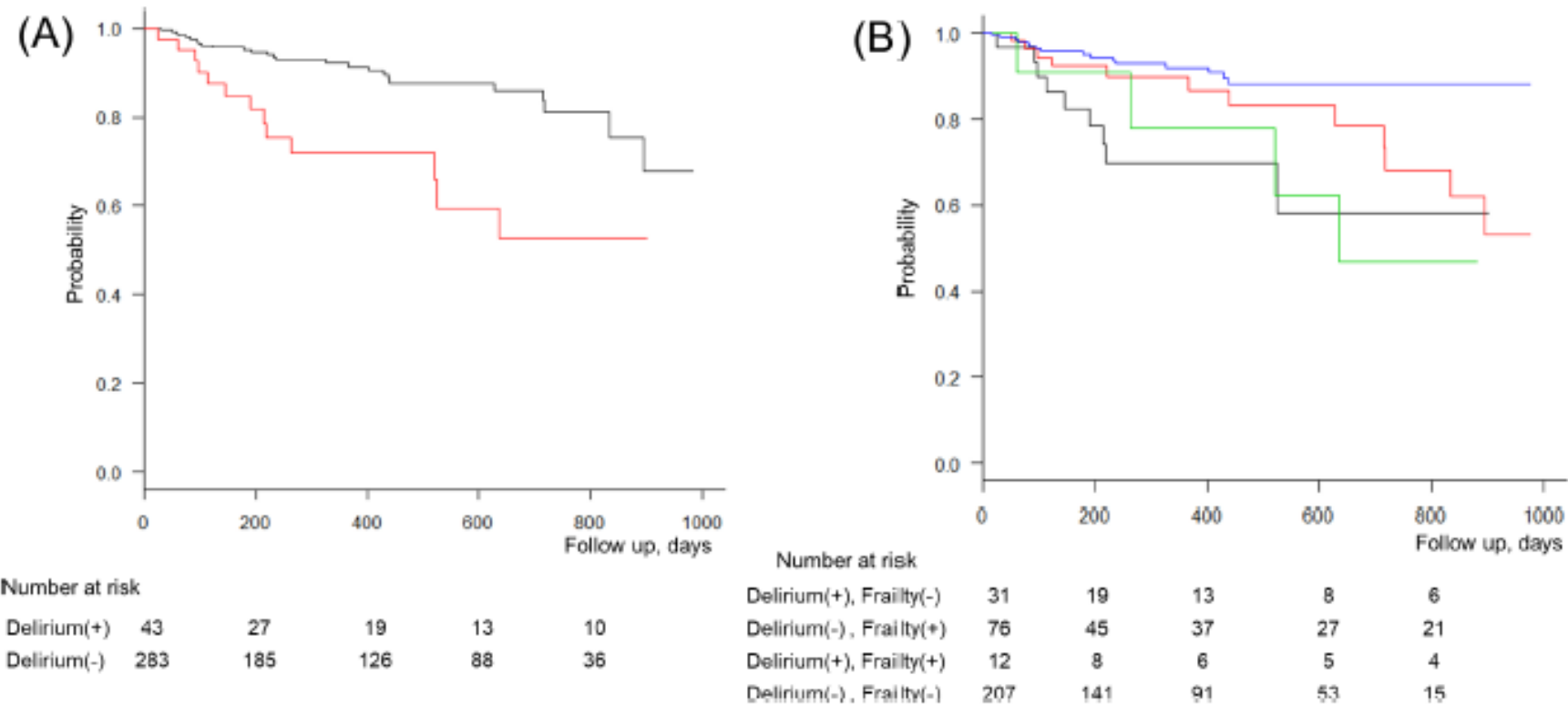
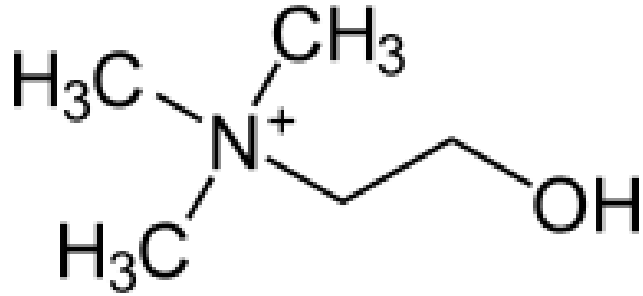


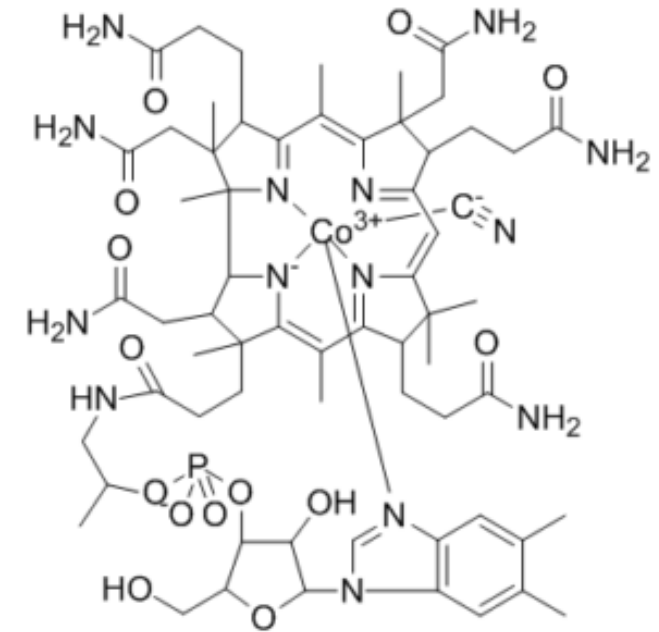
Fig 2. Kaplan–Meier curves for cumulative major adverse cardiac events for (A) presence (red line) or absence (black line) of postoperative delirium (Log-rank test, $p = 0.000733$), (B) a comparison of the four groups robust (blue line), delirium (black line), postoperative frailty (red line), and combination of both (green line) (Log-rank test, $p = 0.00369$).

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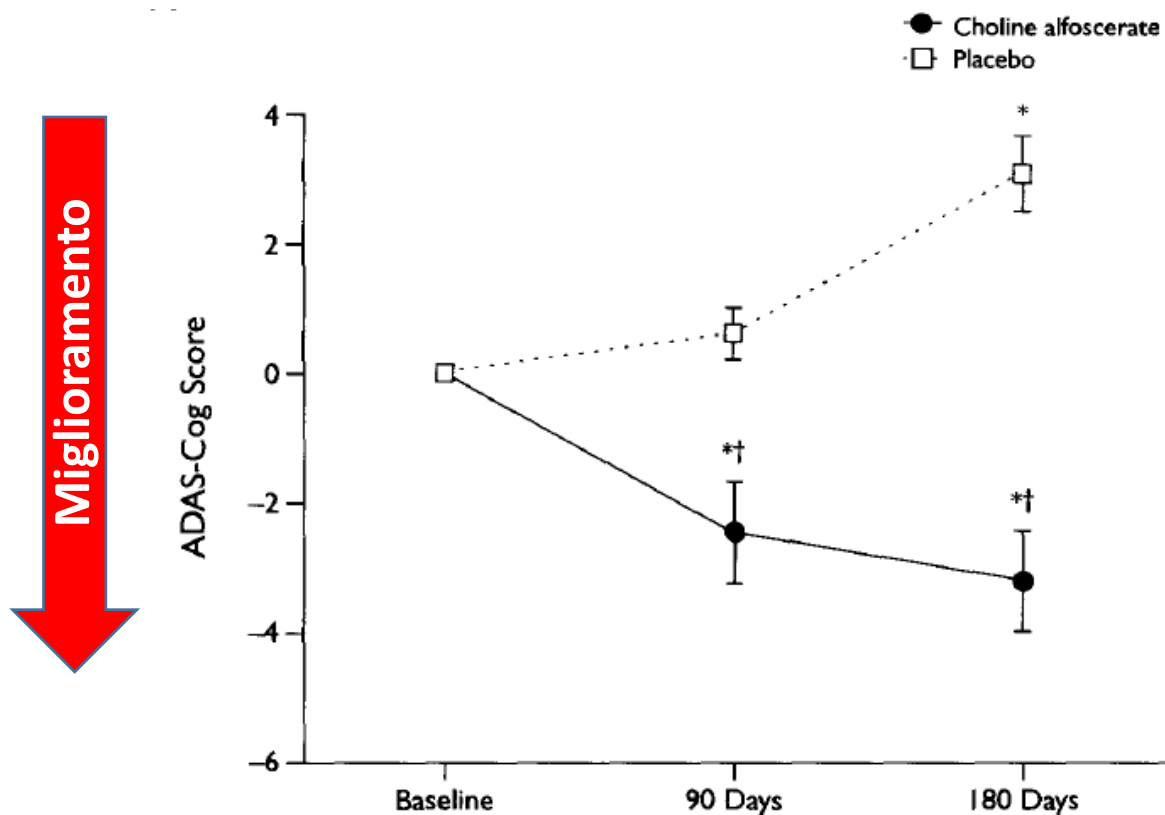
La colina, nutriente essenziale presente in tutte le cellule del corpo umano e precursore del neurotrasmettitore acetilcolina serve a mantenere un buon funzionamento del sistema nervoso e della **trasmissione colinergica**



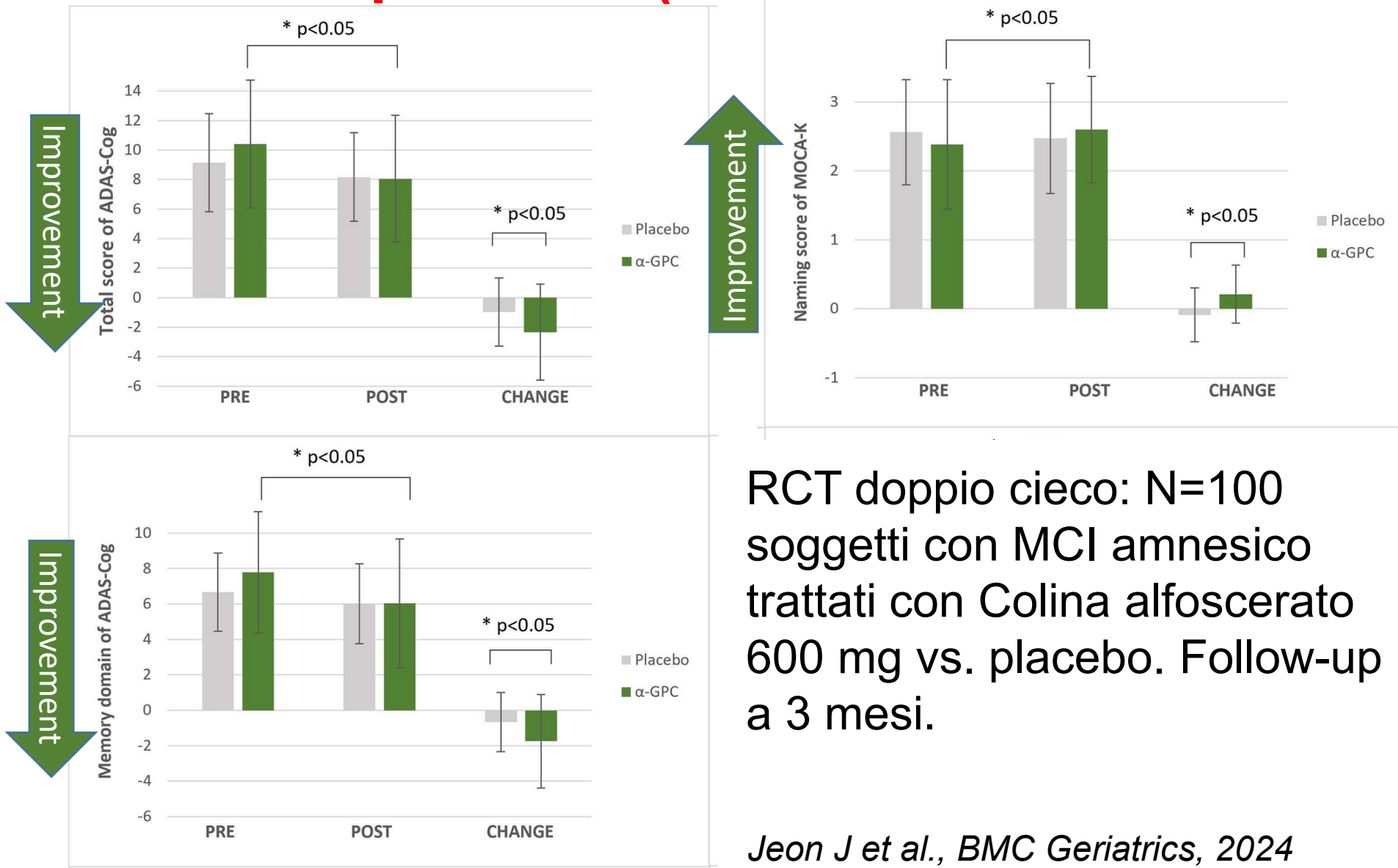
La vitamina B12, necessaria per lo sviluppo dell'organismo, per la formazione di globuli rossi sani e per la sintesi del DNA e della mielina, la guaina che ricopre e protegge le fibre nervose, contribuisce ad uno stato di **protezione neuronale**.

Trial controllato con Colina alfoscerato in Malattia di Alzheimer

N=261 soggetti con AD: colina alfoscerato 1200 mg die vs. placebo per 6 mesi



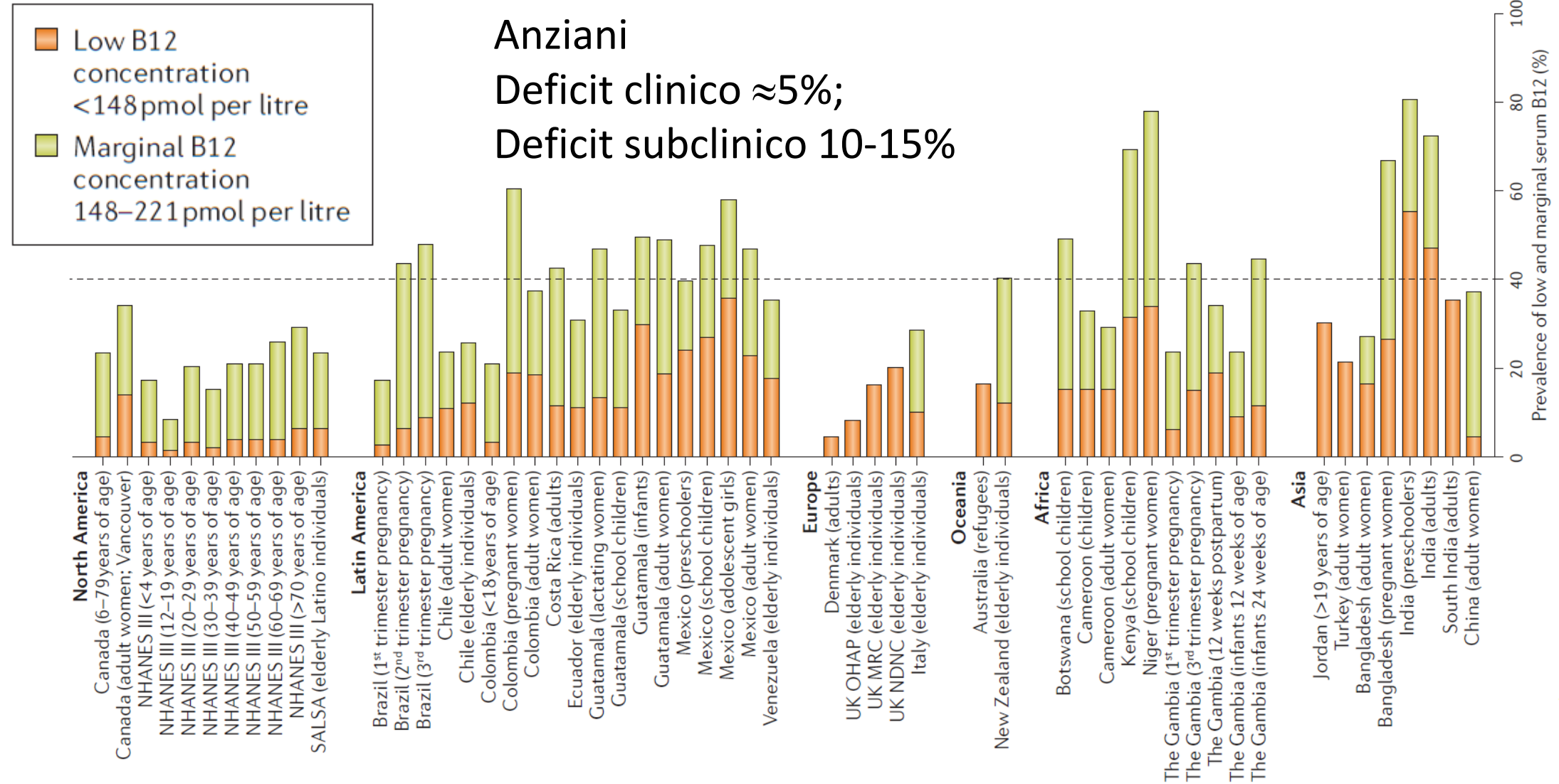
Colina alfoscerato nel Mild Cognitive Impairment (MCI) amnesico



RCT doppio cieco: N=100
soggetti con MCI amnesico
trattati con Colina alfoscerato
600 mg vs. placebo. Follow-up
a 3 mesi.

Jeon J et al., BMC Geriatrics, 2024

Prevalenza di deficit clinico e subclinico di vitamina B12



Green R et al., Nat Rev Dis Primers, 2017



Possibili esiti clinici dell'insufficienza di vitamina B12

Outcome	Study	References
Neural tube defect	Prospective (in mothers)	Kirke et al. (1993); Molloy et al. (2009)
Infantile tremor syndrome	Prospective (in mothers)	Goraya, Bansal, Singla, and Kaur (2016)
Cognitive deficit in elderly	Cross-sectional	Hin et al. (2006); Mizrahi, Lubart, and Leibovitz, 2017
Cognitive decline in elderly	Prospective	Clarke et al. (2007); Hooshmand et al. (2012); Tangney, Tang, Evan and Morris (2009)
Alzheimer's disease	Cross-sectional	Clarke et al. (1998); Refsum and Smith (2003)
White matter damage	Cross-sectional	de Lau, Smith, Refsum, Johnst and Breteler (2009); Graber, Sherman, Kaufmann, Kolodny, Sathe (2010); van Overbeek, St and van Oostenbrugge (2013)
Impaired regional brain microstructure and memory impairment	Cross-sectional	Kobe et al. (2016)
Whole-brain atrophy	Prospective, cross-sectional	Hooshmand et al. (2016); Tang et al. (2011); Vogiatzoglou et al. (2008)

Depression	Prospective	Kim, Stewart, et al. (2008)
Response to treatment of depression	Prospective	Hintikka, Tolmunen, Tanskanen, and Viinamaki (2003)
Stroke	Prospective	Spence (2016); Weikert et al. (2007)
Cognitive and motor development in children	Prospective	Strand et al. (2013)
	Intervention	Torsvik, Ueland, Markestad, and Bjorke-Monsen (2013); Torsvik, Ueland, Markestad, Midttun, and Bjorke Monsen (2015); Kvestad et al. (2017); Kvestad et al. (2015)
Age-related macular degeneration	Prospective	Gopinath, Flood, Rochtchina, Wang, and Mitchell (2013)
Low bone mineral density in women	Cross-sectional	Dhonukshe-Rutten et al. (2003)
Autonomic dysfunction (orthostatic hypotension)	Clinical (head-up tilt) Treatment intervention	Ganjehei, Massumi, Razavi, and Wilson (2012); Moore et al. (2004); Oner et al. (2014)
DNA damage in lymphocytes	Treatment intervention	Fenech et al. (1998)
Uracil misincorporation into DNA	Cross-sectional	Kapiszewska, Kalemba, Wojciech, and Milewicz (2005)

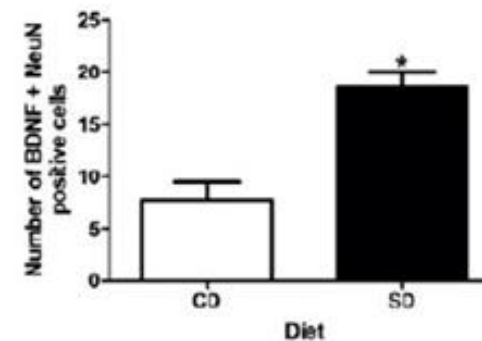
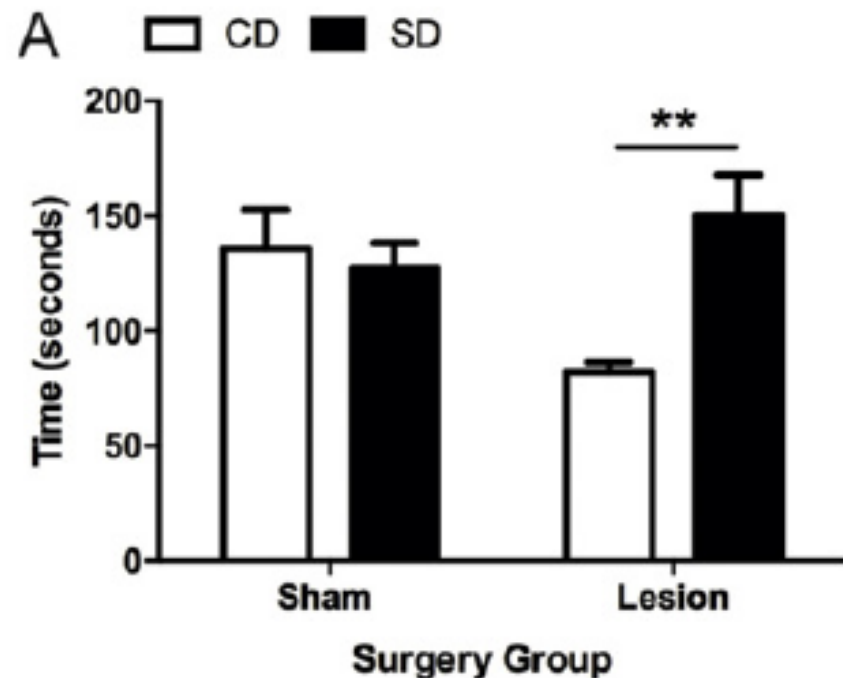
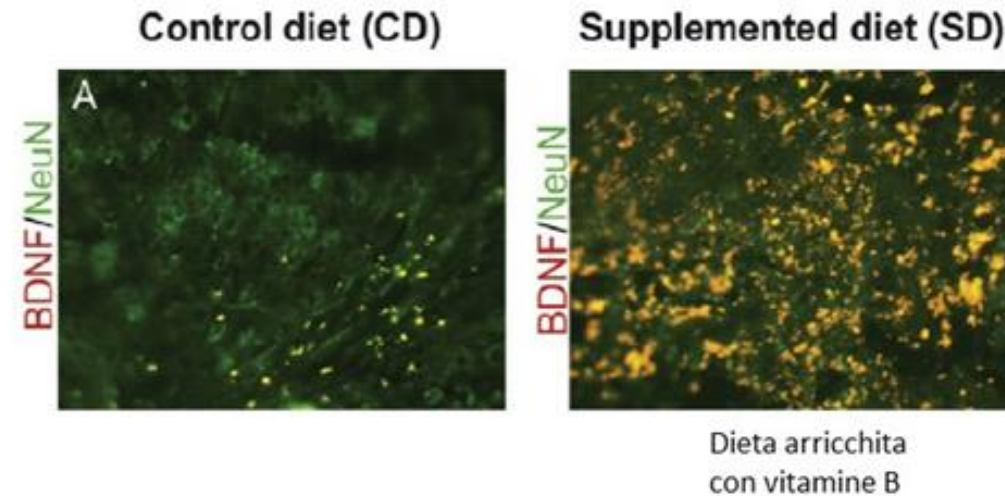
Smith AD et al., *Advances in Food and Nutrition Research*, 2018

B-vitamin and choline supplementation increases neuroplasticity and recovery after stroke

Nafisa M. Jadavji ^{a,b,*}, Joshua T. Emmerson ^a, Amanda J. MacFarlane ^c, William G. Willmore ^{d,e}, Patrice D. Smith ^{a,*}



Espressione di BDNF (brain-derived neurotrophic factor)





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Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs



Combining choline bitartrate and vitamin B12 ameliorates cognitive impairment in hypertensive elders with cognitive frailty

- To test the effects of combining Choline Bitartrate (CB) and B12 on cognitive impairment in hypertensive elders with CF.
- Cognitive frailty (CF) evaluated in presence of MCI (defined as a CDR score: 0,5) and physical frailty (defined by the presence of at least 3 of 5 Fried Criteria)
- Inclusion criteria: age > 65 yo; confirmed diagnosis of hypertension and CF
- Exclusion criteria: no previous stroke and/or acute myocardial infarction, no coronary artery bypass grafting, EF >50%; Montreal Cognitive Assessment (MoCA) Score <26
- Global cognitive function at baseline and after 3 months using the MoCA test

- 137 anziani ipertesi con Fragilità cognitiva.
- Dei pazienti selezionati, 27 non soddisfacevano i criteri e 11 non hanno dato il consenso a partecipare.
- In totale 99 pazienti hanno completato lo studio.

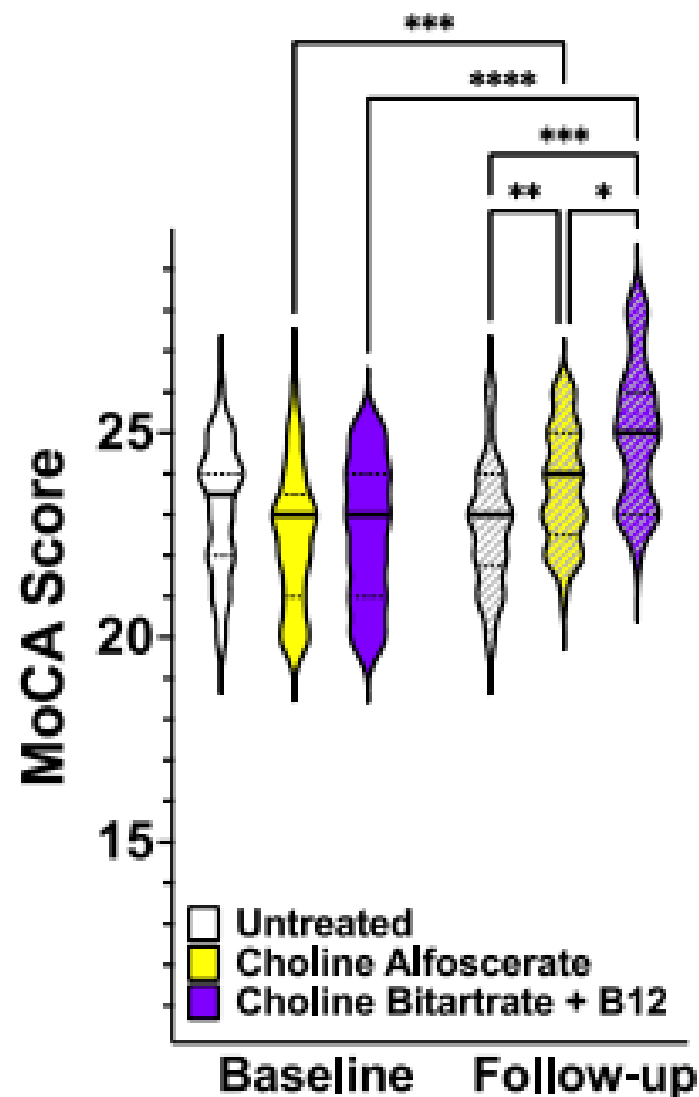


Fig. 1. Montreal Cognitive Assessment (MoCA) Score assessed in the indicated groups at baseline and after 3 months. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.005$; ****: $p < 0.001$ (ANOVA and Tukey-Kramer post hoc test).

Quali implicazioni e quali passi per il futuro

- L'attuale definizione di “fragilità cognitiva” presenta alcune lacune e non ha avuto successo sulla comunità dei geriatri
- Per le sue caratteristiche cliniche e fisiopatologiche, il delirium potrebbe rappresentare un buon marcatore di “fragilità cognitiva”
 - Ipotesi generale: fragilità e delirium possono essere manifestazioni alternative, talvolta concomitanti, di un processo di invecchiamento accelerato sottostante.
- Viste l'impatto sulle funzioni cognitive, e i suoi correlati fisiopatologici, potrebbe essere utile testare l'effetto di supplementazioni con colina e B12 in pazienti con delirium