



HAL
open science

Screening for intrinsic capacity impairments with a focus on the locomotion domain: a risk-stratifying approach in the context of the W.H.O. integrated care for older people

Emmanuel Gonzalez Bautista

► To cite this version:

Emmanuel Gonzalez Bautista. Screening for intrinsic capacity impairments with a focus on the locomotion domain: a risk-stratifying approach in the context of the W.H.O. integrated care for older people. Human health and pathology. Université Paul Sabatier - Toulouse III, 2022. English. NNT : 2022TOU30235 . tel-04047849

HAL Id: tel-04047849

<https://theses.hal.science/tel-04047849v1>

Submitted on 27 Mar 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



THÈSE

**En vue de l'obtention du
DOCTORAT DE L'UNIVERSITÉ DE TOULOUSE
Délivré par l'Université Toulouse 3 - Paul Sabatier**

**Présentée et soutenue par
Emmanuel GONZALEZ BAUTISTA**

Le 5 décembre 2022

**Dépister les anomalies des capacités intrinsèques avec l'avance
en âge dans le cadre du programme ICOPE de l'OMS : exemple de
l'approche centrée sur la locomotion**

Ecole doctorale : **EDMITT - Ecole Doctorale Mathématiques, Informatique et
Télécommunications de Toulouse**

Spécialité : **Epidémiologie**

Unité de recherche :
**CERPOP - Centre d'Epidémiologie et de Recherche en santé des POPulations
de Toulouse**

Thèse dirigée par
Sandrine ANDRIEU et Philippe DE SOUTO BARRETO

Jury

M. Cédric ANNWEILER, Rapporteur
M. Hubert BLAIN, Rapporteur
M. Bruno VELLAS, Examineur
M. Yves ROLLAND, Examineur
Mme Yuka SUMI, Examinatrice
Mme Betty Soledad MANRIQUE ESPINOZA, Examinatrice
Mme Sandrine ANDRIEU, Directrice de thèse
M. Philippe DE SOUTO BARRETO, Co-directeur de thèse

Title in English:

Screening for intrinsic capacity impairments with a focus on the locomotion domain: a risk-stratifying approach in the context of the W.H.O. integrated care for older people

President of the jury: Prof. Bruno VELLAS

Contents

Acknowledgements	5
Aims	7
Abstract	8
Resume en Français.....	12
Communication of Research Results.....	17
Main articles included in the Thesis:	17
Articles published related to the thesis:.....	17
Oral communications:	18
Chapter 1. Background.....	19
1.1 Health care for older people needs to adapt to the demographic and epidemiologic changes	19
1.2 What does healthy aging mean in the World Health Organization framework?	20
1.3 Intrinsic capacity as a proxy measure of health and functioning	25
1.4 The Comprehensive Geriatric assessment as a pioneer of integrated care for older people	29
1.5 World Health Organization’s Integrated Care for Older People Program	33
1.6 ICOPE Step 1 screening for intrinsic capacity impairments: lack of validation as a risk-stratification tool.....	34
1.7 What has the ICOPE Step 1 tool revealed from international older adult populations?	37
1.8 The ability to perform the basic activities of daily living are a relevant outcome for older adults... 40	
1.9 The role of the intrinsic capacity locomotion domain in functional ability and the disabling cascade	42
1.10 The determinants of the five-repetition chair stand test to assess locomotion	43
1.11 Rationale and research questions.....	46
Chapter 2. The ICOPE Step 1 screening tool for impairments in intrinsic capacity is able to detect people at higher risk of functional decline	47
2.1 Rationale for this study.....	47
The ICOPE program and the IC framework are supposed to identify people at-risk for care dependency.	47
2.2 Methods	47
2.3 Results	53
2.4 Interpretation of main findings.....	62

2.5 Strengths and limitations	64
Chapter 3. An age-stratified cut point for the five-repetition chair stand test improves the test’s clinimetric properties	67
3.1 Rationale for this study.....	67
3.2 Methods	68
3.3 Results	74
3.4 Interpretation of main findings	82
3.5 Strengths and limitations	87
Chapter 4. The clinically meaningful change in the five-repetition chair stand test was estimated according to anchor-based and distribution-based methods.....	89
4.1 Rationale for this study.....	89
4.2 Methods	89
4.3 Results	94
4.4 Interpretation of main findings.....	99
4.5 Strengths and limitations	104
Chapter 5. Integrative discussion.	105
5.1 Summary of main findings	105
5.2 Methodological limitations for the studies in this thesis	106
5.3 Screening for intrinsic capacity impairments aiming at disability prevention: implications for clinical practice.....	109
5.3.1 Limitations faced for the definition of cut points for chair stand test to assess the locomotion domain of IC.....	110
5.4 The interplay of the chronological and phenotypical metrics of aging	112
5.5 Non-linear functional decline with aging: Implications for health measurement in older people ..	114
5.6 The challenges of predicting incident disability based on physical impairments in older adults....	116
5.7 Future directions.....	119
Conclusions	125
References	126
ANNEXE. Published articles	137

Acknowledgements

Dr Bruno Vellas, Dr Sandrine Andrieu, Dr Philippe de Souto Barreto, Dr Yves Rolland

Thank you for the opportunity to join the CHU Toulouse and INSPIRE team, it has been a wonderful experience. I am grateful to learn from people like you whose efforts always go beyond the expectations. Thank you for guiding me through the fascinating journey of research.

Dr Luis Miguel Gutiérrez Robledo, Dr Enrique Vega, Dra Betty Manrique, Dr Aarón Salinas

Gracias por ser mis mentores, por confiar en mí y por apoyar a la juventud científica.

Claudia Amore

Gracias por decidir acompañarme en esta aventura en Francia. Sin ti no habría podido terminar este doctorado. Te amo mucho y quiero seguir viajando por el mundo contigo.

Aurora, Sara

Gracias por ser unas hijas asombrosas y por acompañarme en estos años de doctorado. Las amo mucho.

Mamá, Papá, Vico, Pepe

Gracias por hacerme sentir su cercanía en este periodo del doctorado. Gracias por las oportunidades de reforzar nuestras raíces de fuego, a pesar de la distancia. Los amo mucho.

A toda mi familia en México, a mis abuelas y abuelos con lazos de sangre y de fe

Gracias por ayudarme a seguir buscando mi lugar en este mundo. Gracias por todo su apoyo siempre.

A big thank you to Penny Wan-Hsuan LU and to all the colleagues in the Institute of Aging

Thank you for all our constructive discussions and for walking together through the “ups and downs” of our scientific careers.

Thanks Nature. Thanks God because the force of Gravity is not responsible for people *falling* in love.

Acknowledgements

To the Cancer, Ageing and Rejuvenation CARE Graduate School for their support.

Aims

General aim

To contribute to the validation process of a screening tool for intrinsic capacity impairments in older adults to be used in primary care, with a focus on the locomotion domain.

Specific aims

1. To assess if a tool for screening intrinsic capacity impairments identified individuals at higher risk of incident disability.
2. To develop an age-stratified cut point for the chair stand test and validate its predictive ability for incident disability.
3. To estimate the absolute and relative clinically meaningful changes for the five-repetition chair stand test vis a vis incident disability.

Abstract

BACKGROUND. The epidemiological and demographical transitions demand adjustments in our societies. Specifically, the health systems must adapt to address the needs of an aging society. For instance, in 9 out of the 49 countries in the Americas, there are more people older than 60, than children and adolescents under age 15. In response to the complex health needs of the aging population, the World Health Organization (WHO) has launched the Integrated Care for Older People (ICOPE) program. The idea is to organize health care services around the preservation of the functionality of older adults rather than only controlling their diseases.

Intrinsic capacity is an essential concept in the healthy aging of WHO and the ICOPE. Intrinsic capacity (IC) is the aggregate of all physical and mental capacities of that individuals draw upon as they age. It is operationalized by five domains: locomotion, cognition, sensory, psychological and vitality. We focused on the locomotion domain of IC given its central role in the disability cascade. The locomotion domain is assessed in the ICOPE Step 1 tool by the five-repetition chair stand test. In the context of monitoring the locomotion domain of intrinsic capacity using the five-repetition chair stand test, it is convenient to distinguish mild changes from clinically meaningful ones.

The ICOPE clinical care pathways propose a series of steps aimed at preventing prevent disability in older age: Step1 - screen for declines in intrinsic capacity, Step2 - provide a person-centred assessment in primary care, Step3 - define the care goal and develop a personalized care plan, Step4 - ensure a referral pathway (including geriatrics) and monitoring of the care plan and Step5 - engage the community and support the caregivers. ICOPE has face validity because it was designed by a group of experts. Yet, there are still gaps in its validation process.

OBJECTIVES. This thesis aims to contribute to the validation process of a screening tool for intrinsic capacity impairments in older adults to be used in primary care, with a focus on the locomotion domain. Our specific objectives were a) to assess if a tool for screening intrinsic capacity impairments identified individuals at higher risk of incident disability; b) to develop an age-stratified cut point for the chair stand test and validate its predictive ability for incident disability, and c) to estimate the absolute and relative clinically meaningful changes for the five-repetition chair stand test vis a vis incident disability.

METHODS. We used data from community-dwelling older adults to evaluate the ICOPE Step 1 properties as a good risk-stratifying tool for functional decline. We applied Cox proportional hazards models in data from the Multidomain Alzheimer Preventive Trial (MAPT) to assess if the intrinsic capacity impairments screening tool was able to detect older adults at higher risk of disability (Chapter 2). Secondly, we applied ROC analyses to two population-based cohorts (the Study on Aging and Adult Health –SAGE- Mexico and the Toledo Study on Healthy Aging – TSHA- to develop an age-stratified cut point for the chair stand test and then applied linear mixed-effects models to cross-validate them. Further, we tested the obtained cut points using Cox proportional hazards models and logistic regression in two populations from different clinical contexts –MAPT and the Toulouse frailty clinic-. Thirdly, we applied anchor- and distribution-based methods to the SAGE Mexico data to obtain the clinically meaningful changes to the chair stand test. We also verified if the obtained clinically meaningful changes worked in the MAPT population.

RESULTS. Each additional IC impairment increased the risk of disability for IADLs by 27% (aHR CI95% 1.06; 1.53) and for ADLs by 23% in MAPT participants (aHR CI95% 1.00;1.52). An

adaptation of the ICOPE Step 1 screening tool showed a good predictive ability based on the Harrell C statistic ($0.70 < C < 0.83$).

We found that optimal cut points to discriminate people at high risk of disability were 14 and 16 seconds, for the 70-79 and 80+ age groups, accordingly. We tested these cut-offs with other adverse outcomes – frailty- and different populations -frailty day-hospital-. Changing the current cut point of 14 seconds to 16 in adults aged 80 and over leads to improvements of up to 42% in clinimetric parameters.

Absolute meaningful changes for the five-repetition chair stand time ranged from 0.5 s to 1.7 s and from 3.0 s to 4.7 s applying distribution-based and anchor-based methods, respectively. Relative meaningful changes ranged from 9.6% to 30.4% using distribution-based and anchor-based methods, respectively. The results from the ROC analyses showed that ≥ 2.6 s and $\geq 27.7\%$ were coherent with distribution-based and anchor-based methods. Furthermore, we corroborated that older adults with a clinically meaningful decline in the chair stand time were at higher risk of incident ADL disability in an external population (the MAPT study).

CONCLUSIONS.

A modified version of the ICOPE Step 1 screening tool, the MAPT Step 1 screening tool showed good clinimetric properties to identify people at higher risk of frailty and disability for the activities of the daily living. The IC score obtained from the screening tool (range 0-6) reported a good predictive ability for the five-year incidence of frailty, and a moderate predictive ability for IADL and ADL disability incidence over the same period, according to the Harrel's C index. Mobility impairment was significantly associated with a higher risk of frailty and incident ADL disability over five-year follow-up.

The cut points found for the chair stand test were 14 seconds for the 70-79 age group and 16 seconds for those aged 80+ for incident ADL disability. These cut-offs predicted frailty and ADLs disability in older adults from different clinical settings. Our results showed that slow chair standers had a faster decline in their ADL status and sooner frailty worsening than fast chair standers. Moreover, the cut points discriminated frail from non-frail individuals and ADL disabled from non-disabled people among patients of the frailty day-hospital.

An increase in the time for five-repetition chair stand test of ≥ 2.6 s or $\geq 27.7\%$ from baseline time over three years is clinically meaningful vis a vis the risk of incident ADL disability in older people.

We contributed to the validation process of the ICOPE Step 1 screening tool. Yet, further research is needed from other populations using prospective data.

CONTEXTE. Les transitions épidémiologiques et démographiques exigent des ajustements de nos sociétés. Ce qui fait que les systèmes de santé doivent s'adapter pour répondre aux besoins d'une société vieillissante. Par exemple, dans 9 des 49 pays des Amériques, il y a plus de personnes âgées de plus de 60 ans que d'enfants et d'adolescents de moins de 15 ans. En réponse aux besoins de santé complexes d'une population vieillissante, l'Organisation Mondiale de la Santé (OMS) a lancé le programme de soins intégrés pour les personnes âgées (ICOPE). Tout d'abord, l'idée est d'organiser les services de santé autour de la préservation de la fonctionnalité des personnes âgées plutôt que de surveiller uniquement leurs maladies.

A savoir que la capacité intrinsèque (CI) est un concept essentiel dans le vieillissement en bonne santé propose pour l'OMS et l'ICOPE. C'est-à-dire que la CI est l'ensemble de toutes les capacités physiques et mentales des individus auxquelles ils font appel à mesure qu'ils vieillissent. Elle est opérationnalisée par cinq domaines : la locomotion, la cognition, le sensoriel, la psychologique et la vitalité. Nous nous sommes concentrés sur le domaine de la locomotion de l'IC compte tenu de son rôle central dans la cascade d'invalidité. Notamment, le domaine de la locomotion est évalué dans l'outil ICOPE Step 1 par le test de chaise à cinq répétitions (TC5). En particulier, dans le cadre de la surveillance du domaine de locomotion de la CI à l'aide du test de support de chaise à cinq répétitions, il est pratique de distinguer les altérations légères des changements cliniquement significatifs.

Les parcours de soins cliniques ICOPE proposent une série d'étapes visant à prévenir l'invalidité chez les personnes âgées : En premier lieu, (Étape 1) le dépistage des déclin de la CI, en deuxième (Étape 2) l'approvisionnement d'une évaluation centrée sur la personne en soins

primaires, en troisième lieu l'étape 3, la définition d'un objectif de soins et le développement d'une approche personnalisée de plan de soins, ensuite, l'étape 4, assurer un parcours clinique (dont compris la gériatrie) et le suivi du plan de soins. En fin, (Étape 5) l'implication de la communauté et le soutien des soignants. L'ICOPE a une validité apparente car il a été conçu par un groupe d'experts. Pourtant, il y a encore des lacunes dans son processus de validation.

OBJECTIFS. Cette thèse vise à contribuer au processus de validation d'un outil de dépistage des déficiences intrinsèques des capacités chez les personnes âgées à utiliser en soins primaires, en mettant l'accent sur le domaine de la locomotion. Nos objectifs spécifiques étaient a) d'évaluer si un outil de dépistage des déficiences intrinsèques des capacités identifiait les personnes à risque plus élevé d'incapacité incidente ; b) pour développer un seuil stratifié selon l'âge pour le test de se lever d'une chaise et valider sa capacité prédictive pour l'incapacité incidente, et c) pour estimer les changements absolus et relatifs cliniquement significatifs pour le test de se lever d'une chaise à cinq répétitions vis-à-vis d'handicap incidente.

MÉTHODES. **Premièrement** nous avons utilisé des données provenant d'adultes âgés vivant dans la communauté pour évaluer les domaines d'ICOPE Étape 1 comme un outil sensible de stratification du risque de déclin fonctionnel. Puis nous avons appliqué les modèles à risques proportionnels de Cox dans les données de l'essai préventif multi-domaine sur la maladie d'Alzheimer (MAPT) pour évaluer si l'outil de dépistage des déficiences intrinsèques des capacités était capable de détecter les personnes âgées à risque plus élevé d'invalidité (chapitre 2). **Deuxièmement**, nous avons appliqué des analyses ROC à deux cohortes basées sur la population (l'étude sur le vieillissement et la santé des adultes -SAGE-Mexique et l'étude de Toledo sur le vieillissement en bonne santé -TSHA- pour développer un seuil stratifié par âge pour le test de se lever de chaise, puis appliqué modèles linéaires à effets mixtes pour les valider de manière croisée.

En outre, nous avons testé les seuils obtenus à l'aide de modèles à risques proportionnels de Cox et d'une régression logistique dans deux populations de contextes cliniques différents -MAPT et la clinique de fragilité de Toulouse-. Les méthodes sont basées sur la distribution aux données SAGE Mexique pour obtenir les modifications cliniquement significatives du test de se lever de chaise. Finalement nous avons également vérifié si les modifications cliniquement significatives obtenues fonctionnaient dans la population MAPT.

RÉSULTATS. Du fait que **chaque** anomalie d'IC supplémentaire augmentait le risque d'invalidité pour les activités instrumentaux du quotidienn (IADLs) de 27 % (aHR CI95 % 1,06 ; 1,53) et pour les activités basiques du quotidienn (ADL) de 23 % chez les participants MAPT (aHR IC95 % 1,00 ;1,52). Une adaptation de l'outil de dépistage ICOPE Step 1 a montré une bonne capacité prédictive basée sur la statistique Harrell C ($0,70 < C < 0,83$).

D'ailleurs nous avons constaté que les limites optimales pour discriminer les personnes à haut risque d'invalidité étaient de 14 et 16 secondes, pour les groupes d'âge 70-79 et 80+, respectivement. Nous avons testé ces seuils avec d'autres critères de jugement défavorables – la fragilité - et différentes populations – la fragilité – l'hôpital de jour -. En sorte que changer la limite actuelle de 14 secondes à 16 chez les adultes âgés de 80 ans et plus entraîne des améliorations allant jusqu'à 42 % des paramètres clinimétriques.

Également, les changements significatifs absolus pour le temps de repos de la chaise à cinq répétitions allaient de 0,5 s à 1,7 s et de 3,0 s à 4,7 s, respectivement les méthodes basées sur la distribution et basées sur l'ancrage. Ainsi que, les changements significatifs relatifs allaient de 9,6 % à 30,4 % en utilisant respectivement les méthodes basées sur la distribution et les méthodes basées sur les ancrés. Les résultats des analyses ROC ont montré que $\geq 2,6$ s et $\geq 27,7$ % étaient

cohérents avec les méthodes basées sur la distribution et sur les ancrés. De plus, nous avons corroboré le fait que les personnes âgées présentant une augmentation cliniquement significative du temps pour le test du cinq-répétition du lever d'une chaise présentaient un risque plus élevé d'handicapé incidente dans les ADLs dans une population externe (l'étude MAPT).

CONCLUSIONS.

Pour conclure, une version modifiée de l'outil de dépistage ICOPE Step 1, l'outil de dépistage MAPT Step 1 a montré de bonnes propriétés clinimétriques pour identifier les personnes à risque plus élevé de fragilité et d'invalidité pour les activités de la vie quotidienne. Par suite, le score IC obtenu à partir de l'outil de dépistage (gamme de 0 à 6) a rapporté une bonne capacité prédictive de l'incidence de la fragilité sur cinq ans et une capacité prédictive modérée de l'incidence de l'invalidité IADL et ADL sur la même période, selon l'indice C de Harrel . C'est ainsi que la mobilité réduite était associée de manière significative à un risque plus élevé de fragilité et d'incidence d'incapacité dans les ADL sur un suivi de cinq ans.

Du fait que les limites trouvées pour le test de la chaise debout étaient de 14 secondes pour le groupe d'âge 70-79 ans et de 16 secondes pour les personnes âgées de 80 ans et plus pour l'incapacité incidente des ADL. Ainsi, ces seuils prédisaient la fragilité et l'incapacité des ADL chez les personnes âgées de différents contextes cliniques. En vue de nos résultats ont montré que les personnes debout lentement sur une chaise avaient un déclin plus rapide de leur statut dans les ADL et une aggravation plus rapide de la fragilité que les personnes debout rapidement sur une chaise. De plus, les points de coupure discriminaient les personnes fragiles des personnes non fragiles et les ADL handicapés des personnes non handicapées parmi les patients de l'hôpital de jour de fragilité.

Une baisse du test de position debout de $\geq 2,6$ s ou $\geq 27,7$ % par rapport à la période de référence sur trois ans est cliniquement significative vis-à-vis du risque d'incapacité incidente des ADL chez les personnes âgées.

En effet nous avons contribué à combler le manque de preuves concernant la validité de l'outil de dépistage ICOPE Step 1 en attirant l'attention sur le domaine de la locomotion et de la capacité intrinsèque (CI) (c'est-à-dire l'ensemble des capacités physiques et mentales à partir desquelles les gens peuvent puiser lorsqu'ils agissent). En somme, nous avons utilisé des données provenant d'adultes âgés vivant dans la communauté pour évaluer les propriétés ICOPE Étape 1 comme un bon outil de stratification du risque de déclin fonctionnel. Pourtant, des recherches supplémentaires sont nécessaires auprès d'autres populations à l'aide de données prospectives.

Communication of Research Results

Main articles included in the Thesis:

1. ***González-Bautista E**, de Souto Barreto P, Andrieu S, Rolland Y, Vellas B. Screening for intrinsic capacity impairments as markers of increased risk of frailty and disability in the context of integrated care for older people: Secondary analysis of MAPT. *Maturitas* [Internet]. 2021 Aug 1 [cited 2021 Jun 14];150:1–6. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0378512221000815>
2. ***Gonzalez-Bautista E**, Barreto P de S, Salinas-Rodriguez A, Manrique Espinoza B, Sourdet S, Rolland Y, et al. Development and validation of a cut-off for the chair stand test as a screening for mobility impairment in the context of the integrated care for older people (ICOPE) program. *J Gerontol A Biol Sci Med Sci*. 2022 Feb;
3. ***Gonzalez-Bautista E**, Barreto P de S, Salinas-Rodriguez A, Manrique-Espinoza B, Rolland Y, Andrieu S, et al. Clinically meaningful change for the chair stand test: monitoring mobility in integrated care for older people. *J Cachexia Sarcopenia Muscle* [Internet]. 2022 Aug 26 [cited 2022 Sep 9]; Available from: <https://onlinelibrary.wiley.com/doi/full/10.1002/jcsm.13042>

Articles published related to the thesis:

4. **Gonzalez-Bautista E**, Andrieu S, Gutiérrez-Robledo LM, García-Chanes RE, De Souto Barreto P. In the Quest of a Standard Index of Intrinsic Capacity. A Critical Literature Review. *J Nutr Health Aging* [Internet]. 2020;(5). Available from: <https://doi.org/10.1007/s12603-020-1394-4>
5. **González-Bautista E**, Barreto PDS, Giudici KV, Andrieu S, Rolland Y, Vellas B. Frequency of Conditions Associated with Declines in Intrinsic Capacity According to a

Screening Tool in the Context of Integrated Care for Older People. *J Frailty Aging* 2020 [Internet]. 2020 Aug 7 [cited 2020 Aug 10];1–9. Available from:

<https://link.springer.com/article/10.14283/jfa.2020.42>

6. **González-Bautista E**, de Souto Barreto P, Andrieu S, Rolland Y, Vellas B. What day is today? Cognitive capacity and the risk of incident dementia in the context of integrated care for older people (ICOPE Step 1). *Aging Clin Exp Res* [Internet]. 2021; Available from: <https://doi.org/10.1007/s40520-021-01803-4>

Oral communications:

1. The Gerontological Society of America (GSA) Annual Scientific Meeting. Virtual Congress due to pandemic restrictions. November 10, 2021. Session 1280. Mobility 2. VALIDATION OF THE INTEGRATED CARE FOR OLDER PEOPLE SCREENING TOOL: FOCUS ON THE CHAIR RISE TEST TO ASSESS LOCOMOTION. **Emmanuel Gonzalez-Bautista**, Philippe de Souto Barreto, Aaron Salinas-Rodriguez, Sandrine Sourdet, Yves Rolland, Leocadio Rodriguez-Mañas, Sandrine Andrieu, and Bruno Vellas.
2. 11th International Conference on Frailty & Sarcopenia Research (ICFSR) September 29–October 2, 2021, 100% Virtual conference. DIFFERENCES IN INTRINSIC CAPACITY AND BIOLOGICAL PROFILE ACCORDING TO LONGITUDINAL FRAILITY TRAJECTORIES IN COMMUNITY-DWELLING OLDER ADULTS. **Emmanuel Gonzalez Bautista**, Wan-Hsuan Lu, Bruno Vellas, Philippe de Souto Barreto. Symposia — Conferences — Oral Communications. *J Frailty Aging* [Internet]. 2021;10(1):1–40. Available from: <https://doi.org/10.14283/jfa.2021.34>

Chapter 1. Background

1.1 Health care for older people needs to adapt to the demographic and epidemiologic changes

The profile of the typical user of health systems is changing from adults to older persons due to global demographic transformations. The demographic transition resulted from low birth rates and increasing life expectancy. (1) Since 2018, the population aged 65 and over has been higher than that of children under 5. (2) The epidemiological transition resulted from a switch from the predominance of episodic infectious diseases to non-communicable chronic conditions. (3) However, a mosaic of epidemiological transitions may occur in one country depending on its public health policies and interventions. For example, in Mexico, communicable diseases disproportionately afflict the southern states' population compared to the northern ones, yet non-communicable diseases also affect them. (4)

A recent Global Burden of Disease Study (GBD) investigation showed lagging performance on effective coverage indicators for non-communicable diseases relative to infectious illnesses/maternal and child health. However, non-communicable diseases accounted for more potential health gains in 2019. Health systems around the world are not keeping pace with the rising non-communicable disease burden and associated population health needs(5).

Epidemiological and demographical transitions demand adjustments in our societies to overcome the predicted resource shortage for health and pension systems with decreasing working-age population and increased demand for these services (6). Specifically, the health systems must adapt to address the needs of an aging society. For instance, in 9 out of the 49 countries in the Americas, there are higher chances that the health system (HS) will *meet* a person older than 60 than a child or adolescent younger than 15 years. (7)

Critical factors related to a population's healthy or unhealthy aging are multimorbidity, physical and mental capabilities, and the physical and social environment (8). A central element of the social environment is the organized societal response to health and health care, i.e., the health system.

Current health systems were designed under an episodic model of health service. Such a model was reasonable when infectious diseases were the most common cause of consultation, but they are not anymore. To be sustainable, the episodic and fragmented manner of providing health services should evolve into person-centred integrated care. This will favour efficiency in health systems and adequate care for the complex and diverse needs of the older population. For instance, approximately 2/3 of older persons will exhibit multimorbidity, defined as two or more chronic conditions.

However, is it possible to live healthy aging with chronic conditions? Given the high proportion of older adults with chronic conditions, the Public Health understanding of healthy aging cannot exclude them. The definition of healthy aging should not focus on age-related diseases but on what allows older people to be and do what gives meaning to their lives.

1.2 What does healthy aging mean in the World Health Organization framework?

The WHO has recognized global aging as a driver of current health systems. (9) In response, the Aging and Life course team of WHO and its regional offices have designed a strategy to push healthy aging forward in the global agenda. A few milestones relevant to this thesis are the World Report on Aging and Health, (8) the Integrated Care for Older People program (ICOPE), (10) and the United Nations Decade for Healthy Aging. (11)

The World Report on Aging and Health provided a common ground for discussions among researchers, clinicians, policymakers, older adults, and health system managers. It was a milestone because it proposed a comprehensive concept for healthy aging and sketched concrete actions to foster healthy aging, like adapting the health systems for the aging of the population and working to implement long-term care services.

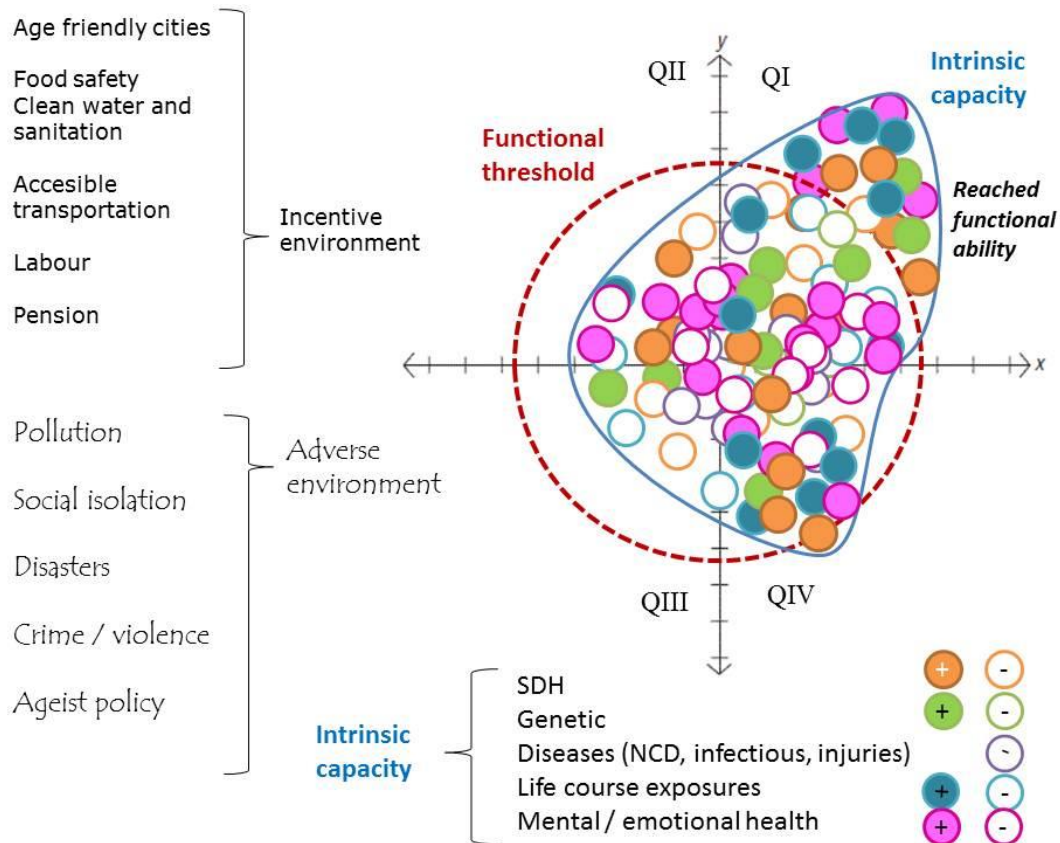
The principle of the healthy aging concept in the WHO report is to intervene to provide older people with the opportunity to be and do what gives meaning to their lives. This is a revolutionary idea within the modern health systems because health care has focused on solving a disease episode rather than establishing a person-centered care and a dialogue with the patient (like in the classical clinical school). Healthcare providers cannot learn what gives meaning to their patients' lives if they do not dialogue with them. It may sound utopic, but it is feasible. (12) The clinical dialogue does not need to be lengthy but close and human. A couple of questions may be enough for healthcare providers to discover what impedes older adults from being and doing what is meaningful for them. That is the starting point for healthy aging in primary care.

The operationalization of healthy aging is to keep functional ability to optimally cope in daily life. Functional ability is defined in the world report as the interaction between the social and physical environment and intrinsic capacity. (13) Intrinsic capacity (IC) represents the more "biological" side of the coin. The term "intrinsic" in IC alludes to the individual dimension, a sum of physical and mental capabilities in the human body. Therefore, the WHO framework for healthy aging includes contextual and personal factors, i.e., the environment and intrinsic capacity, respectively. It makes sense to distinguish between environment and IC because of their different levels of complexity. For instance, if an intervention is to be designed to improve the social environment of an older adult, most of the activities might fall outside of the health system's scope. Thus the social

and civil sectors might develop most of the tasks in coordination (or not) with the health sector. On the contrary, interventions to improve IC might be done mainly by healthcare professionals. The functional ability would result from the interaction at those two levels of complexity.

The diagram shown below was elaborated by me to understand how the interaction of intrinsic capacity and the environment would lead to different outcomes in functional ability (Figure 1.1). I have had the opportunity to discuss around the concepts of healthy aging and IC with WHO staff during the preparation of the world report on aging and health. Indeed, thanks to the invitation of Dr Somnath Chatterji (WHO official), I participated in one of the review meetings before the World Report on Aging and Health was published.

Figure 1.1 Healthy aging model of the interaction between intrinsic capacity and environment with different resulting functional ability outcomes



*SDH=social determinants of health
Source: Unpublished work by the author.

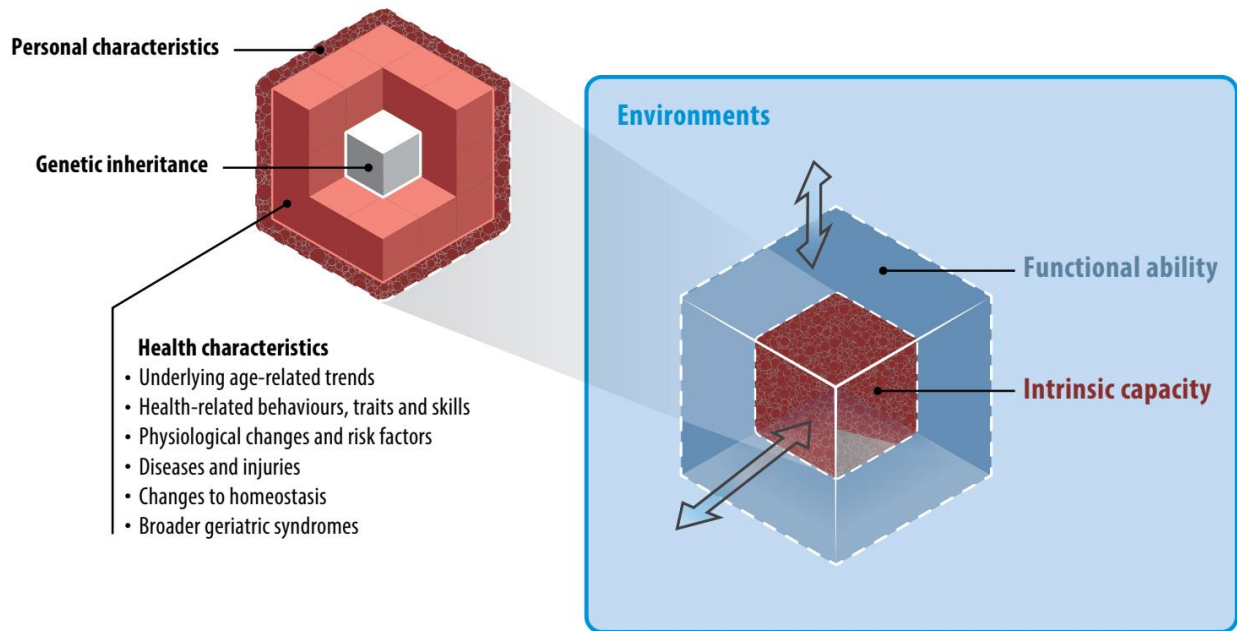
This figure describes the following:

1. The core of healthy aging is exercising functional ability.
2. The intrinsic capacity is constituted by positive or negative elements different in nature but which interact among them to expand or weaken the human potential. The little circles represent those.
3. Intrinsic capacity is represented in the x-axis, and the environments in the y-axis.

4. The intrinsic capacity is a dynamic pool of elements that keeps flowing by filling or emptying according to the positive or negative exposures/assets that build it. The blue shape represents its boundaries.
5. In quadrants I and II, the environment is favourable to functional ability, as opposed to QIII and QIV.
6. The red dashed circle is the functional threshold, representing the minimum limit intrinsic capacity needs to push to perform an activity or function.
7. When many positive exposures (coloured circles) concentrate in the same place and time, the individual might be able to cross the functional threshold and reach the functional ability. However, the environment is not favourable (QIV).
8. Functional ability may be reached by gaining intrinsic capacity and/or creating a better environment.

Some of the elements in Figure 1.1 were used for the report's final version of the healthy aging diagram. (Figure 1.2)

Figure 1.2 The healthy aging framework showing the interaction of intrinsic capacity and the environment to result in functional ability



Source: World Report on Aging and Health. WHO. (2015).

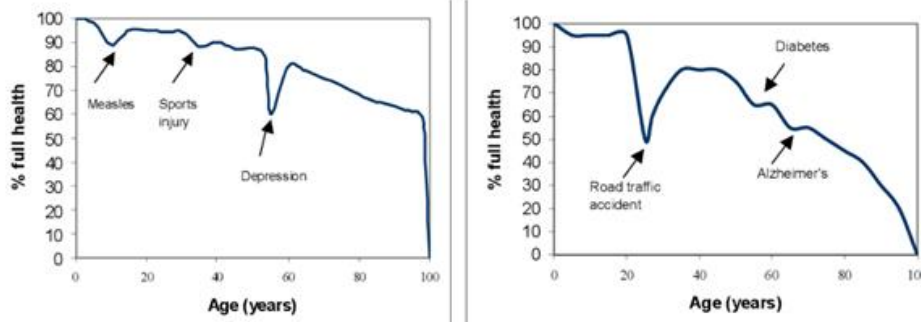
1.3 Intrinsic capacity as a proxy measure of health and functioning

Intrinsic capacity is the composite of physical and mental abilities individuals draw upon as they age. Intrinsic capacity is a summary of five domains: cognition, locomotion, psychological, nutrition and sensory. (14) This concept was presented by the World Health Organisation (WHO) in the World Report on Aging and Health in 2015. (8)

Intrinsic capacity is enrooted in the dissertation by Chatterji et al. entitled *The conceptual basis for measuring and reporting on health*. (15) In that text, the authors distinguish the direct measures of health from the indirect measures of health in parallel to the intrinsic capacity and functional ability. For instance, they postulate that health can be measured by the direct domains of mobility, cognition, vision, hearing, affect and vitality. Another parallelism between the seminal paper and the World Report is the life course trajectories of health which depict stereotypical pathways that intrinsic capacity could take depending on intrinsic factors. (Figure 1.3)

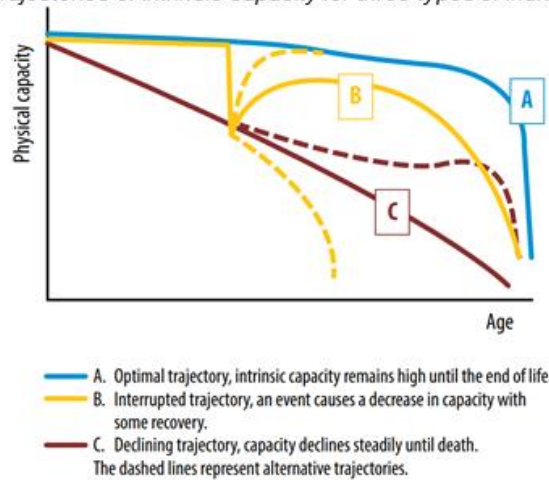
Figure 1.3. Life course health trajectories, hypothetical (panels A and B) and empirical (panel C).

Panel A. Health trajectories for two persons with slow (left) and fast (right) health declines



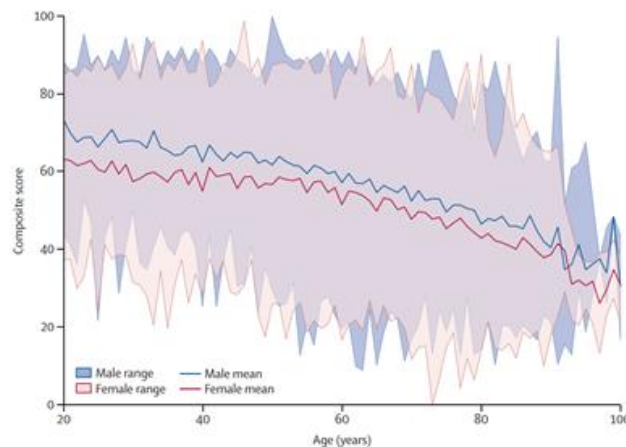
Source: Chatterji, S. et al. *The conceptual basis for measuring and reporting on health.* (2002).

Panel B. Hypothetical trajectories of intrinsic capacity for three types of individuals.



Source: World Health Organization. *World Report on Ageing and Health.* (WHO Press, 2015).

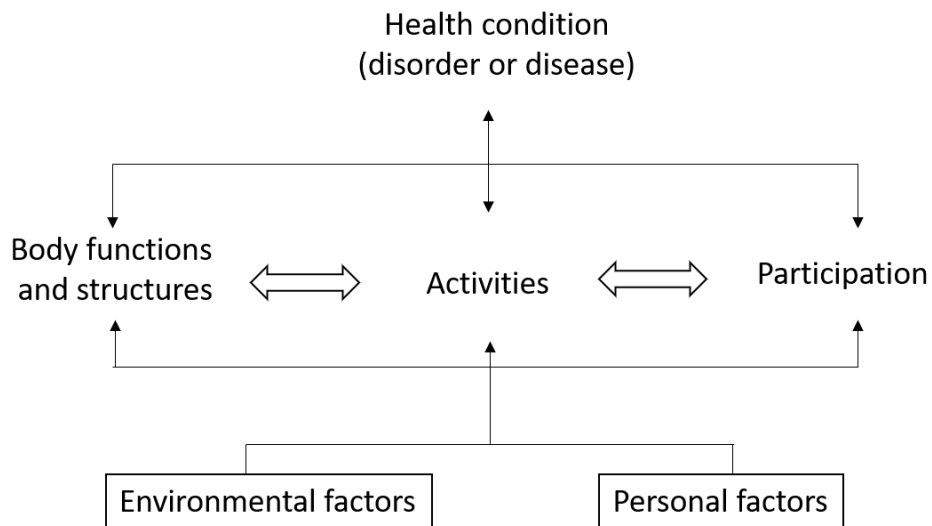
Panel C. Mean and range of a composite score of intrinsic capacity depicting a cross-sectional trajectory in participants of the Study on Ageing and Adult Health (SAGE).



Source: Beard, J. R. et al. *The World report on ageing and health: A policy framework for healthy ageing.* *The Lancet* vol. 387 2145–2154 (2016).

According to Cesari et al. (16), intrinsic capacity is enrooted in the WHO’s International Classification of Function Disability and Health (ICF) (17). The ICF integrated the physiological (18) and the sociological (19) perspectives of functioning and disability. Intrinsic capacity is comprehended in the ICF framework in the “body functions and structures” component. Individual health characteristics such as life course beneficial/harmful exposures, pathophysiological patterns, health-related behaviours, traits and skills are determinants of intrinsic capacity. (16) (Figure 1.4)

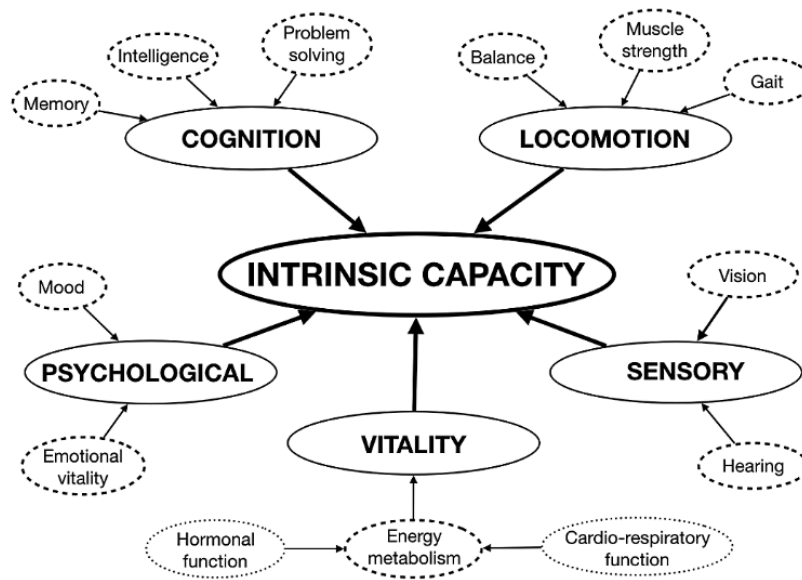
Figure 1.4. The International Classification of Function Disability and Health framework (ICF)



Source: International Classification of Function Disability and Health (ICF) (OMS 2001)

Recently, Cesari et al. have summarized evidence that supports the construct of intrinsic capacity as an aggregate of functional domains(16). (Figure 1.5)

Figure 1.5. Five domains of the intrinsic capacity construct with examples of possible sub domains



Source: Cesari, M. *et al.* Evidence for the domains supporting the construct of intrinsic capacity. *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* **73**, 1653–1660 (2018).

The authors briefly highlight that impairments in the IC domains are frequent in older age. For instance, they mention how locomotion impairments are associated with subclinical increased atherosclerotic formation, decreased aerobic capacity, or inflammation(20). Yet, this article does not describe how the IC domains could be interrelated.

The validation of the intrinsic capacity index started with the pioneering work by Beard et al. They obtained an intrinsic capacity index by applying structural equation modelling to data from the British cohort English Longitudinal Study of Aging (ELSA). (21) They concluded that functioning measures commonly used in older age have a common variance compatible with the concept of intrinsic capacity. A low IC index was associated with a higher burden of chronic diseases and disability. Moreover, IC was a mediator of the effect of multimorbidity in disability and a moderator of the impact of chronological age in incident disability. (14)

Intrinsic capacity and its essential role in healthy aging have a background in the field of Geriatrics, as several Geriatricians participated in the WHO expert meetings to develop the healthy aging framework. (22)

1.4 The Comprehensive Geriatric assessment as a pioneer of integrated care for older people

Specialized medical developments for older adults in the health system started formally in the first half of the 20th century. In 1914, Ignatz Leo Nascher, a Viennese doctor, published the book: “Geriatrics: The Diseases of Old Age and Their Treatment”, inspired by the flourishing medical care for older people in Austria. (23) Later, Marjory Warren, a British doctor in the West Middlesex hospital in the UK pushed for the birth of modern Geriatrics. She introduced environmental improvements, active rehabilitation programs, and increased motivation for older people. (23) She wrote 27 articles on geriatrics. (24) The comprehensive geriatric assessment (CGA) resulted from the increasing need for a geriatric approach in modern societies.

The Sepulveda VA Geriatric Evaluation Unit operationalized the CGA principles. Larry Rubenstein, the leader of this unit, had defined CGA as a multidimensional, interdisciplinary diagnostic process focused on determining a frail older person’s medical, psychological, and functional capability to develop a coordinated and integrated plan for treatment and long-term follow-up. (25) The principle of the CGA is to determine an older person’s medical, psychosocial, functional, and environmental resources and problems, linked with an overall plan for treatment and follow-up. (26) Some tools used in the CGA are mentioned in Table 1.1.

Table 1.1 Examples of domains assessed and tools used as part of the Comprehensive Geriatric Assessment (CGA)

Tool by Domain	Abnormal Score
Demographic and social status Conditions of living, marital status, educational level, financial resources, social activities, family support	
Identification of the caregiver and burden (Zarit Burden Interview)	>20
Comorbidity Charlson comorbidity index CIRS CIRS-G Physical Health Section (subscale of OARS) Simplified comorbidity score	
Polypharmacy Beers criteria STOPP and START criteria	
Functional status ADL (Katz index)	<6
IADL (Lawton scale)	<8
Visual and/or hearing impairment, regardless of use of glasses or hearing aids	
Mobility problem (requiring help or use of walking aid) Five-repetition chair stand test	>15 s
Timed Get Up and Go	
Hand grip strength	<27kg for men and <16kg for women
Walking problems, gait assessment, and gait	<1 m/s

speed	
Self-reported No. of falls (within different time frames)	
<hr/>	
Cognition	
Mini-Mental State Examination	<24
Montreal Cognitive Assessment	<26
Clock-drawing test	<5
Blessed Orientation- Memory-Concentration Test	>4
Mini-Cog	<4
<hr/>	
Mood	
GDS (Mini-GDS, GDS-15, GDS-30)	Mini- GDS < 1; GDS-15 >5 GDS-30 >10
Hospital Anxiety and Depression Scale	>7
Distress thermometer	
<hr/>	
Nutrition	
Body-mass index (weight and height)	<23
Weight loss (unintentional loss in 3 or 6 months)	
Mini-Nutritional Assessment	<24
<hr/>	
Dentition	
<hr/>	
Fatigue	
MOB-T	
<hr/>	
Geriatric syndromes	
Dementia	
Delirium	
Incontinence (fecal and/or urinary)	
Osteoporosis or spontaneous fractures	

Neglect or abuse
Failure to thrive
Pressure ulcer
Sarcopenia

Sources: Cruz-Jentoft, A. J. *et al.* Sarcopenia: revised European consensus on definition and diagnosis. *Age Aging* **48**, 16–31 (2019). And Loh, K. P. *et al.* What Every Oncologist Should Know About Geriatric Assessment for Older Patients With Cancer: Young International Society of Geriatric Oncology Position Paper. *J. Oncol. Pract.* **14**, 85–94 (2018).

The explosion of interest in CGA could be attributed to Rubenstein’s 1984 New England Journal of Medicine paper “Effectiveness of a geriatric evaluation unit. A randomized clinical trial”. (27)

This novel paper went beyond the strong face validity of CGA and evidenced its effectiveness in improving the health and quality of life of older persons by an RCT. Following this experience, several Geriatric Evaluation Units were implemented in the USA and worldwide across different settings. (28) Professor Bruno Vellas and Professor Albarede from CHU Toulouse (previously CHU Purpan-Casselardit) significantly extended geriatric awareness across Europe. (23)

The CGA integrates information on physical and mental health, functional status, social adaptability, and environmental conditions. This essential information allows the development and implementation of individualized, multidisciplinary, supportive care plans to maximize independence and quality of life. (29)

The CGA allows for the risk stratification of patients. The CGA helps establish prognosis and evaluate the risk of interventions where the risk-benefit ratio is not so evident—for example, risks related to surgery or cancer chemotherapy in older patients. (30) CGA is superior to most prognostic indexes and specialty tools in predicting mortality, surgical complications, and iatrogenesis. (31) The aggregate of tests and batteries included in the CGA results in a summary score. Clinicians may then identify patients that would not benefit from more invasive interventions and should privilege conservative alternative strategies or require extra surveillance and follow-up.

The utilization of CGA can identify older persons with complex multi-morbidity and multiple clinical problems that are difficult to handle because of socioeconomic and mental health constraints. The simple identification of these subjects improved the quality of care, as reviewed by Pilotto et al. on the effectiveness of CGA in different healthcare settings. (31)

Yet, the CGA still lacks diffusion in the medical setting. Reasons for this include the high cost (resources and time), departure from the traditional biomedical model, and ageism in stakeholders across the health systems. (32) The objection also comes from the lack of evidence that the problems discovered through this method can be reversed. (32) Additionally, consider that the world's fastest-growing age group is the oldest (aged 80+). (33) Thus, it is not feasible to implement the CGA at a large scale in rapidly aging populations.

Given the unattended need for improving health care systems for older people, the World Health Organization (WHO) developed a series of expert meetings and consultations with the Clinical Consortium on Healthy Aging (CCHA)WHO. As a result, the Integrated Care for Older People (ICOPE) program was launched in 2019 by WHO. The ICOPE program was built on the principles of the CGA. Yet, its goal is to risk-stratify older people in the primary care setting with a comprehensive but succinct assessment.

1.5 World Health Organization's Integrated Care for Older People Program

In response to the need for switching from a disease-based health system to a person- and function-centred health system, the World Health Organization (WHO) has launched the Integrated Care for Older People Program (ICOPE). (34) Health systems worldwide are organized around the episodic care-providing for diseases. Such a model was reasonable when infectious diseases were the most common cause of consultation, but they are not anymore. The disease-centred model risks

being unsustainable vis a vis the complex health needs of the elderly. For instance, the presentation of diseases in older people is quite heterogeneous. (13)

For all these reasons, stakeholders like the World Health Organization have recognized the need to adapt the health systems to the special needs of older adults.(8,13)

The WHO proposed the Integrated Care for Older People (ICOPE) strategy based on a series of international expert consultations. One of the main aims of the ICOPE is to preserve functional ability and delay care dependency(8). According to the ICOPE framework, healthy aging is achieved when people use their functional ability to be and do what has meaning for them. (8) Functional ability is compounded by intrinsic capacity, the environment and the interaction among them. (13)

One major novelty in the ICOPE program is that it provides the first toolkit following a group of experts under a common conceptual framework for healthy aging. For instance, the ICOPE handbook (34) and the ICOPE scorecards (10) are concrete materials at the service-providing and system-management level, respectively, that allow health professionals to take a step forward in adapting health systems for aging.

1.6 ICOPE Step 1 screening for intrinsic capacity impairments: lack of validation as a risk-stratification tool

The ICOPE assessment is advantageous to balance a comprehensive scope with the feasibility of implementing it in primary care. It is not meant to replace the comprehensive geriatric assessment. The ICOPE care pathways are organized in five steps to preserve intrinsic capacity. Step1 - screen for declines in intrinsic capacity, Step2 - provide a person-centred assessment in primary care,

Step3 - define the care goal and develop a personalized care plan, Step4 - ensure a referral pathway (including geriatrics) and monitoring of the care plan and Step5 - engage the community and support the caregivers. (34)

The present thesis is based on ICOPE Step 1, which is not targeted at an in-depth IC domain measurement. Studies using an in-depth measurement of IC domains (like the ones suggested in the ICOPE handbook during the Step 2 assessment) have been published under a predominantly academic perspective. For example, Beard et al. used a structural equation to model an intrinsic capacity index. (21) Other recent international reports have followed this “Step-2” approach. (35–38)

The ICOPE Step 1, because of its screening nature, was designed as a practical way of identifying high-risk individuals privileging feasibility at the primary care settings. This screening tool was defined by the Clinical Consortium for Healthy Aging of the WHO (CCHA) (39)with one or two items per IC domain (detailed operationalization in Table 1.2).

Table 1.2 Operationalization of the ICOPE Step 1 screening tool according to the ICOPE handbook

Item	Condition
Cognitive impairment*	
Orientation in time and space: What is the full date today? Where are you now (home, clinic, etc.)?	Wrong to either question or does not know
Remember three words. Recalls the three words?	Cannot recall all the three words
Limited mobility	
Chair rise test: rise from a chair five times without using arms. Did the person complete five chair rises within 14 seconds?	No
Malnutrition	
Weight loss: have you unintentionally lost more than 3 kg over the last three months?	Yes
Appetite loss: have you experienced a loss of appetite?	Yes
Visual impairment	
Do you have any problems with your eyes: difficulties in seeing far, reading, eye diseases or currently under medical treatment (e.g. diabetes, high blood pressure)?	Yes
Hearing loss	
Hears whispers (whisper test) or screening audiometry result is 35dB or less or passes the automated app-based digits-in-noise test	Fail
Depressive symptoms	
Over the past two weeks, have you been bothered by a) feeling down, depressed or hopeless?	Yes
b) little interest or pleasure in doing things?	Yes

*The ICOPE handbook uses “decline” as synonym of impairment. We prefer not to use decline interchangeably with impairment. We reserve the use of “decline” to refer to a loss of function over time.

The WHO has released the ICOPE strategy, and member states might be interested in implementing the ICOPE clinical pathways.

The ICOPE framework has face validity because experts have agreed on it. Nevertheless, the validation process of a tool requires several studies with various approaches in different populations. (40)

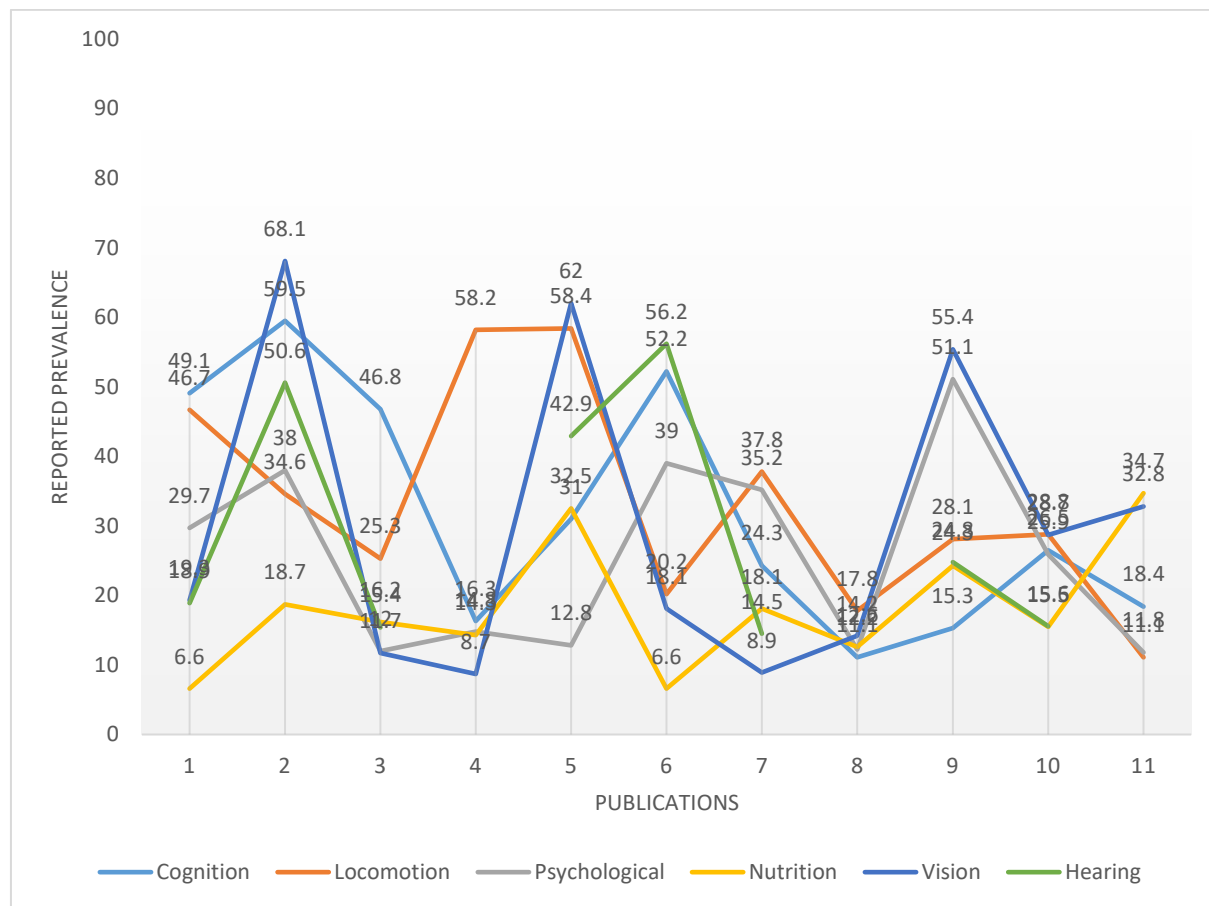
Yet, evidence is lacking to support the ICOPE Step 1 as a tool able to identify older adults at higher risk of adverse health outcomes. Publications regarding its validity and clinimetric properties did not exist by the time we started working on this thesis in October 2019.

1.7 What has the ICOPE Step 1 tool revealed from international older adult populations?

Publications coming from China,(41) France,(12) Hong Kong,(42) and Taiwan(43) have exemplified the application of the ICOPE approach to assessing intrinsic capacity in older adults. For example, Tavassoli and cols. have reported the implementation of the ICOPE step 1 in the French health system using a mobile app.(44).

An updated literature review of the studies reporting the prevalence of intrinsic capacity domain impairments is summarized in Figure 1.7, along with relevant features of the studies in Table 1.3.

Fig. 1.7. Intrinsic capacity domain prevalence on published studies.



Sources:

1. Liu, S. *et al.* Intrinsic Capacity predicts adverse outcomes using Integrated Care for Older People screening tool in a senior community in Beijing. *Arch. Gerontol. Geriatr.* **94**, 104358 (2021).
2. Tavassoli, N. *et al.* Implementation of the WHO integrated care for older people (ICOPE) programme in clinical practice: a prospective study. *Lancet Heal. Longev.* **3**, e394–e404 (2022).
3. Ma, L. *et al.* Integrated Care for Older People Screening Tool for Measuring Intrinsic Capacity: Preliminary Findings From ICOPE Pilot in China. *Front. Med.* **7**, 576079 (2020).
4. Liu, S. *et al.* Trajectory and Correlation of Intrinsic Capacity and Frailty in a Beijing Elderly Community. *Front. Med.* **8**, 2456 (2021).
5. Zeng, X. *et al.* The Impact of Intrinsic Capacity on Adverse Outcomes in Older Hospitalized Patients: A One-Year Follow-Up Study. *Gerontology* **67**, 267–275 (2021).
6. González-Bautista, E. *et al.* Frequency of Conditions Associated with Declines in Intrinsic Capacity According to a Screening Tool in the Context of Integrated Care for Older People. *J. Frailty Aging* **2020** 1–9 (2020) doi:10.14283/JFA.2020.42.
7. Leung, A. Y. M., Su, J. J., Lee, E. S. H., Fung, J. T. S. & Molassiotis, A. Intrinsic capacity of older people in the community using WHO Integrated Care for Older People (ICOPE) framework: a cross-sectional study. *BMC Geriatr.* **22**, 304 (2022).
8. Ma, L. *et al.* Cross-sectional study examining the status of intrinsic capacity decline in community-dwelling older adults in China: prevalence, associated factors and implications for clinical care. *BMJ Open* **11**, e043062 (2021).
9. Ramírez-Vélez, R., Correa-Bautista, J. E., García-Hermoso, A., Cano, C. A. & Izquierdo, M. Reference values for handgrip strength and their association with intrinsic capacity domains among older adults. *J. Cachexia. Sarcopenia Muscle* **10**, 278–286 (2019).
10. Prince, M. J. *et al.* Intrinsic capacity and its associations with incident dependence and mortality in 10/66 Dementia Research Group studies in Latin America, India, and China: A population-based cohort study. *PLoS Med.* **18**, (2021).
11. Zhao, J. *et al.* Intrinsic Capacity vs. Multimorbidity: A Function-Centered Construct Predicts Disability Better Than a Disease-Based Approach in a Community-Dwelling Older Population Cohort. *Front. Med.* **8**, 1656 (2021).

Table 1.3 Features of the studies that have reported the prevalence of intrinsic capacity domain impairments.

No.	Country(ies)	n	age group	Population setting	Type of IC measurement	Community-dwelling
1	China(45)	212	75+	Care retirement community	Step 1	no
2	France(12)	10903	60+	Health system users	Step 1	no
3	China(41)	376	50-97	Hospital admission (Geriatric unit)	Step 1	no
4	China(46)	230	75+	Care retirement community	Step 2	no
5	China(47)	532	60+	Hospitalized	Step 2	no
6	France(48)	759	70+	RCT volunteers	Step 1	yes
7	Hong Kong(42)	304	60+	Population-based	Step 1	yes
8	China(49)	5823	60-98	Population-based	Step 2	yes
9	Colombia(50)	5237	60+	Population-based	Step 2	yes
10	Peru, Mexico, China, India, Cuba, Dominican Republic, Puerto Rico, and Venezuela(51)	17031	65+	Population-based	Step 2	yes
11	China(52)	7298	65+	Population-based	Step 2	yes

The following synthetic exercise is aimed at exploring what has been reported. We consider that the heterogeneity of the currently reported studies does not lend itself to a fair comparison and a meta-analysis. Yet, we include the summary of findings in the search for patterns.

The left-hand side of the figure shows the studies with hospitalized, institutionalized, or care-seeking populations. The prevalence tends to be higher in these groups, and overall, the prevalence tends to be lower in studies representing the community-dwelling population (right-hand half of the figure). An exception to the latter is the SABE Colombia study (number 9), with a high prevalence of vision and psychological impairments.

The prevalence of nutrition impairment is consistently lower than 1/5, with a few exceptions. Also, the high prevalence of cognitive and locomotion impairments might characterise populations with higher general health deterioration.

Several other studies have been published on intrinsic capacity but have not been included here because they do not report domain-specific prevalence. López-Ortíz and cols. published a systematic review on intrinsic capacity assessment in older adults on August 2022.(53)

1.8 The ability to perform the basic activities of daily living are a relevant outcome for older adults

The functional ability for the basic activities of daily living is a crucial outcome in the health of older adults. In the ICOPE perspective, the aim is preserving the older adult's functionality to allow them to be and do what is meaningful for them. Such definition of functionality can be very heterogeneous and varies from one person to another. From a clinically based individual perspective, the ICOPE assessment should start by asking the older adults what is meaningful for him/her to be and do. However, in Epidemiology, with a population-level perspective, the basic activities of the daily living are a good reference of the core activities indispensable for the daily self-maintenance, namely, having a bath, dressing, continence, using the toilet, going from the bed to the couch/chair, and feeding by themselves.

The basic activities of daily living (ADLs), assessed with the Katz scale, can be understood as “a true measure of primary biological and psychosocial function”. (54) In the paper: “Studies of Illness in the Aged”, Katz and colleagues present the temporal patterns of functional losses in 1,001 patients (of whom 541 with repeated follow-up measures). Furthermore, they argue that the construct validity of the Katz index relies on the parallelism between the order in which older adults lose and the children win function for activities. Katz and cols. described the following pattern of

progressive function loss. First, they are independent, then they accumulate dependency for bathing → dressing → toileting → transferring → continence → feeding. The authors argue that this is inverse to the order in which children win function. They mention that all the activities require organized locomotor and neurologic functioning. Yet, they distinguish between the “simple vegetative functions” (feeding, continence and transferring), and “activities influenced by cultural forces and learning” (toileting, dressing, bathing).

Interestingly, they mention anthropologic studies that support their observations, because normal children achieve functionality for the “vegetative” activities regardless of their cultural habits. Whereas dressing and bathing are strongly shaped by the cultural normality (e.g. dressing is not a habit in some peoples). (54) The authors conclude that the index reflects the adequacy of the organized neurological and locomotor response of the organism; and that it can be used for monitoring functionality over time.

Dissertations on how to assess functionality were active in the late 70’s and early 80’s. By 1983, there was scientific understanding that functionality could be assessed using three categories of functional types: a) ADLs, b) IADLs and c) mobility in older people.(55) In a conference at the National institutes of Health of the U.S.A., scientists agreed that these functionality measures were clinically useful at the individual level, but also at the health system level for program evaluation and planning. (55)

Finally, the ADLs scale is correlated with the degree of assistance needed by the older adult. (54) At the health system level, the amount of assistive care needed by older adults is relevant for planning and management issues. Specially in public health systems, the demand of long-term care may raise financial concerns. (56)

1.9 The role of the intrinsic capacity locomotion domain in functional ability and the disabling cascade

Locomotion is the ability to move within one's environment and includes activities like walking, turning and stair climbing.(17) Locomotion is related directly to the basic ADLs thru transferring. However, locomotion is indirectly linked to all the other activities of the daily living because they all take place in different locations within the lodgement.

According to Nagi's model, the disabling cascade starts with "active pathology" as a disruption from normal processes and organismal efforts to regain normality. In the context of this study, aging -pathological aging- represents this disruption. The cascade then progresses from impairments to functional limitations and finally to disability (19,57,58). Impairments are defined as physical or mental abnormalities or losses. Functional limitations are the organismal level limitations in performance (whole individual). Under Nagi's framework, disability is the limitation in performance of social tasks implying the interaction with the environment.

From the Public Health and preventive perspective, the challenge is to look for a population-wide-feasible strategy to detect older adults early in the disabling cascade, e.g., in the context of our study, screening for intrinsic capacity domain impairments.

The role of locomotion in the disabling cascade was depicted in a study by Jung and cols. who used path analysis to describe the relationship between locomotion impairment (muscle strength and knee and hip ranges of motion), limitations (measured by the hurdle walking and side-step tests), and disability (self-reported ADL mobility) in community-dwelling older adults. They found that

locomotion impairments impact disability thru functional limitations with pathway coefficients

going $impairment \xrightarrow{0.45} limitation \xrightarrow{0.73} disability$ ($p < 0.05$). (59)

1.10 The determinants of the five-repetition chair stand test to assess locomotion

Chronological age.

The five-repetition chair stand test has been used as a proxy measure of lower limb strength (60). The protocol for the five-repetition chair-stand test starts by verifying if the older adults feel safe and can go from the sitting to the standing position with his/arms crossed on the chest without help from another person. If this is confirmed, the tests begins when at the signal of the evaluator who starts the chronometer. The older person goes from the sitting to the standing position five times, and the chronometers stops when he/she reaches the fifth stand. The result of the test is recorded in seconds (s).

A meta-analysis by Bohannon reported age-stratified mean values for the five-repetition chair stand times (11.4 sec for 60-69 years; 12.6 sec for 70 to 79 years; 14.8 sec for 80 to 89 years)(61). The time tends to increase with age.

Also, in one of the first studies conducted on the Step 1 tool in the MAPT population, we found that almost half of the people older than 80 was classified as limited mobility when using the cut point of 14 seconds. This observation suggested that the 14 seconds cut point might have low discrimination ability in adults older than 80 to classify those at high risk of incident disability.(48)

Power, strength, velocity, balance and coordination.

There is a non-linear relationship between strength and functional performance for the lower limbs. Ferrucci and cols. reported that the association between knee extension and hip flexion strength was significant for women with strength lower than 10 and 15 kg respectively, but became insignificant for values higher than those, after controlling for age, weight and the difference knee-to-chair height. (62) Their findings suggest that increases in strength would not represent a gain in functional performance for women in the WHAS (measured by the five-repetition chair stand test).

An equation has been derived from the five-repetition chair stand test to obtain the lower limb power. (63) Leg muscle power is the ability to exert force with the lower limbs quickly (Power= Force x Velocity)(64). The ability to generate force quickly with the legs is fundamental for ambulation, and it is recommended that exercise interventions are targeted to increase power rather than force or lean mass. (65)

Velocity is another determinant of power. Velocity is related to physio-anatomic features such as the muscle composition of type 2 fibres(64), muscle stiffness (66) and extra-muscular features such as joint flexibility and stability.

Bean and cols. found that power was more closely correlated to functionality than strength cross-sectionally in mildly impaired older adults. (64) They measured muscle strength and power with pneumatic resistance machines and used gait speed and chair rise time (10 repetitions) as measures of functional performance (n=45). The models which included muscle power explained a higher fraction of the outcome variability than those with strength (adjusted for age, BMI and chronic conditions). E.g., the model that included “power” had an $R^2_{\text{chair}}=0.24$ for the chair stand time vs $R^2_{\text{chair}}=0.20$ for the model with strength. Interestingly, the models for gait speed had R^2 thrice higher than those for chair rise, suggesting that there are several other factors affecting the chair

stand time than power or strength (e.g. balance and coordination (67)) ($R^2_{\text{gait}}=0.61$ for power and $R^2_{\text{gait}}= 0.57$ for strength).

1.11 Rationale and research questions

By the time this thesis was started, there was a lack of validation of the ICOPE Step 1 screening tool. There is currently a growing interest on the topic and several articles have been published recently. Validation of the ICOPE Step 1 screening tool is still an unfinished process as there are unsolved questions regarding its ability to identify older adults at higher risk of incident disability, how to improve its clinimetric properties for the cross-sectional and longitudinal monitoring of intrinsic capacity.

1. Is the ICOPE Step 1 screening tool an appropriate instrument to identify older adults at higher risk of incident disability?
2. Is it suitable to use the 14 seconds cut point for the five-repetition chair stand test that has been suggested by the WHO ICOPE handbook for older people regardless of their age? Or could we improve the clinimetric properties of the locomotion screening by developing an age-stratified cut point?
3. When comparing a baseline and a follow-up assessment of the locomotion domain of IC with the WHO ICOPE Step 1, what is a clinically meaningful change for the five-repetition chair stand time?

Chapter 2. The ICOPE Step 1 screening tool for impairments in intrinsic capacity is able to detect people at higher risk of functional decline

2.1 Rationale for this study

The ICOPE program and the IC framework are supposed to identify people at-risk for care dependency.

By the time we started this thesis, there were no reports of a screening tool for IC impairments to detect people at higher risk of events in the disabling cascade (frailty/disability). (14,16,68). It is essential to investigate if the ICOPE screening can detect high-risk population because they are the starting point of the ICOPE clinical pathways. (34,69,70)

The rationale was to contribute to the validation of the ICOPE screening tool towards adverse outcomes relevant for older people (predictive validity).

Therefore, our study aimed to evaluate a screening IC tool's ability to identify people at high risk of developing frailty and disability in basic (ADL) and instrumental (IADL) daily living activities among community-dwelling older adults.

2.2 Methods

This study used longitudinal data of the Multidomain Alzheimer Preventive Trial (MAPT). The detailed methodology of MAPT has been described elsewhere(71,72). In summary, MAPT was a randomized controlled trial (RCT) testing the effect of a multidomain intervention (nutritional counseling, physical exercise, and cognitive stimulation) with and without supplementation of omega-3 polyunsaturated fatty acids (PUFA) versus usual care on the prevention of cognitive

decline among community-dwelling adults aged 70 years and older recruited in memory clinics in France. The Ethical Committee (CPP SOOM II) based in Toulouse approved the study (ClinicalTrials.gov identifier: NCT00672685). All participants signed a consent form before study assessments. After a three-year-long RTC period, MAPT continued as an observational study for an additional 2 years.

2.2.1 Participants

MAPT inclusion criteria were meeting at least one of a) spontaneous memory complaints expressed to their physician, b) limitation in one instrumental activity of daily living (IADL), or c) slow gait speed (≤ 0.8 m/s). Exclusion criteria comprised: a) participants with a Mini-Mental State Examination (MMSE) score < 24 , b) diagnosis of dementia, c) limitation for one or more basic activities of daily living (ADLs), and d) those taking PUFA supplements at baseline.

Of the 1,679 participants enrolled, 759 had complete information for the IC domains since they received a preventive consultation as part of the multidomain intervention. A physician assessed their hearing and vision.

2.2.2 IC domains assessment – Step 1 (screening)

Using a retrospective approach, we operationalized an IC screening tool similar to the ICOPE Step 1, based on the detection of conditions associated with declines in IC domains. We follow the exact definition of the ICOPE Step 1 tool (34) for three domains: cognition (time and space orientation plus word recall), locomotion (perform five chair rises within 14 seconds), and vitality/nutrition (self-reported weight loss or appetite loss). Due to data availability, we had to adapt the operationalization of *vision*: answering "yes" to any of: "Even if wearing glasses, do you have

visual problems to a) distinguish the faces of people in the same room? b) move indoors/outdoors? c) other activities (reading a paper, watching television)?"; *hearing*: answering "sometimes" or "yes" to the question "Do you have difficulty hearing when someone speaks in a whisper?" (HHSE-S(73,74)); *psychological function*: answering "yes" to the item 2 of Geriatric Depression Scale (GDS-15) "Have you dropped many of your activities and interests?", or responding "no" to the item 7 of the GDS-15 "Do you feel happy most of the time?" (75). Three experts (one geriatrician, one general practitioner, and one researcher in clinical gerontology) judged these GDS items as the closest ones to the ICOPE screening (34). The resulting set of items was called "MAPT Step 1" (Table 2.1).

Table 2.1. Comparison of the operationalization of the conditions associated with declines in IC between the ICOPE handbook and the definitions applied in MAPT study.

ICOPE handbook(34)		MAPT study	
Item	Condition	Item	Condition
Cognitive decline			
Orientation in time and space: What is the full date today? Where are you now (home, clinic, etc.)?	Wrong to either question or does not know	The same as ICOPE ^a	
Remember three words. Recalls the three words?	Cannot recall all the three words	The same as ICOPE ^a	
Limited mobility			
Chair rise test: Did the person complete five chair rises within 14 seconds?	No	The same as ICOPE	
Malnutrition			
Weight loss: have you unintentionally lost more than 3 kg over the last three months?	Yes	The same as ICOPE	
Appetite loss: have you experienced a loss of appetite?	Yes	The same as ICOPE	
Visual impairment			
Do you have any problems with your eyes: difficulties in seeing far, reading, eye diseases or currently under medical treatment (e.g. diabetes, high blood pressure)?	Yes	Even wearing glasses, do you have visual problems to a) distinguish the faces of people in the same room? b) move indoors/outdoors? c) other activities (reading a paper, watching television)	Yes to any question
Hearing loss			
Hears whispers (whisper test) or screening audiometry result is 35dB or less or passes the automated app-based digits-in-noise test	Fail	"Do you have difficulty hearing when someone speaks in a whisper?" (item 3 of HHIE-S)	If "sometimes" or "yes" ^b
Depressive symptoms			
Over the past two weeks, have you been bothered by a) feeling down, depressed or hopeless?	Yes	Do you feel happy most of the time? (item 7 of GDS-15)	No
b) little interest or pleasure in doing things?	Yes	Have you dropped many of your activities and interests? (item 2 of the GDS-15)	Yes

^aParticipants were explicitly asked for each of the items in the time and spatial orientation, and not only an open-ended question. The participant was recorded as with cognitive decline if he/she was wrong to tell the date (number and name of the day, month, year), or wrong to tell the name of the hospital, the level of the building, department and region.

^b We used item number 3 of the HHIE-S because of its similarity with the whisper test.

Several states linked to diminished IC were used to tag the attrition in the IC domains. To be consistent with the WHO naming of these states/conditions associated with impairments of IC, we used "cognitive decline," "limited mobility," "malnutrition," "visual impairment," "hearing loss," and "depressive symptoms." These terms do not represent clinical diagnoses and are not based on comparisons over time.

Besides, we calculated a "total score" by adding the number of IC impairments (score range 0-6, higher is worst).

2.2.3 Incident frailty

Participants were assessed for frailty at baseline and 6, 12, 24, 36, 48, and 60 months of follow-up. We used the phenotype criteria of frailty proposed by L. Fried and cols.(76): reported unintentional weight loss, slowness, low physical activity, weakness, and exhaustion. Participants who met ≥ 3 criteria were classified as frail, with one or two criteria, pre-frail, and otherwise, robust. We excluded participants frail at baseline.

2.2.4 Incident disability

Disability for IADL was assessed according to Lawton(77) (baseline, 36, 48, and 60 months from follow-up). IADLs included were: use the phone, do the grocery, cooking, housekeeping, laundry, use of means of transportation, handle own medication and manage finances. Incident disability for IADLs was defined if the participant had an increase in the number of IADLs during follow-up, compared to the baseline status. We defined incident IADL disability whenever participants developed disability for a new IADL, regardless the baseline number of IADLs affected. ADL disability was assessed according to Katz(78) at baseline and 48 and 60 months of follow-up. ADLs

included were: showering, getting dressed, using the toilet, displacing inside a room, continence, and self-feeding. Incident ADL disability was registered if the participant reported needing help or being care dependant for at least one of the ADLs.

2.2.5 Definition of the clinimetric properties

Sensitivity is the proportion of true positives that are correctly identified by the test.(79)

Specificity is the proportion of true negatives that are correctly identified by the test.(79)

Positive predictive value is the proportion of patients with positive test results who are correctly diagnosed.(80)

Negative predictive value is the proportion of patients with negative test results who are correctly diagnosed.(80)

The likelihood ratio summarises how many times more (or less) likely patients with the disease are to have that particular result than patients without the disease. In our case it is the ratio of the probability of the specific test result (e.g., IC score ≥ 2) in people who had incident outcome to the probability in people who did not. (81)

Area under the ROC curve is the probability that predicted risks correctly identify a random pair of a diseased and a non-diseased individual. (82)

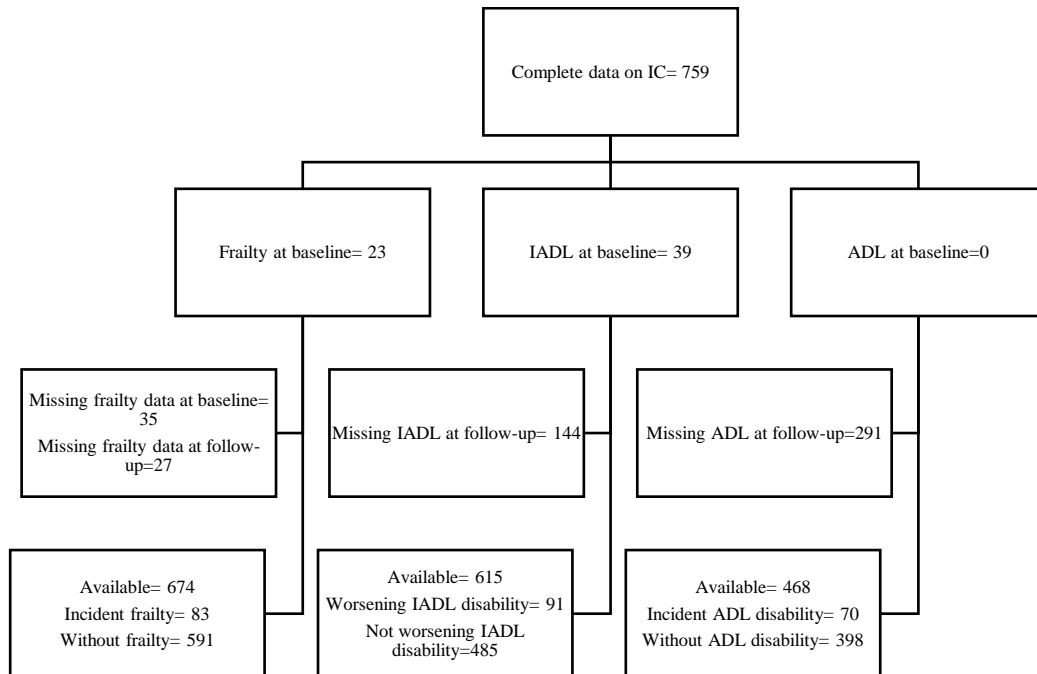
2.2.6 Statistical Analysis

Besides descriptive statistics, we used Cox's proportional hazards models for non-recurrent events to estimate the hazard ratios for frailty, IADL, and ADL disability incidence. For each outcome,

we ran one separate model testing each condition of interest. (Model 1), another mutually adjusted model including the six conditions simultaneously to detect which were the strongest predictors (Model 2), and one model with the "total score" to see if the risk increased with each additional condition (Model 3). We adjusted the frailty models for pre-frail/robust baseline status and the IADL models for baseline IADL to account for different baseline risks. All models were adjusted for age, sex, level of education, MAPT group (multidomain intervention, multidomain intervention + omega 3 supplementation), and multimorbidity (defined as self-reporting 2 or more of COPD/asthma, stroke, active cancer, ischemic heart disease, diabetes, hypertension or heart failure). The proportionality assumption was confirmed by plotting the cumulative risk function against the analysis time and verifying that the predictor-time interactions were not statistically significant at $\alpha=0.05$, and by the Schoenfeld residuals (Table 2.4). Adjusted Kaplan-Meier curves were obtained considering standardized baseline covariates: age, sex, education and MAPT group. The difference among the KM curves was tested using the log rank test (Table 2.4). We estimated the predictive ability of models 2 and 3 using Harrell's C ($C > 0.5$ and close to 1.0 indicate higher discrimination(83)). We compared the characteristics of the participants lost to follow-up, looking for any differences that could impact our modelling of the outcomes (t-test or χ^2 as appropriate). Receiver operator characteristic (ROC) analyses were performed *vis à vis* the three outcomes of interest. Data were analysed using STATA 14®.

2.3 Results

The baseline characteristics and sampling algorithm are described in Table 2.2 and Figure 2.1, respectively. **Figure 2.1. Flow diagram of the study sample**



IADL= instrumental activities of the daily living

ADL= basic activities of the daily living

Briefly, the baseline frailty status of participants with complete data on frailty and IC domains was: robust 56.5% (n=409), pre-frail 40.3% (n= 292) and frail 3.2% (n=23). The cumulative incidence of frailty, IADL and ADL disability was 11.8%, 14.8%, and 15% respectively over five years.

On average, participants lost to follow-up had a slightly higher number of deficits in IC domains (difference= -0.27, p=0.0015), but were not older (diff age = -0.53, p=0.057) than nor had a worst physical performance (chair-rise time difference = 0.20 s, p= 0.7156) than the ones retained. The adjusted Kaplan- Meier curves confirmed the lack of impact of informative censoring on our results (84) (Figures 2-4). We decided not to perform a competing risk approach because we observed a mean follow-up period of 4.8 years and low cumulative mortality (n=14, 1.8% of the study sample).

In model 1, we found an association of limited mobility, depressive symptoms, and visual impairment with an increased risk of frailty. Model 2 showed that limited mobility imposed a three-

fold risk, depressive symptoms a two-fold risk, and visual impairment a 70% higher risk of incident frailty over five years, after adjusting for covariates and the other five conditions. Each additional condition associated with IC declines increased the risk of becoming frail by 47% (model 3).

Table 2.2. Description of the population according to incident frailty, IADL and ADL disability in MAPT participants over 5 years.

n(%) or mean (SD)	Total		Incident frailty				Incident IADL disability				Incident ADL disability			
	n=759		No=591		Yes=83		No=524 ^a		Yes=91		No=398		Yes=70	
Age	75.2	(4.3)	74.8	(4.1)	78	(4.6)*	74.7	(4.0)	77.2	(4.9)*	74.3	(4.0)	76.2	(4.2)*
Sex (female)	483	(63.6)	372	(87.5)	53	(12.5)	342	(87.2)	50	(12.8)	251	(81.5)	57	(18.5)*
Education														
Less than primary	31	(4.1)	20	(3.4)	8	(9.6)*	23	(4.4)	2	(2.2)	14	(3.6)	4	(5.8)
Primary	122	(16.2)	85	(14.5)	17	(20.5)	72	(13.9)	22	(24.4)	52	(13.2)	8	(11.6)
Secondary	271	(36.1)	219	(37.4)	21	(25.3)	194	(37.4)	30	(33.3)	141	(35.9)	27	(39.1)
High-school	111	(14.8)	88	(15.0)	12	(14.5)	69	(13.3)	15	(16.7)	54	(13.7)	12	(17.4)
Graduate or higher	216	(28.8)	174	(29.7)	25	(30.1)	161	(31.0)	21	(23.3)	132	(33.6)	18	(26.1)
Multimorbidity (yes)	128	(16.9)	90	(15.2)	20	(24.1)*	75	(14.3)	29	(31.9)*	57	(14.3)	14	(20.0)
Frailty														
Robust	409	(56.5)	373	(94.9)	20	(5.1)*	312	(92.0)	27	(8.0)*	242	(89.6)	28	(10.4)*
Pre-frail	292	(40.3)	218	(77.6)	63	(22.4)	178	(76.7)	54	(23.3)	129	(78.2)	36	(21.8)
Frail	23	(3.2)	^b	^b	^b	^b	9	(52.9)	8	(47.1)	9	(69.2)	4	(30.8)
Intrinsic capacity impairments														
Cognitive decline	396	(52.2)	301	(86.0)	49	(14.0)	257	(82.1)	56	(17.9)*	201	(87.0)	30	(13.0)
Limited mobility	146	(20.2)	84	(71.2)	34	(28.8)*	82	(75.9)	26	(24.1)*	59	(74.7)	20	(25.3)*
Malnutrition	50	(6.6)	35	(85.4)	6	(14.6)	32	(82.1)	7	(17.9)	23	(79.3)	6	(20.7)
Visual impairment	137	(18.1)	90	(77.6)	26	(22.4)*	79	(79.0)	21	(21.0)	57	(79.2)	15	(20.8)
Hearing loss	426	(56.2)	332	(87.4)	48	(12.6)	282	(82.5)	60	(17.5)*	218	(84.5)	40	(15.5)
Depressive symptoms	296	(39.0)	216	(83.1)	44	(16.9)*	183	(81.0)	43	(19.0)*	129	(81.1)	30	(18.9)
Total score														
0	81	(10.7)	69	(93.2)	5	(6.8)*	67	(93.1)	5	(6.9)*	50	(86.2)	8	(13.8)*
1	210	(27.7)	179	(93.2)	13	(6.8)	168	(92.8)	13	(7.2)	124	(85.5)	21	(14.5)
2	248	(32.7)	199	(90.0)	22	(10.0)	167	(83.9)	32	(16.1)	136	(91.3)	13	(8.7)
3	149	(19.6)	103	(81.1)	24	(18.9)	80	(72.7)	30	(27.3)	63	(76.8)	19	(23.2)
4	58	(7.6)	34	(66.7)	17	(33.3)	37	(80.4)	9	(19.6)	23	(74.2)	8	(25.8)
5	12	(1.6)	6	(75.0)	2	(25.0)	5	(71.4)	2	(28.6)	2	(66.7)	1	(33.3)
6	1	(0.1)	1	(100.0)	0	(0.0)	524	(85.2)	91	(14.8)	398	(85.0)	70	(15.0)

Abbreviations: MAPT= Multidomain Alzheimer Preventive Trial; MI=multidomain intervention; IADLs= instrumental activities of daily living; ADL= basic activities of daily living

^a We included the participants with any number of IADL at baseline for consistency with the population in the models

^b Excluded because they already had the event of interest at baseline

* Bivariate t-test for continuous or χ^2 for categorical variables, p-value <0.05

Table 2.3. Adjusted hazard ratios for the Cox's models linking intrinsic capacity declines and incident frailty and Disability during a five years follow-up among MAPT participants.

	Hazard ratio	CI 95%	p value	Hazard ratio	CI 95%	p value
Frailty (n=674)		Model 1 ^a			Model 2 ^a	
Depressive symptoms	1.88	1.20 - 2.92	0.005	2.07	(1.03 - 4.19)	0.042
Cognitive decline	1.12	0.71 - 1.76	0.620	1.38	(0.70 - 2.74)	0.345
Limited mobility	2.80	1.76 - 4.44	<0.001	2.97	(1.85 - 4.74)	0.000
Malnutrition	1.45	0.63 - 3.35	0.365	0.97	(0.41 - 2.32)	0.954
Visual impairment	1.95	1.20 - 3.17	0.007	1.70	(1.01 - 2.86)	0.044
Hearing loss	0.92	0.58 - 1.43	0.701	0.81	(0.52 - 1.31)	0.430
		Model 3				
Total IC score	1.47	(1.22 - 1.78)	0.000			
IADL disability (n=615)		Model 1			Model 2 ^b	
Depressive symptoms	1.47	(0.96 - 2.23)	0.071	1.47	(0.94 - 2.27)	0.089
Cognitive decline	1.19	(0.76 - 1.85)	0.431	1.25	(0.78 - 2.00)	0.347
Limited mobility	1.39	(0.85 - 2.30)	0.193	1.42	(0.86 - 2.35)	0.169
Malnutrition	1.05	(0.49 - 2.29)	0.888	0.75	(0.30 - 1.86)	0.533
Visual impairment	1.45	(0.88 - 2.38)	0.140	1.25	(0.73 - 2.12)	0.408
Hearing loss	1.30	(0.83 - 2.02)	0.250	1.25	(0.78 - 1.98)	0.356
		Model 3				
Total IC score	1.27	(1.06 - 1.53)	0.010			
ADL disability (n=468)		Model 1			Model 2	
Depressive symptoms	1.60	(0.98 - 2.53)	0.055	1.60	(0.98 - 2.64)	0.060
Cognitive decline	0.73	(0.45 - 1.18)	0.199	0.72	(0.44 - 1.18)	0.202
Limited mobility	1.92	(1.12 - 3.30)	0.021	1.82	(1.06 - 3.15)	0.029
Malnutrition	1.36	(0.59 - 3.17)	0.464	1.22	(0.52 - 2.91)	0.643
Visual impairment	1.49	(0.84 - 2.64)	0.177	1.40	(0.78 - 2.52)	0.301
Hearing loss	1.14	(0.70 - 1.84)	0.597	1.14	(0.70 - 1.87)	0.595
		Model 3				
Total IC score	1.23	(1.00 - 1.52)	0.051			

All models were adjusted for age, sex, education, MAPT group and multimorbidity. Model 1 shows the HR for the intrinsic capacity declines assessed separately. Model 2 shows HR for intrinsic capacity declines mutually-adjusted. Model 3 shows the HR according to the IC sum score.

Abbreviations: CI= confidence interval; MAPT= Multidomain Alzheimer Preventive Trial; MI=multidomain intervention; IADLs= instrumental activities of daily living; ADL= basic activities of daily living.

^aAdjusted for baseline frailty status.

^bAdjusted for baseline IADL disability.

Figure 2.2. Kaplan-Meier curve for incident frailty

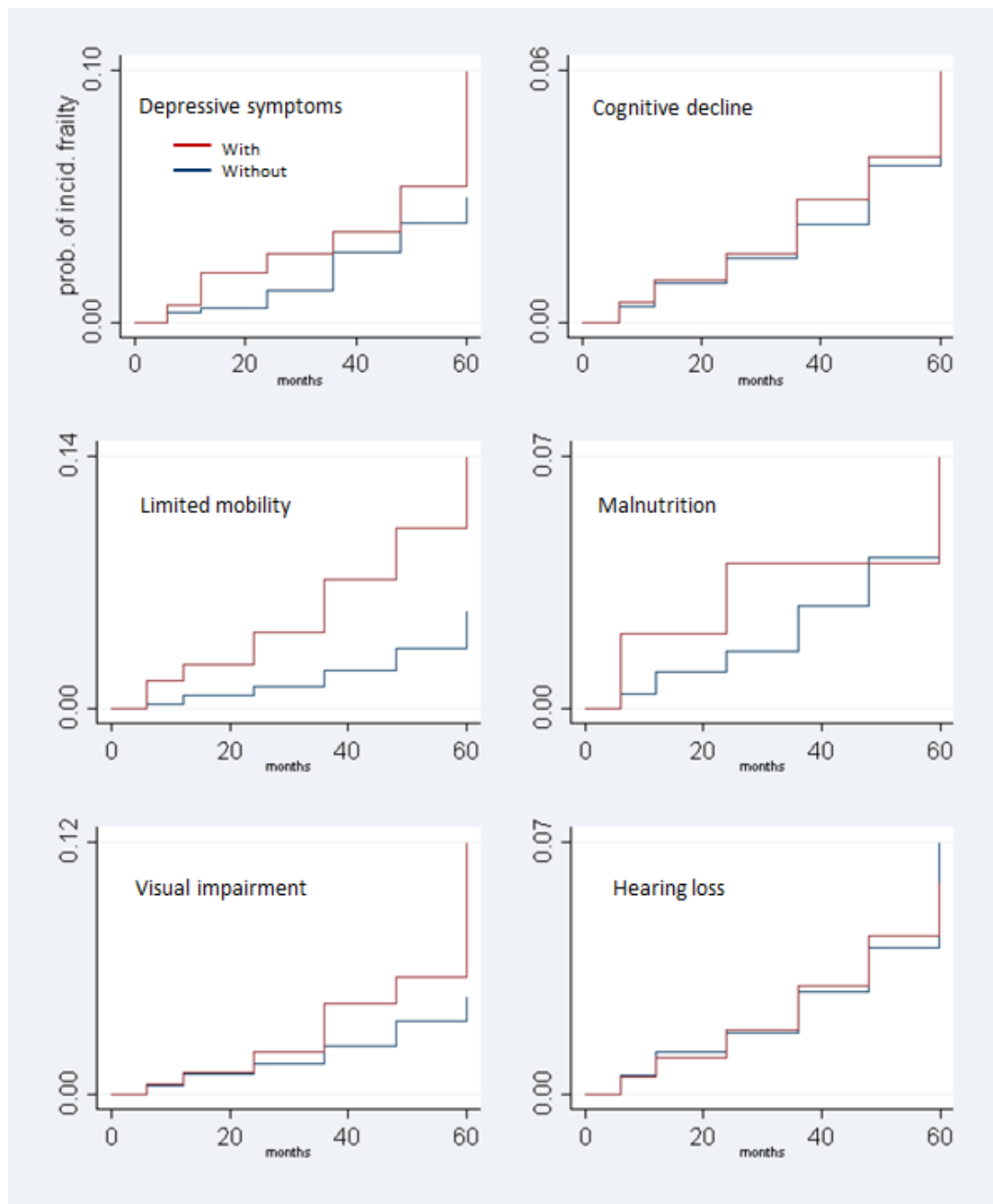


Figure 2.3. Kaplan-Meier curve for incident disability for IADLs

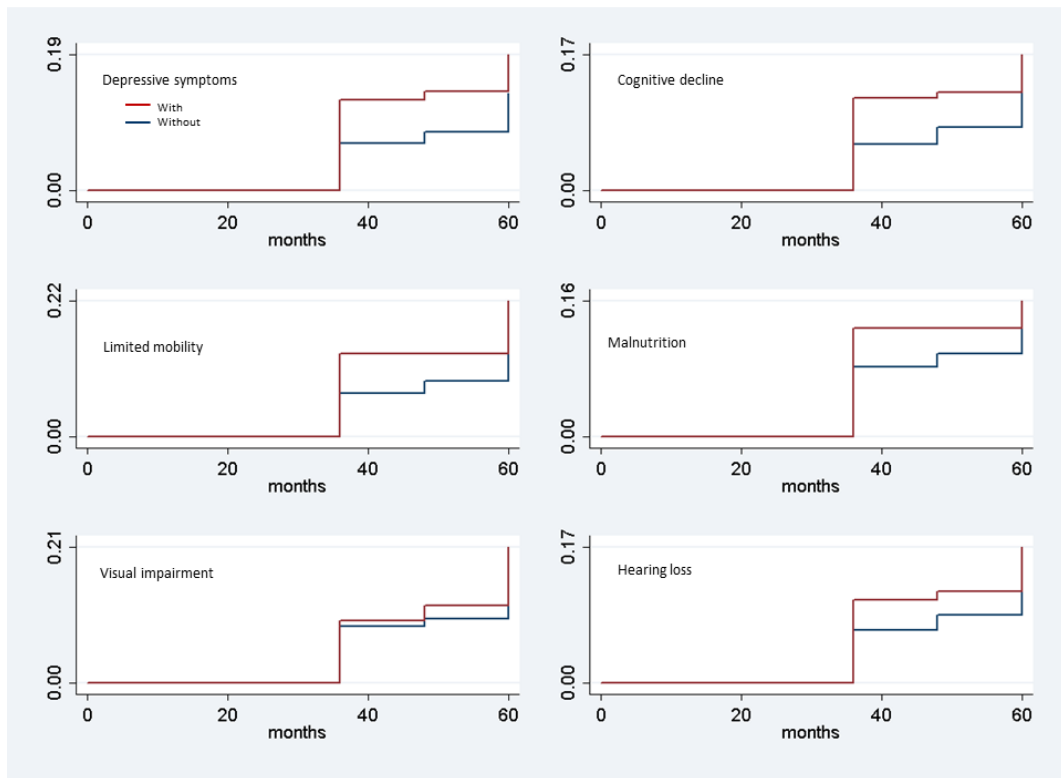


Figure 2.4. Kaplan-Meier curve for incident disability for ADLs

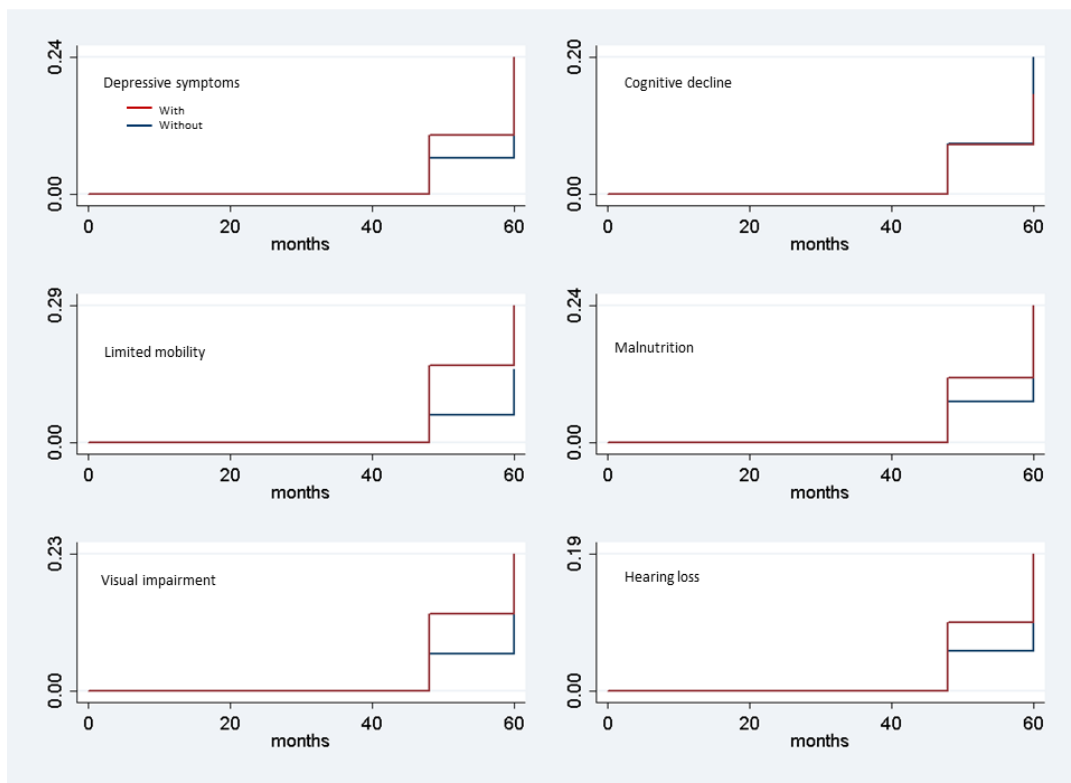
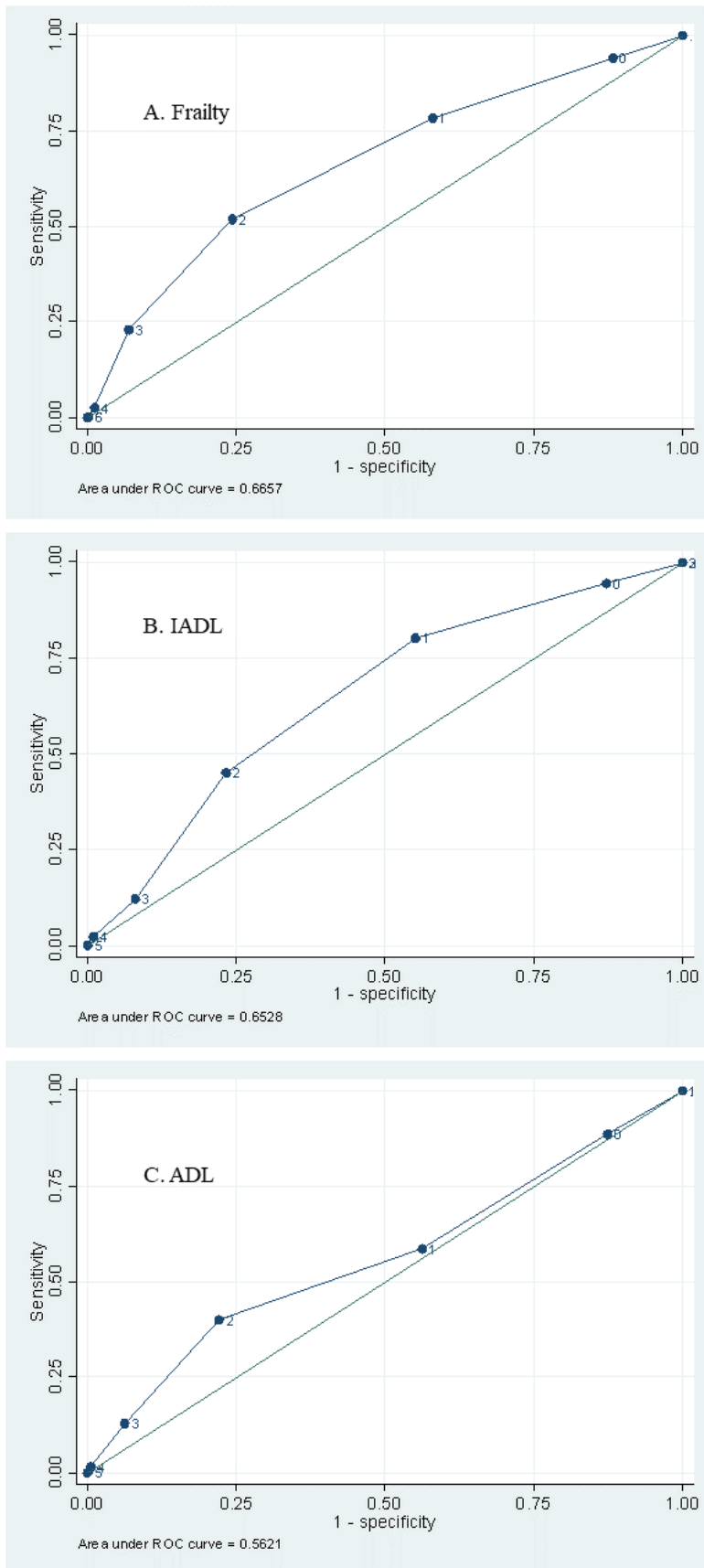


Figure 2.5. ROC curves for the intrinsic capacity impairment score of the MAPT step 1



Each additional condition increased the risk of incident IADL disability in the next five years by 27% (model 3). Depressive symptoms marginally (p=0.055) increased the risk of incident ADL disability (model 1). Limited mobility was associated with 92% and 82% increase in the risk of incident disability in models 1 and 2, respectively. Each additional IC condition increased the risk of disability for ADLs by 23% (Table 2.3).

All models showed a good predictive ability based on the Harrell C statistic (0.70<C<0.83)(83). Cut points for the ICOPE sum score were ≥ 3 for incident frailty and incident ADL disability and ≥ 2 for incident IADL, according to Youden's index(85). (Table 2.4).

Table 2.4. Cut points for the ICOPE Step 1 sum score obtained by the Youden index and their parameters for physical function outcomes

Intrinsic		Incident frailty			Incident IADL			Incident ADL		
		param.	95% CI		param.	95% CI		param.	95% CI	
capacity	Incidence*	12%	10%	15%	15%	12%	17.90%	15%	12%	18.50%
IC score 0-6	AUC	0.67	0.60	0.73	0.65	0.60	0.71	0.56	0.48	0.64
	Harrel's C	0.70	0.62	0.76	0.68	0.61	0.74	0.65	0.55	0.76
IC cutpoint=2	Sensitivity	78.3%	67.9%	86.6%	<u>80.2%</u>	<u>70.6%</u>	<u>87.8%</u>	58.6%	46.2%	70.2%
	Specificity	42.0%	37.9%	46.1%	<u>44.8%</u>	<u>40.5%</u>	<u>49.2%</u>	43.7%	38.8%	48.7%
	PPV	15.9%	12.5%	19.9%	<u>20.2%</u>	<u>16.2%</u>	<u>24.7%</u>	15.5%	11.3%	20.4%
	NPV	93.2%	89.5%	95.9%	<u>92.9%</u>	<u>89.0%</u>	<u>95.7%</u>	85.7%	80.1%	90.2%
	LR	1.35	1.18	1.54	<u>1.45</u>	<u>1.28</u>	<u>1.65</u>	1.04	0.839	1.29
	AUC	0.601	0.553	0.65	<u>0.625</u>	<u>0.579</u>	<u>0.672</u>	0.511	0.448	0.574
	aHR	2.57	1.51	4.36	<u>2.33</u>	<u>1.38</u>	<u>3.96</u>	1.14	0.70	1.84
IC cutpoint=3	Sensitivity	<u>51.8%</u>	<u>40.6%</u>	<u>62.9%</u>	45.1%	34.6%	55.8%	<u>40.0%</u>	<u>28.5%</u>	<u>52.4%</u>
	Specificity	<u>75.6%</u>	<u>72.0%</u>	<u>79.0%</u>	76.7%	72.9%	80.3%	<u>77.9%</u>	<u>73.5%</u>	<u>81.9%</u>
	PPV	<u>23.0%</u>	<u>17.2%</u>	<u>29.7%</u>	25.2%	18.7%	32.5%	<u>24.1%</u>	<u>16.7%</u>	<u>33.0%</u>
	NPV	<u>91.8%</u>	<u>89.0%</u>	<u>94.1%</u>	88.9%	85.7%	91.7%	<u>88.1%</u>	<u>84.2%</u>	<u>91.3%</u>
	LR	<u>2.13</u>	<u>1.65</u>	<u>2.73</u>	1.94	1.47	2.55	<u>1.81</u>	<u>1.29</u>	<u>2.54</u>
	AUC	<u>0.637</u>	<u>0.58</u>	<u>0.694</u>	0.609	0.554	0.663	<u>0.589</u>	<u>0.528</u>	<u>0.651</u>
	aHR	<u>2.96</u>	<u>1.91</u>	<u>4.60</u>	1.60	1.03	2.50	<u>2.02</u>	<u>1.23</u>	<u>3.32</u>
IC cutpoint=4	Sensitivity	22.9%	14.4%	33.4%	12.1%	6.2%	20.6%	12.9%	6.1%	23.0%
	Specificity	93.1%	90.7%	95.0%	92.0%	89.3%	94.2%	93.7%	90.9%	95.9%
	PPV	31.7%	20.3%	45.0%	20.8%	10.8%	34.1%	26.5%	12.9%	44.4%
	NPV	89.6%	86.9%	91.9%	85.8%	82.6%	88.5%	85.9%	82.3%	89.1%
	LR	3.3	2.02	5.4	1.51	0.807	2.82	2.05	0.998	4.2
	AUC	0.58	0.533	0.626	0.956	0.882	1.04	0.533	0.492	0.574
	aHR	3.06	1.81	5.16	1.06	0.55	2.04	2.14	1.05	4.36

Data for the cut points obtained by the Youden index are underlined.

*Cumulative incidence

Param= parameter

aHR= Cox hazard ratio model adjusted for age, sex, education, MAPT group and multimorbidity.

The proportional hazards assumption was met. The Kaplan-Meier curves showed significant differences for the cognition, mobility, visual and psychological domains in the unadjusted models, but only for the mobility domain in the adjusted model. (Table 2.5)

Table 2.5 Schoenfeld’s residual for proportional hazards assumption and Log rank tests for difference in Kaplan-Meier curves

	Incident Frailty			Incident IADL disability			Incident ADL disability		
	Schoenfeld's residuals test	Log rank test for KM curves		Schoenfeld's residuals test	Log rank test for KM curves		Schoenfeld's residuals test	Log rank test for KM curves	
	p	unadjusted p	adjusted p	p	unadjusted p	adjusted p	p	unadjusted p	adjusted p
Cognitive decline	0.487	0.050	0.728	0.812	0.021	0.356	0.829	0.281	0.130
Limited mobility	0.487	0.000	0.018	0.927	0.001	0.261	0.747	0.002	0.294
Malnutrition	0.310	0.452	0.214	0.934	0.513	0.985	0.952	0.334	0.887
Visual impairment	0.158	0.000	0.991	0.888	0.046	0.005	0.834	0.075	0.159
Hearing loss	0.496	0.729	0.878	0.953	0.040	0.282	0.736	0.682	0.904
Depressive symptoms	0.531	0.000	0.083	0.836	0.013	0.122	0.965	0.066	0.118
IC (0-6)	0.595	0.000	0.608	0.900	0.000	0.007	0.429	0.011	0.412

2.4 Interpretation of main findings

A modified version of the ICOPE Step 1 screening tool, the MAPT Step 1 screening tool showed good clinimetric properties to identify people at higher risk of frailty and disability for the activities of the daily living.

The IC score obtained from the screening tool (range 0-6) reported a good predictive ability for the five-year incidence of frailty, and a moderate predictive ability for IADL and ADL disability incidence over the same time frame, according to the Harrel’s C index.

Our findings highlight the added value of screening for intrinsic capacity impairments because with a few items it covers five functional domains. When these domains are put together in the MAPT step 1 screening tool, any additional IC impairment significantly increases the risk of frailty and disability up to 47%.

Based on ROC analyses, we found that with a cut point of ≥ 3 IC impairments for incident frailty and ADLs (≥ 2 for IADLs) maximized the sensitivity and specificity of the tool's score. The tool reached good sensitivity and specificity values. However, the area under the curve was not high, implying that the baseline IC score was not able to discriminate the populations with and without incidence of adverse outcomes in the future. One reason for the latter is that the ROC analyses are not adjusted for the time elapsed between the baseline measurement of the score and the observation of the outcome. (Figure 2.5)

On the other hand, the Harrel's C index considers the time-to-follow-up and the time-to-event inside its estimation of the predictive ability. The lack of ADL data for the first four years of the study might be interfering with the accuracy of its corresponding C index (lower estimate and wider confidence intervals).

However, integrating the findings it seems that the MAPT step 1 screening tool reached the ceiling of its predictive ability for adverse outcomes at 70%.

Those parameters describe the tool's predictive ability. Yet, we have included the PPV and NPV because of their usefulness in clinical practice. The values of the PPV are also useful if we consider the aggregation of IC impairments. For example, a patient with a baseline IC score of ≥ 3 has 23% chances of developing frailty in the following five years. Before implementing the IC score (pre-test probability), the clinician supposed a 12% chance of developing frailty (12% is the cumulative incidence). But after applying the IC screening, if it was positive, the post-test almost doubled. The difference between the pre-test and the post-test probability is what the clinician wins if she/he decides to use the Step 1 screening tool.

Additionally, if we apply a domain-by-domain approach, we can find that impairments in the psychological, vision and mobility domains were associated with a higher risk of frailty. Mobility impairment was associated with a higher risk of ADL disability.

Previous research had described the association between functionality in these domains and frailty. Chaudhry and cols. showed that an increasing number of geriatric impairments (corresponding to some of the IC domains) was associated with a higher risk of ADL and mobility disability (86). Also, locomotion and psychological domains play a role in the multisystem dysregulation underlying frailty and disability (87–89). Mobility impairments can cause or result from low levels of physical activity and sarcopenia, which are hallmarks of frailty(88,90,91).

Recently, Swenor and cols. have reported that older adults with objectively measured vision impairment are more likely to progress to frailty than their counterparts due to its direct and indirect effects on physical functioning(92). On the other hand, exhaustion might explain the overlapping of the psychological domain and the disability cascade. Exhaustion is an indicator of poor endurance within the frailty phenotype (76). In parallel, studies recognize it as a depressive symptom in the psychological domain (76,93).

Cognitive decline, malnutrition, and hearing loss were not significant predictors of frailty or disability in our study. This does not mean these IC domains are not involved in the disabling cascade.

A potential explanation is that the study measurements were not designed to evaluate the domain-by-domain association. We used a screening approach, as similar as possible as the ICOPE Step 1 screening tool, with a few indicators for each domain.

2.5 Strengths and limitations

Our study has strengths. This study was the first exploration of how well an intrinsic capacity screening tool worked to identify people at higher risk of adverse health outcomes. Before this study, there was no data on the clinimetric properties of a modified version of the ICOPE Step 1 screening tool.

The MAPT study was suitable for testing the screening tool because 50% of the IC domains were measured exactly as in the ICOPE guidelines, the measurement of the frailty phenotype and disability was conformed to the standard definitions, and enough follow-up to detect incident disability cases.(72)

Some limitations were that the main independent variable (MAPT screening tool) was collected before our study was designed, and before the formal definition of intrinsic capacity in the ICOPE guidelines. Retrospective analyses carry limitations because the data collection instruments and procedures were tailored to the main MAPT's objectives, and thus all secondary analyses might potentially be affected by misclassification. In our case, we were able to find the same items in MAPT as for the ICOPE Step 1 tool for 3/6 domains (cognition, mobility and nutrition). We found items for the other three domains: the items were extracted from previously validated scales for two of them (depression and hearing). (GDS(94) and HHIE-S (73)). Yet, using an incomplete scale does not guarantee the validation of the items used. For the vision domain, we used the item available in MAPT for self-report of vision problems.

Recall we used only half of MAPT's population because some of the intrinsic capacity items were assessed only in those undergoing a medical consultation before being exposed to the multidomain intervention. All our participants were exposed to it, but not the omega-3 supplementation. In this case the MAPT's intervention effect is not affecting internal validity because all the people included in the study sample underwent the multidomain intervention. One potential problem would be the omega-3 exposure. However, previous literature showed that omega 3 exposure does not affect the risk of frailty or disability. (95)

For example, the accuracy of the Harrel's C index for disability was affected by data collection issues in MAPT. The lack of data collection for IADL incidence in the first three, and ADLs in the first four years of MAPT affects the respective Cox's estimates, and the Harrel's C indices.

Such data collection issues are depicted in the Kaplan-Meier curves without the steady stairway shape seen for frailty (frailty was collected throughout the MAPT study).

Limitations in detriment of the external validity are potentially introduced in our study due to MAPT's "healthy volunteer bias". The MAPT population was relatively fit for their age at baseline. Compared to a random sample used in the French Three-City Study published by Avila-Funes et al. (96), our population was slightly older (mean age 74.1, SD=5.2 vs. 75.2 years, SD=4.3), reported higher levels of educational attainment (>12 years: 17.0% vs. 28.9%) and a lower frequency of frailty (7.0% vs. 3.2%). Therefore, our findings might be underestimating the frequency of IC declines detected by MAPT Step 1 in a real-world population of users of the healthcare system (except for cognitive decline).

The "healthy volunteer bias" affects the study estimated parameters when the population who join the clinical trial tend to have healthier life behaviours and better outcomes than the overall source population. (97) The healthy volunteer effect can be due to specific inclusion/exclusion criteria in the study protocol, specific targeting of healthier individuals in recruitment, self-selection of persons with above average education or income or with a healthier lifestyle, and self-exclusion of persons in poor health who otherwise meet study entry criteria. (98) For example, Froom and cols. found that among a population of workers, those who agreed to volunteer for an epidemiologic screening study had 28 percent points lower standardised mortality ratios after eight years of follow-up compared to those who did not agree to join the study. This effect was also associated to older age and with remaining occupationally active for longer. (99)

This research was published as: González-Bautista, E., de Souto Barreto, P., Andrieu, S., Rolland, Y. & Vellas, B. Screening for intrinsic capacity impairments as markers of increased risk of frailty and disability in the context of integrated care for older people: Secondary analysis of MAPT. *Maturitas* **150**, 1–6 (2021).

Chapter 3. An age-stratified cut point for the five-repetition chair stand test improves the test's clinimetric properties

3.1 Rationale for this study

According to the WHO ICOPE handbook (34), if a person performs five chair-stands in more than 14 seconds, he/she should be further assessed for limited mobility with the complete Short Physical Performance Battery (SPPB) test. (100) Face validity via experts' opinion supports this cut point, but an empirical test is lacking.

The five-repetition chair stand test, as part of the SPPB, uses the cut-offs 11.2, 13.7, and 16.7 seconds for defining chair stand performance categories. (100) One meta-analysis has reported age-stratified mean values for the five-repetition chair stand test, but not confronted to functional outcomes. (11.4 sec for 60-69 years; 12.6 sec for 70 to 79 years; 14.8 sec for 80 to 89 years)(61)

Other studies have set cut points for the 5-repetition chair stand test ranging from 9.7 to 14 seconds (101–106). Nevertheless, those studies' validation is limited by the absence of: representative samples, the use of longitudinal outcomes, and a focus on very old adults. To the best of our knowledge, there are not validated cut points for the five-repetition chair stand test against functional outcomes in older and very old adults.

Based on previous observations about the difference in chair stand time by age group (48,100) and the need for validating a cut-off tailored for very old adults, we performed our analysis separately for participants aged 70-79 and those aged 80 and over.

3.2 Methods

We obtained the age-stratified chair stand cut-offs (70-79 and ≥ 80 years) using the harmonized data from two population-based studies, which also served for cross-validation. Then we used data from a RCT and a frailty clinic for external validation. The procedures applied in each dataset are summarized in Table 3.1.

Table 3.1 Summarized description of the studies used

<i>Study features</i>	SAGE Mex + TSHA		MAPT		Toulouse Frailty Clinic	
Used for	Development and cross-validation		External validation		External validation	
Dates of data collection	SAGE: 2014-2017 TSHA: 2011-2013		2008-2013		2011-2019	
Mean follow-up	SAGE: 3 years TSHA: 3 years		4.5 years		cross-sectional	
Type of population	Community-dwelling older adults*. Sampling stratified by sex, age and rural/urban location; representative at the national level for Mexico and at the local level for Toledo		Community-dwelling volunteers in an RCT in 13 memory clinics in France		Users of the health system in Toulouse	
Methods	ROC analysis (Youden's index) and logistic regression with incident ADL as an outcome for cross-validation		Incident outcomes: Cox regression Functional decline: Mixed-effects linear regression		Logistic regression for association with outcomes	
<i>Key variables</i>	SAGE Mex + TSHA		MAPT		Toulouse Frailty Clinic	
n(%) or mean (SD)	70-79	80+	70-79	80+	70-79	80+
n	1229 (77.1)	366 (22.9)	1295 (82.3)	278 (17.7)	786 (32.3)	1648 (67.7)
Age (y)	73.9 (2.9)	82.9 (3.1)	73.7 (2.8)	82.6 (2.5)	75.9 (2.9)	85.9 (3.8)
Women	650 (52.9)	188 (51.4)	849 (65.6)	170 (61.2)	497 (63.2)	1053 (63.9)
Chair stand time (sec)	13.6 (3.9)	14.9 (4.5)	11.4 (3.4)	12.8 (3.8)	13.6 (4.7)	15.2 (5.2)
Incident ADL^b	198 (16.1)	99 (27.1)	109 (13.5)	29 (25.4)	286 ^a (36.5) ^a	765 ^a (46.7) ^a

^aPrevalence (only cross-sectional data are available for the Toulouse frailty clinic)

^b Except for 1.9% of the total population of TSHA who was institutionalized

3.2.1 Chair stand cut points: development and cross-validation

Population

We harmonized the second and third waves of the WHO Study on global Aging and adult health in Mexico (SAGE Mexico) and the Toledo Study for Healthy Aging (TSHA) cohort. The first wave of these two studies did not assess the chair stand test. Therefore, the baseline data for this work corresponds to the second wave of SAGE Mexico and TSHA.

Briefly, SAGE Mexico is a prospective cohort of adults aged 50 and over conducted with a multi-stage, stratified, and clustered sample designed to be representative at the national level. Data for both waves used in the present work were collected using electronic records (CAPI) by previously trained and standardized staff. All participants provided their informed consent, and the scientific board of the National Institute of Public Health approved the SAGE Mexico study. Further information on study design can be found elsewhere. (107)

The TSHA is a prospective cohort that used a two-stage random sampling, stratified by sex, age, and town size designed to represent adults aged 65 and older living in the Spanish province of Toledo and comprising 24% of the census population of this population group. (108) Trained and certified nurses obtained the physical examination and physical performance data. The Clinical Research Ethics Committee approved the TSHA of the Toledo Hospital.

SAGE Mexico and TSHA measured the variables of interest (such as chair stand and activities of daily living (ADL)) using the same standardized tests and scales. Data from these two studies were merged and harmonized. Adults aged 70 years or over were included in the present study; this choice was made since functional decline occurs more often in ≥ 70 years.

Chair stand measurement

Chair stand test: both studies measured the time in seconds taken by the participant to perform five chair rises at maximum speed with their arms folded across their chest. Standardized staff previously verified that at least 1 stand could be performed safely. Time was measured by previously standardized interviewers using a stopwatch to the nearest 0.1 second, from the starting sitting position to the last standing position at the end of the fifth stand. (100)

Outcome measurement

The incidence of disability for the basic activities of daily living (ADLs, Katz scale) (78) was the endpoint for elaborating the chair stand cut points and their cross-validation. Scores on this scale vary from zero (total disability) to six (no disability). Participants with the event at baseline (Katz <6) were excluded from this analysis, and incidence was defined as reporting disability for one or more ADLs at follow-up.

Covariates

Age, sex, level of education (harmonized in seven categories going from less than the primary school to postgraduate education), gait speed at usual pace (harmonized in meters/second), and source (TSHA or SAGE).

Chair stand cut points: external validation

We used data from a randomized controlled trial (RCT – the Multidomain Alzheimer Preventive Trial (MAPT)) and a clinical database of users of the frailty day-hospital of the Toulouse University Hospital.

Populations

MAPT methodology has been described elsewhere. (71,72) In brief, MAPT was a three-year randomized controlled trial examining the effects of a multidomain intervention (nutritional and physical activity counseling, cognitive training, and annual preventive consultations for the management of cardiovascular risk factors) with and without supplementation of omega-three polyunsaturated fatty acids (PUFA) on cognitive function among community-dwelling adults aged 70 years and older. An additional two-year observational period was carried on after the intervention (Total period: 2008-2016). The trial protocol (ClinicalTrials.gov identifier: NCT00672685) was approved by the French Ethical Committee located in Toulouse (CPP SOOM II) and was authorized by the French Health Authority. All participants signed their consent forms before any study assessment. Inclusion criteria were meeting at least one of a) spontaneous memory complaints, b) limitation in one instrumental activity of daily living (IADL), or c) slow gait speed (≤ 0.8 m/s). Exclusion criteria comprised: Mini-Mental State Examination (MMSE) score < 24 , diagnosis of dementia, limitation in ADLs, and taking PUFA supplements at baseline. MAPT study provided data for a total of seven time-points (baseline, six, 12, 24, 36, 48, and 60 months).

We also used cross-sectional data from the frailty day-hospital of the Toulouse University Hospital. This ambulatory service receives patients referred from their primary-care physicians under the indication of frailty. After a comprehensive geriatric assessment focused on cognitive and physical function, an integrative care plan is designed by the Gerontopole's team and informed the patient's caregivers and primary care team. The data was collected on a routine basis from 2011 to 2019. Patients are informed by a notice in the frailty day-hospital that their data might be used for research. All the data from the frailty day-hospital was cross-sectional. In both cases (MAPT and the frailty day hospital), we restricted the sample to people aged ≥ 70 .

Chair stand measurement

MAPT and frailty day-hospital recorded the five-repetition chair stand test using standard procedures as described above. (100)

Outcome measures

-Incident ADL disability from MAPT was measured using the Katz scale;(78) ADL data were available at baseline, 48, and 60 months. In addition, cross-sectional ADL disability from the Frailty day-hospital database was also used.

-Frailty (day-hospital dataset) and incident frailty (MAPT) constituted the secondary outcomes. Frailty was defined by the Fried frailty phenotype (76). Both studies collected gait speed and grip strength (Jamar dynamometer) as performance-based measures and physical activity using a self-reported questionnaire. In addition, fatigue and weight loss were self-reported. Scores vary from zero to five (higher is worse); participants were categorized as: robust (score of zero), pre-frail (score of one or two), and frail (score of \geq three).

Covariates

For the MAPT baseline data: sex, age, MAPT randomization group, level of education, Mini-Mental state examination (MMSE) score, (109) and 15-item Geriatric depression scale (GDS-15). (75)

For the Frailty day-hospital: sex, age, level of education, Mini-Mental state examination (MMSE) score. (109) We did not use GDS due to missing data for half of the population.

Statistical Analysis

Chair stand cut point elaboration and cross-validation

We randomly selected fifty percent of the age-stratified merged populations (70-79 and ≥ 80 years old in SAGE + TSHA) using the “sample” routine in STATA®(110). We explored the distribution of the chair stand times by age group and by incident ADL disability. We graphed and computed the receiver operator characteristics (ROC) curve and its corresponding area under the curve (AUC) for incident ADL disability. We tabulated the range in which the cut point fluctuate by estimating the cut points nearest to the 85%, 90% and 95% levels of sensitivity or specificity (Table 3.5).

For each age group, we performed 1,000 bootstrap repetitions of the estimation of the cut point using Youden’s index with the criteria of maximizing the sum of the sensitivity and specificity according to the incidence of ADL disability. Finally, the corresponding sensitivity, specificity, and area under the ROC curve were computed for the cut points obtained.

The other half of the randomly selected population was used to validate the cut points’ capacity of identifying older adults with a higher probability of incident disability in a binary logistic regression adjusted for age, sex, education, gait speed, and study source. Because we faced sample size restrictions, we employed bootstrap repetitions in the cross-validation models, too. Logistic regression was used to model incident disability because we lacked time data to specify a Cox survival function (only two time points were available, without the exact date of the event).

Chair stand test cut-off external validation

For each age group (70-79 and ≥ 80 years old), we examined the ability of the chair stand cut points to identify older adults at higher risk/probability of adverse outcomes using the following:

- MAPT dataset: we performed Cox models (time-to-first event) for incident frailty and incident ADL disability. We excluded participants with the event at baseline. Models were adjusted by age, sex, education level, MAPT group, baseline MMSE (109), and baseline GDS. (75) The proportionality assumption was confirmed by visual inspection and by the Schoenfeld residuals test. Linear mixed-effect models for frailty (score zero to five) and ADL (zero to six) were used to assess the association between the classification according to the cut-offs and the evolution of the outcomes. Models included a chair stand x time interaction) with a random effect at the participant's level. Models were adjusted by sex, age at baseline, MMSE, and GDS scores. Time (months) was specified as a continuous variable, and an identity covariance matrix was assumed.

- Frailty day-hospital dataset: we ran binary logistic regression models for frailty and ADL disability. We estimated the odds of being frail (frail vs non-frail) or having any ADL disability (\geq one disability vs no disability). Models were adjusted for sex, age, level of education, and MMSE score.

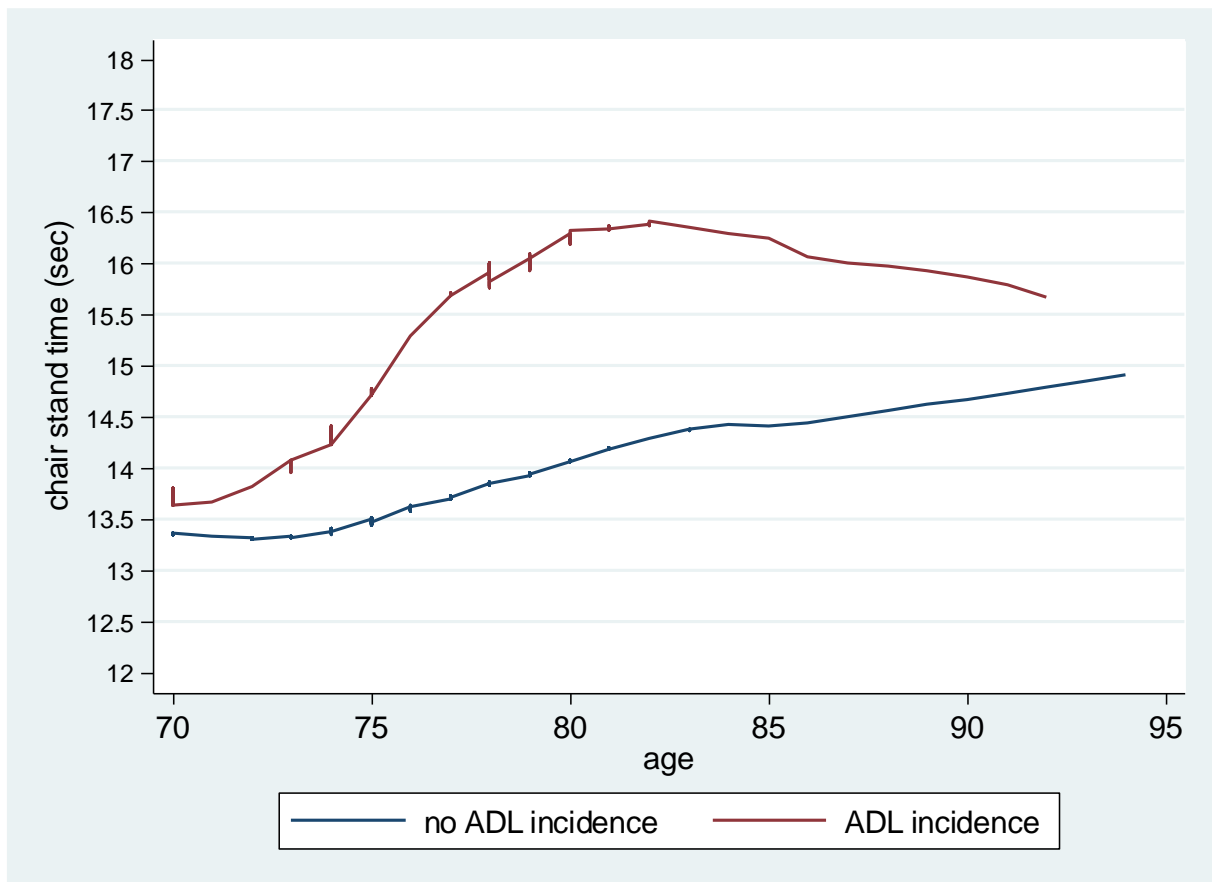
All analyses were performed using STATA®, with $\alpha=0.05$.

3.3 Results

Women were a majority across the three populations used. The mean chair stand time was lower for MAPT participants and higher for the Frailty Clinic participants than for SAGE+TSHA.

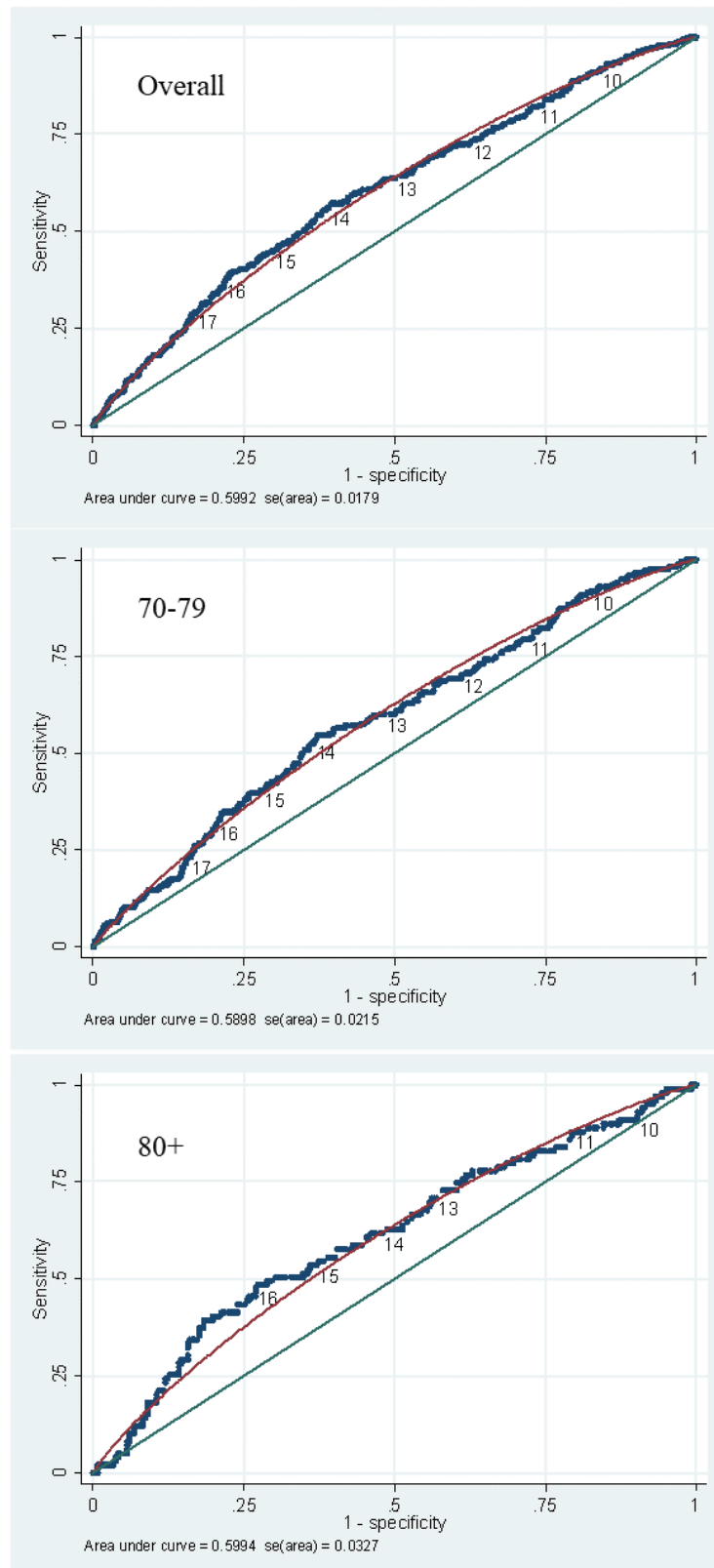
Adults older than 80 had an average chair stand time ≥ 14 s, even if they did not experience incident ADL disability at follow-up. Those aged 80+ with incident ADL disability had an average chair stand time ≥ 16 s. (Figure 3.1).

Figure 3.1. Weighted average of the chair stand time by age and by incident ADL disability in SAGE+TSHA merged cohort



Adults older than 80 had an average chair stand time ≥ 14 s, even if they did not experience incident ADL disability at follow-up. Those aged 80+ with incident ADL disability had an average chair stand time ≥ 16 s.

Figure 3.2 ROC curves for ADL incidence by age group in the SAGE+TSHA merged cohorts



Blue dots and labels: plot of the values of the chair stand time in seconds
 Red line: fitted ROC curve for the chair stand time and incidence of ADLs disability
 Green line: Reference of zero area under the curve

The SAGE+TSHA and MAPT participants showed similar cumulative incidence for ADL disability by age group. Table 1 shows the main characteristics of the studies' populations.

Chair stand cut points: elaboration and cross-validation

The cut points obtained with the Youden's index were 14 s for those aged 70-79 and 16 s for those aged 80 and over. Older adults with a chair stand time above the cut points were regarded as "slow chair standers"; those with chair stand result below the cut point were "fast chair standers." Both cut points provided AUC values higher than 0.5 and slightly higher sensitivity values than specificity (Table 3.2 and Figure 3.2).

Table 3.2. Cut-off points found using the Youden's index and their cross-validation in the joint population SAGE+TSHA

Reference outcome	Incidence of ADL disability							
	70-79			80+				
	Bootstrap estimation	CI95%		Bootstrap estimation	CI95%			
Empirical optimal cut point (sec)	14.0	10.9	- 17.3	16.0	13.0	- 18.4		
Sensitivity at cut point	0.53	0.44	- 0.62	0.40	0.22	- 0.58		
Specificity at cut point	0.63	0.58	- 0.68	0.76	0.67	- 0.85		
Area under ROC curve for the chair stand time	0.58	0.54	- 0.63	0.61	0.56	- 0.68		
<i>Cross-validation of the cut point</i>	Incidence of ADL disability							
	OR	CI95%		p	OR	CI95%		
Slow chair standers ^a	1.72	(1.06	- 2.78)	0.027	2.27	(1.07	- 4.80)	0.032

Note. n=612 for adults aged 70-79 and n= 183 for adults aged 80 and older

^a Chair stand time \geq cut point. Logistic model adjusted for age, sex, education, gait speed and study (Toledo/SAGE)

Cross-validation found that slow chair standers in both age groups had two-fold higher odds of incident ADL disability than their counterparts OR= 1.72 (95%CI 1.06; 2.78) for 70-79y and OR= 2.27 (95%CI 1.07; 4.80) for 80+ (Table 3.2).

Chair stand cut point external validation

MAPT's slow chair standers aged 70-79 had almost thrice higher risk of incident frailty HR=2.74 (95%IC 1.88; 4.00), and 65% higher risk of incident ADL disability than their faster counterparts HR=1.65 (95%IC 1.07; 2.57), in Cox models adjusted for covariates. Similarly, slow chair standers aged 80 and over were at 2.5 times higher risk of incident frailty HR= 2.51 (95%CI 1.39; 4.52), and at 85% higher risk of ADL disability than their faster peers after adjusting for covariates HR= 1.85 (95%CI 0.75; 4.61) (Table 3.3). Mean follow-up periods for Cox models were 58.6 months for incident ADL disability and 43.4 months for incident frailty.

Table 3.3. External validation with disability-relevant outcomes in MAPT and the Toulouse Frailty Clinic

MAPT										
70-79					80+					
Cox model Time-to-first-event	HR	CI95%		p	n	HR	CI95%		p	n
Incident frailty ^a	2.74	1.88	4.00	<0.001	1063	2.51	1.39	4.52	0.002	223
Incident ADL disability ^a	1.65	1.07	2.57	0.025	794	1.85	0.75	4.61	0.072	112

Toulouse Frailty Clinic										
70-79					80+					
Logit model Cross-sectional data	OR	CI95%		p	n	OR	CI95%		p	n
Frailty ^b	4.79	3.40	6.76	<0.001	723	4.22	3.35	5.31	<0.001	1530
ADL disability ^b	2.33	1.68	3.21	<0.001	721	2.08	1.67	2.59	<0.001	1523

^a Hazard ratio adjusted by age, sex, education, MAPT group and baseline MMSE and GDS

^b OR adjusted by age, sex, education level and baseline MMSE

Linear mixed-effect models found slow chair standers did not differ from fast chair standers on the speed of frailty worsening over time in both age groups. However, slow chair standers had a higher baseline frailty score than their counterparts, and thus worsened their frailty status with a clinically-relevant difference earlier than the fast chair standers (about four years before in the 70-79 age group, and about one year before in the ≥ 80 age group) (Table 3.4 and Figure 3.3).

MAPT participants did not show a strong overall ADL functional decline. Yet, slow chair standers declined more on ADL functioning over time in both age groups than fast chair

standers (Figure 3.4) . Between-group differences over five years were 0.038 (95%CI -0.07; -0.01) ADLs in people 70-79 years and about 0.325 (95%CI -0.50; -0.15) points in subjects \geq 80 years old (Table 3.4).

Table 3.4. Between and within-group mean differences in five-year outcomes for the MAPT study

Fried's frailty score ^a	Within-group change in five years			Between-group difference in five years		
	Mean difference	CI 95%	p	Mean difference	CI 95%	p
<i>70-79 years</i>						
Fast chair stand	0.46	(0.41 , 0.51)	<0.001	ref		
Slow chair stand	0.74	(0.64 , 0.85)	<0.001	-0.010	(-0.13 , 0.12)	0.880
<i>80+ years</i>						
Fast chair stand	0.76	(0.60 , 0.92)	<0.001	ref		
Slow chair stand	1.16	(0.78 , 1.54)	<0.001	0.227	(-0.20 , 0.65)	0.290
Katz index for ADLs functioning ^b						
<i>70-79 years</i>						
Fast chair stand	-0.06	(-0.07 , -0.05)	<0.001	ref		
Slow chair stand	-0.10	(-0.12 , -0.07)	<0.001	-0.038	(-0.07 , -0.01)	0.018
<i>80+ years</i>						
Fast chair stand	-0.10	(-0.18 , -0.03)	0.003	ref		
Slow chair stand	-0.41	(-0.56 , -0.26)	<0.001	-0.325	(-0.50 , -0.15)	<0.001

^a Five components of the Fried's frailty phenotype; 0=totally robust, 5= fully frail)

^b Katz index of functioning for the basic activities of the daily life (ADL); 0= fully disabled, 6= fully functional

Figure 3.3. Marginal means for frailty worsening by age group, cross-validation in MAPT

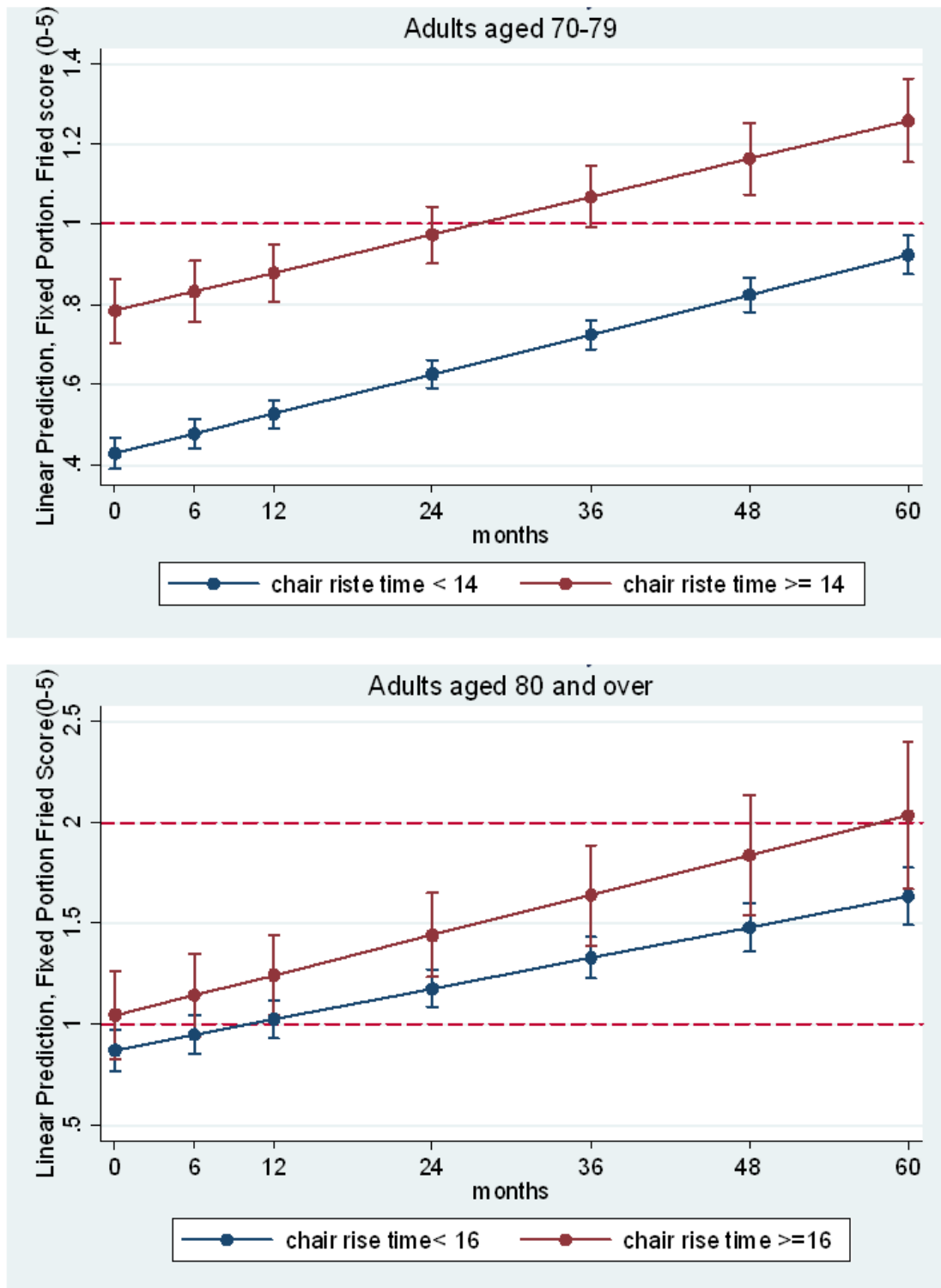
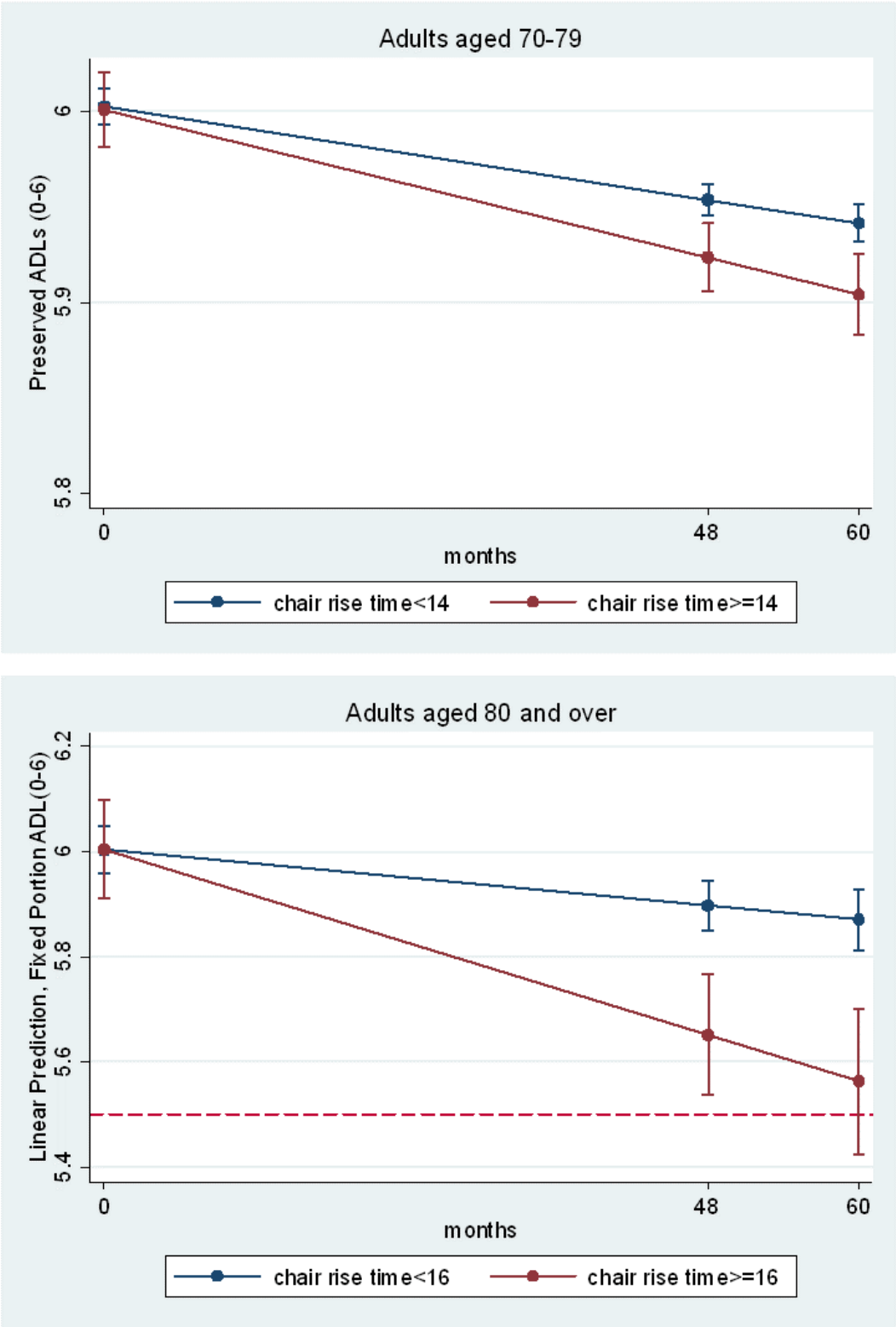


Figure 3.4. Marginal means for declining ADL functionality by age group, cross-validation in MAPT



Slow chair standers from the Frailty day-hospital aged 70-79 had 4.8 times higher odds of being frail and 2.3 times higher odds of being disabled in ADLs than their fast counterparts. Slow chair standers aged 80+ had 4.2 higher odds of frailty and 2.1 higher odds of ADL disability than fast chair standers.

3.4 Interpretation of main findings

The cut points found for the chair stand test were 14 seconds for the 70-79 age group and 16 seconds for those aged 80+ for incident ADL disability. These cut-offs predicted frailty and ADLs disability in older adults from different clinical settings. Our results showed that slow chair standers had a faster decline in their ADL status and sooner frailty worsening than fast chair standers. Moreover, the cut points discriminated frail from non-frail individuals and ADL disabled from non-disabled people among patients of the frailty day-hospital.

Our results confirm that the 14 s cut point suggested in the ICOPE Step 1 guidelines is valid for adults aged 70-79. (34) It is also congruent with cut-offs found by five out of ten previous studies from different countries(101–103,111–117) (Table 3.6). Makizako and cols. (114) and Seino and cols. (101) reported lower cut points than ours (10 and 9.7 seconds, respectively), which may be explained by their younger / healthier populations (mean age=71 years, SD=5), with lower cumulative incident disability (overall 3.7% in two-year follow-up) compared to our study's population. Moreover, Seino and colleagues based their cut point on the 35.8th percentile of gait speed. (101)

Table 3.7 review of cut points found in older adults from different countries

Author	N	age (age group)	sex	country	Cut-off	type of test
Cesari(111)	3,024	70+	both	USA	14.5	5 times
Dodds(112)	7,190	65+	both	UK	15	5 times
Gunasekaran (118)	69	70+	male	India	8	30 sec
Gunasekaran (118)	10	70+	fem	India	7	30 sec
Staartjes (113)	237	30-60	both	Netherlands	10.4	5 times
Makizako (114)	4,335	65+	both	Japan	10	5 times
Moeldrup (119)	144	65+	both	Denkmark	8	30 sec
Nishimura (103)	629	40+	both	Japan	13	5 times
Pinheiro (102)	173	60+	fem	Brazil	13	5 times
Santos (106)	286	60+	both	Brazil	14	5 times
Seino (101)	340	75+	fem	Japan	9.7	5 times
Shimada (104)	455	65+	both	Japan	13	5 times
Velazquez-Alva (105)	137	65+	fem	Mexico	13.8	5 times

We did not find any previous study focusing on the age group 80+, highlighting the importance of the present work. In this vein, our cut point is congruent with Bohannon’s meta-analysis reporting a mean time of 14.8 seconds for those aged 80-89 (61). It coincides with the mean value for the 80+ age group for women in the validation study of the SPPB. (100)

Our selection of the cut point was informed by the estimation of the cut point range according to different levels of specificity and sensitivity. (Table 3.5) Depending on its capacity to intervene after finding a mobility decline, the health services might need to adjust their cut point along this range. We have decided to report the cut point found by the Younden index because a) it is congruent with the Epidemiologic distribution of the chair rise times across different populations, (101–103,111–117) b) it is supported by the ROC analyses in population-based studies and c) it was able to detect older adults at higher risk of functional decline.

Table 3.5 Range of cut-off points for chair stand test according to Youden’s index and alternative criteria

	70-79				80+			
	AUC	[95% CI]			AUC	[95% CI]		
	0.58	[0.52; 0.64]			0.58	[0.48; 0.68]		
	Cut-off >=	Sens	Spec	CC	Cut-off >=	Sens	Spec	CC
High sensitivity	8.6	97%	6%	22%	8.4	98%	6%	28%
	10.2	91%	21%	33%	9.6	91%	9%	30%
	10.6	85%	24%	34%	11.1	82%	21%	36%
High specificity	17.1	19%	85%	73%	17.8	33%	86%	73%
	19.3	15%	90%	77%	21.0	13%	91%	72%
	21.6	7%	95%	80%	26.0	2%	96%	73%
Optimal empirical (Youden’s)	14	53%	63%	61%	16.0	40%	76%	68%

AUC: Area under the ROC’s curve *vis à vis* ADL incidence.

95%CI: confidence interval at 95%.

Sens: sensitivity

Spec: specificity

CC: percentage of correctly classified

According to our results, the cut-offs found can predict differential patterns of functional decline through time. Compared to fast standers, the faster functional decline of slow chair standers was clinically relevant (≥ 1 ADL affected).

As for frailty,(76) both slow and fast chair standers had a significant worsening over time. There was a significant difference in the baseline frailty status between the two groups, suggesting that the cut point distinguished two groups with different physiological reserve levels. Also, slow chair standers had a clinically relevant change in frailty much sooner than their counterparts. (Table 3.4 and Figure 3.3)

The 14 seconds cut-off proposed in the WHO ICOPE handbook (34) was validated in our study for the older adults aged 70-79, but not for older individuals. Our results suggest that the cut-off of 16 seconds for adults aged 80 and over would be more appropriate. (34) The implementation of these cut points in the context of ICOPE might help the health systems. Monitoring the mobility domain of IC can lead to better allocate health system’s often limited resources by targeting the population with greatest potential benefit of interventions.

In conclusion, we found that the cut points of 14 seconds and 16 seconds are helpful to identify individuals at higher risk of functional decline using the five-repetition chair stand test in adults aged 70-79 and 80+ years, respectively. Changing the cut point from 14 to 16 s for people aged 80+ can lead to improvements in the clinimetric properties of up to 42% (Table 3.7), reducing the burden that false positives may carry to the health system.

Ideally, each country would produce nationally representative normative data for performance-based measures of health. As this is not yet the case, we suggest validating these cut points in datasets from different countries and settings. The WHO ICOPE implementation pilot program will facilitate the validation of ICOPE screening tools. (12,44).

Table 3.6 Age-, sex- and age-and-sex stratified cut points found using the Youden's index and their psychometric properties compared to the current cut point

		NO AGE STRATIFICATION			70-79		80+				
		param.	95% CI	% change	param.	95% CI	param.	95% CI	% change		
		new cut point found			cut point found is the same as current 14 s		new cut point found				
		14 s			14 s		16 s				
NO SEX STRAT	Sensitivity	0.56	(0.50 ; 0.62)	-	0.53	(0.46 ; 0.60)	0.44	(0.35 ; 0.55)	-28		
	Specificity	0.61	(0.58 ; 0.64)	-	0.63	(0.60 ; 0.66)	0.74	(0.69 ; 0.79)	42	*	
	ROC area	0.58	(0.55 ; 0.62)	-	0.58	(0.54 ; 0.63)	0.61	(0.56 ; 0.68)	7		
	Accuracy	0.60	(0.57 ; 0.63)	-	0.62	(0.58 ; 0.65)	0.66	(0.61 ; 0.71)	21	*	
	PPV	0.25	(0.21 ; 0.28)	-	0.22	(0.18 ; 0.26)	0.39	(0.30 ; 0.49)	20	*	
	NPV	0.86	(0.83 ; 0.88)	-	0.88	(0.85 ; 0.90)	0.78	(0.73 ; 0.83)	0		
WOMEN		14.6 s			14 s		14.6 s				
	Sensitivity	0.57	(0.49 ; 0.65)	-8	0.58	(0.48 ; 0.67)	0.71	(0.57 ; 0.83)	0		
	Specificity	0.62	(0.58 ; 0.66)	11	*	0.58	(0.54 ; 0.63)	0.55	(0.47 ; 0.64)	22	*
	ROC area	0.59	(0.55 ; 0.64)	1		0.58	(0.53 ; 0.63)	0.63	(0.56 ; 0.71)	9	
	Accuracy	0.61	(0.56 ; 0.65)	7		0.58	(0.53 ; 0.63)	0.60	(0.49 ; 0.70)	14	*
	PPV	0.27	(0.22 ; 0.32)	6		0.23	(0.18 ; 0.28)	0.36	(0.27 ; 0.47)	15	*
	NPV	0.85	(0.82 ; 0.88)	0		0.86	(0.82 ; 0.90)	0.85	(0.76 ; 0.91)	3	
MEN		15.8 s			14 s		17.1 s				
	Sensitivity	0.35	(0.27 ; 0.44)	-28	0.48	(0.36 ; 0.59)	0.36	(0.23 ; 0.51)	-31		
	Specificity	0.83	(0.79 ; 0.85)	24	*	0.69	(0.65 ; 0.73)	0.84	(0.76 ; 0.90)	41	*
	ROC area	0.59	(0.55 ; 0.63)	2		0.58	(0.52 ; 0.64)	0.60	(0.52 ; 0.67)	7	
	Accuracy	0.74	(0.71 ; 0.77)	17	*	0.66	(0.61 ; 0.70)	0.70	(0.64 ; 0.76)	23	*
	PPV	0.30	(0.23 ; 0.37)	26	*	0.20	(0.14 ; 0.26)	0.46	(0.30 ; 0.63)	39	*
	NPV	0.86	(0.83 ; 0.89)	0		0.89	(0.86 ; 0.92)	0.77	(0.69 ; 0.84)	1	

3.5 Strengths and limitations

Our study has several strengths: Our findings provide the first validation of age-stratified cut points for the chair stand test vis a vis the risk of ADL disability in older adults. The cut points were derived from population-based studies with randomly selected samples, which enhances external validity. Besides cross-validation, our cut points were also tested in populations with heterogeneous health and functionality levels. (i.e., a RCT and a frailty clinic).

Our validation models were targeted at clinically relevant outcomes (i.e., frailty and ADL disability), essential for the WHO ICOPE program and major services within the health care sector e.g., long-term care. (120)

There are limitations to the use of our cut points in other populations such as the Asian, which has reported faster chair stand times on average. (121) Also, our findings apply only to participants able to perform the chair stand test at baseline and at follow-up. Further research is needed on older people from Asian countries and other geographies, and in older people who were unable to safely perform the chair stand test.

We obtained relatively low values for the AUC=0.58 (CI95% 0.54, 0.63) for 70-79 years and 0.61 (CI95% 0.56, 0.68) for the 80 and over (Table 3.2). Previous studies have published AUC values < 0.70 for chair stand discrimination of incident disability. (114) The relatively low AUC values found throughout studies might mean that the chair stand test alone is not an overwhelming predictor of ADL decline over time. A higher predictive ability of ADL could be reached when combining all the domains of intrinsic capacity.(122)

Limitations to the prediction of incident disability might also come from the long latency of disability incidence in younger populations. Because it is not always feasible to fund extended follow-up periods, it might be practical to use the frailty phenotype as an intermediate outcome

in adults younger than 80. In this study, we confirmed that the cut points work well with frailty as the outcome.

This research was published as: Gonzalez-Bautista, E. *et al.* Development and validation of a cut-off for the chair stand test as a screening for mobility impairment in the context of the integrated care for older people (ICOPE) program. *J. Gerontol. A. Biol. Sci. Med. Sci.* (2022)
doi:10.1093/gerona/glac055.

Chapter 4. The clinically meaningful change in the five-repetition chair stand test was estimated according to anchor-based and distribution-based methods

4.1 Rationale for this study

The relevance of clinically meaningful change for performance measures in the geriatric clinical and research settings has been recently highlighted by the International Conference of Frailty and Sarcopenia Research Task Force (ICFSR-TF)(123). In mobility/locomotion, previous reports have integrated distribution-based and anchor-based methods to provide overall recommendations for meaningful change of gait speed, short physical performance battery (SPPB) score, and 6-minute distance walk for older adults. Still, they did not include estimates and recommendations for the chair stand test (124,125).

Among the studies approaching the clinically meaningful mobility performance changes, we did not find any reporting data for the chair stand test(125–127).

There is a knowledge gap about the magnitude of the clinically meaningful change that could be applied to the chair stand test to monitor the locomotion in older adults. Given the increasing international implementation of ICOPE, understanding the clinically meaningful amount of decline in chair stand test becomes crucial to inform timely interventions and decrease the risk of disability. Therefore, our study aimed to derive recommendations for absolute and relative (percent) clinically meaningful change for the chair stand test in older adults.

4.2 Methods

We used data from a population-based study: the World Health Organization (WHO) Study on global Aging and adult health in Mexico also known as SAGE Mexico. Based on previous reports (123), we derived the clinically meaningful absolute and relative changes in the chair

stand test that could warn clinicians of older adults' higher risk of becoming disabled for basic activities of daily living (ADL). Absolute clinically meaningful change was defined as the difference in seconds (s) between the baseline and follow-up measurements of the chair stand time. Relative clinically meaningful change (%) was defined as the percentage change between baseline and follow-up measures. We used distribution methods, which are based on the statistical distribution of the chair stand test. Anchor-based methods were also applied, which are "anchored" to patient-reported mobility outcomes (e.g. "how much difficulty did you have in walking a long distance such as a kilometer?").

Finally, we tested if participants with clinically meaningful absolute and relative declines were at significantly higher risk of incident ADL disability.

4.2.1 Data Sources

SAGE Mexico

We used the second and third waves (three-year apart from each other) of SAGE Mexico, given that the first wave of this study did not assess the chair stand test. Briefly, SAGE Mexico is a prospective cohort study with a multi-stage, stratified, and clustered sample designed to represent non-institutionalized older adults at the national level. Data were collected at the participant's lodgment by standardized trained staff using electronic records (CAPI). All participants provided their informed consent, and the scientific board of the National Institute of Public Health approved the SAGE Mexico study. In this study, we included participants aged 60 and older. Further information on study design can be found elsewhere. (107)

MAPT (Multidomain Alzheimer Preventive Trial)

We used data from the MAPT randomized controlled trial, which methodology has been

described elsewhere. (71,72) In brief, MAPT was a three-year randomized controlled trial among community-dwelling adults aged 70 years and older examining the effects on cognitive function of a multidomain intervention (nutritional and physical activity counseling, cognitive training, and annual preventive consultations for the management of cardiovascular risk factors) with and without supplementation of omega-three polyunsaturated fatty acids (PUFA). After the intervention, an additional two-year observational period was carried out (Total period: 2008- 2016). The trial protocol (ClinicalTrials.gov identifier: NCT00672685) was approved by the French Ethical Committee located in Toulouse (CPP SOOM II) and was authorized by the French Health Authority. All participants signed their consent forms before any study assessment. Inclusion criteria were meeting at least one of a) spontaneous memory complaints, b) limitation in one instrumental activity of daily living (IADL), or c) slow gait speed (≤ 0.8 m/s) Exclusion criteria comprised: Mini-Mental State Examination (MMSE) score < 24 , diagnosis of dementia, limitation in ADLs, and taking PUFA supplements at baseline. MAPT study provided data for several time points (baseline, six, 12, 24, 36, 48, and 60 months).

SAGE Mexico and MAPT studies have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

4.2.2 Measures

Chair stand test

Both SAGE Mexico and MAPT measured the time in seconds the participant took to perform five chair stands at maximum speed with their arms folded across their chest. The protocol started by the interviewer by asking the question: “Do you think it would be safe for you to try to stand up from a chair five times without using your arms?” The interviewer then demonstrated and explained the test using the chair usually employed by the participant placed

with its back against a wall. Following, the interviewer indicated: “Please stand up straight as quickly as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. I’ll be timing you with a stopwatch”. Trained assessors measured time from the starting sitting position to the end of the fifth stand. (100)

The test was stopped if the participants: Became tired or short of breath during repeated chair stands; used their arms; after 1 minute, they had not yet completed five rises; at the interviewers’ discretion, if concerned for their safety.

Disability for the basic activities of daily living

The incidence of ADL disability (Katz scale) (78) was the outcome for elaborating the clinically meaningful change cut point. Scores on this scale vary from zero (total disability) to six (no disability). Participants with the event at baseline (Katz <six) were excluded from this analysis, and incidence was defined as reporting disability for one or more ADLs. We applied the exact definition in SAGE Mexico and MAPT.

Anchor measures

We used three items from the self-reported activities questionnaire in SAGE Mexico. These items were chosen because they are closely related to the locomotion domain.

Item 1: *Overall, in the last 30 days, how much difficulty did you have with moving around?*

Item 2: *Overall, in the last 30 days, how much difficulty did you have in vigorous activities?*

(‘vigorous activities’ require hard physical effort and cause significant increases in breathing or heart rate)

Item 3: *Overall, in the last 30 days, how much difficulty did you have in walking a long distance such as a kilometer?*

These items were initially scored by self-reported difficulty levels using a Likert-type scale from one to five. For our study, and following literature (128), we re-coded them in four strata: no change, small meaningful worsening (those who worsened within the mild-moderate difficulty), substantial, meaningful worsening (those who declined to severe and extreme difficulty), and no possibility of worsening (extreme difficulty at baseline or observed improving at follow-up).

4.2.3 Data Analysis

Overview

Using data from the SAGE Mexico study and based on previous reports (123), we derived the clinically meaningful absolute and relative changes in the chair stand test that could warn clinicians of older adults' higher risk of becoming disabled. The relative clinically meaningful difference was calculated using $(\Delta \text{ chair-stand-time} \times 100 / \text{baseline chair-stand-time})$. The absolute and relative clinically meaningful changes were obtained by a) applying distribution-based (effect size and standard error of measurement SEM), b) anchor-based approaches (comparison of means between those who did and did not self-report decline in mobility items), and c) ROC- derived Youden's index. We verified that these clinically meaningful changes were lower than the mean decline observed in participants with incident ADL disability (marginal means).

Using the effect size formula $(\delta = (\mu_1 - \mu_2) / \sigma_1)$ and conventional definitions of small and moderate effect (129–131), we calculated the small and moderate meaningful changes as $0.2 \times \sigma_1$ and $0.5 \times \sigma_1$, respectively. μ_1 and μ_2 accounted for the mean chair stand.

Next, we computed the adjusted risk ratios of incident disability for ADLs based on those participants with clinically meaningful declines in SAGE Mexico and MAPT using a logistic model adjusted for age, sex, and baseline chair stand time. Finally, we estimated the hazard ratio for incident disability for MAPT participants with clinically meaningful declines using Cox models adjusted for age, sex, education level, MAPT allocation group, and baseline chair stand time. The proportional hazards assumption was confirmed by Schoenfeld residuals and by time-varying covariates. All analyses were performed using STATA® 17.

4.3 Results

SAGE Mexico participants included in this study were mostly younger than 75 (age range= 60-96; mean (SD) = 69.0 (6.2)) and female (54.4%); 23% of them had achieved secondary school or higher. Their baseline time averaged 12.1 s (SD=3 sec) and 14.7 s (SD= 4.9 sec) after three years of follow-up. (Table 4.1) The chair stand test time increased (thus locomotion capacities diminished) for 68.8% of the study sample, and the opposite was true for 31.1%. The mean chair stand performance was slightly better for those who remained in the study than those lost to follow-up (-0.30 s, $p= 0.0016$).

Table 4.1. Description of the study populations of SAGE Mexico and MAPT

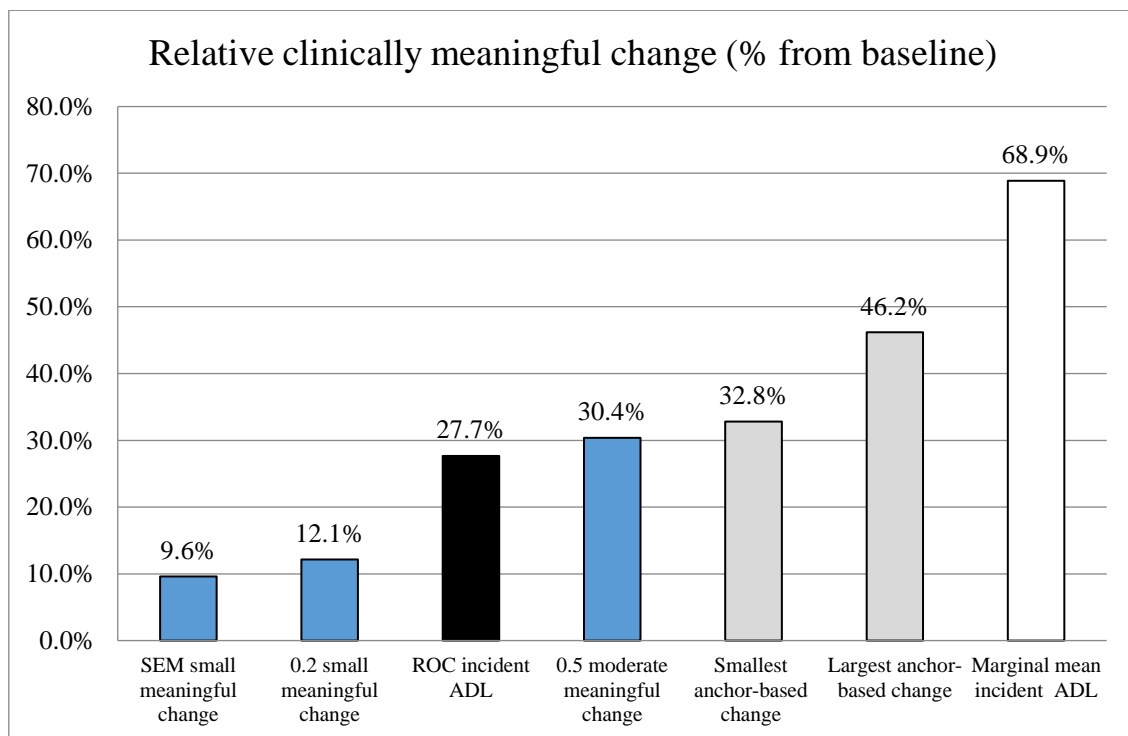
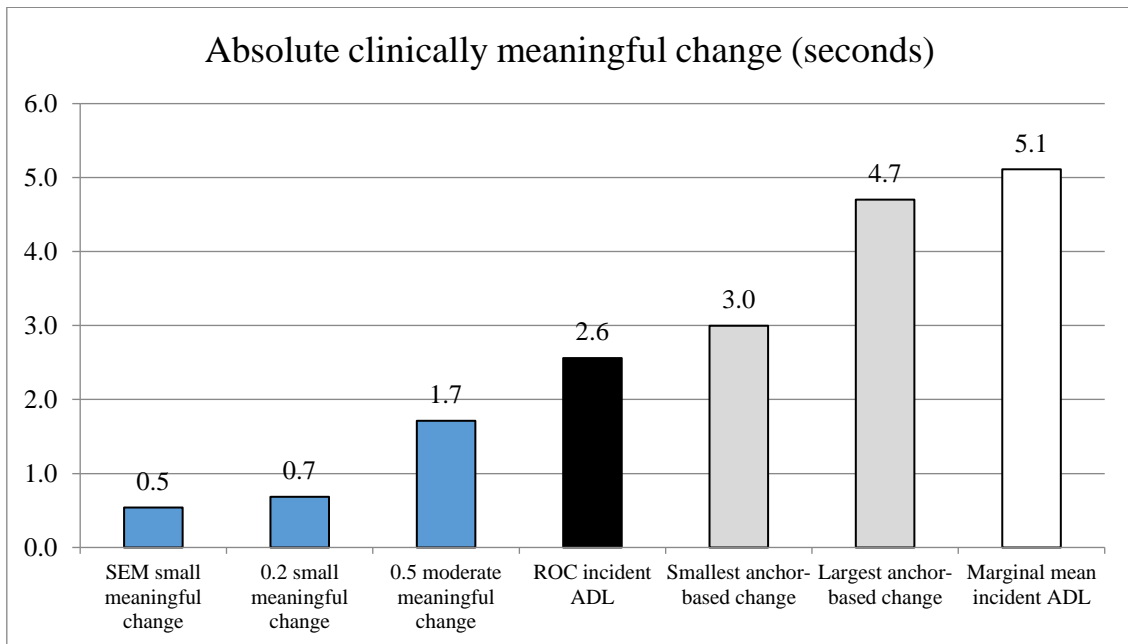
	SAGE Mexico		MAPT	
mean (SD) unless shown otherwise	n=897		n=1575	
Age (years)	69.0	(6.2)	75.3	(4.4)
Participants aged 80+, n (%)	57	(6.4)	278	(17.7)
Female, n (%)	488	(54.4)	1021	(64.8)
Five-repetition chair stand time at baseline	12.1	(3.4)	11.6	(3.5)
Five-repetition chair stand time 3y follow-up	14.7	(4.9)	11.7	(3.5)
Mean absolute change	2.6	(4.9)	0.2	(3.5)
Mean relative change	29.0	(60.7)	6.2	(30.7)
Incidence of ADL disability, n (%)*	48	(5.6)	145	(14.8)

*3 year follow-up for SAGE Mexico, 5 years follow-up for MAPT

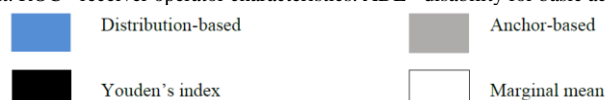
Summary of clinically meaningful changes for the five-repetition chair stand test

The sorted estimates of absolute and relative clinically meaningful changes are graphed in Figure 4.1.

Figure 4.1. Sorted estimations of clinically meaningful changes in the time for performing the five-repetition chair stand test according to the estimation method



SEM= standard error measurement. ROC= receiver operator characteristics. ADL= disability for basic activities of daily living.



As shown in Figure 4.1, the estimates are consistent across methodologies as they remain within a reasonable range. The smallest is the SEM, followed by the clinically meaningful change according to the effect size and the clinically meaningful change derived from the ROC analyses. Subsequently, there is the anchor-based clinically meaningful change based on the changes in the mobility items, and the largest is the marginal means of the time changes observed in those older adults with incident ADL disability.

SAGE Mexico participants with an absolute clinically meaningful decline showed a 93% increased risk of ADL disability (aRR= 1.93; p= 0.0381; 95%CI (1.05; 3.46)), and the risk for those with a relative decline was 2.27 times higher (aRR= 2.27; p= 0.0157; 95%CI (1.22; 4.10)) compared with those without a clinically meaningful decline. See Table 4.2.

Table 4.2. Contingency tables and adjusted risk ratios of incident disability for the absolute and relative declines in the five-repetition chair stand test

Absolute decline in the five-repetition chair stand test and ADL incidence						
	<i>SAGE</i>			<i>MAPT</i>		
<i>Contingency table</i>	<i>Decline</i>	<i>No decline</i>	<i>Total</i>	<i>Decline</i>	<i>No decline</i>	<i>Total</i>
Incident ADL	28	18	46	29	96	125
No incident ADL	355	457	812	132	625	757
Total	383	475	858	161	721	882
<i>RR for incident ADLs</i>	<i>aRR*</i>	<i>95%CI</i>		<i>aRR*</i>	<i>95%CI</i>	
Clinically meaningful decline	1.93	(1.05;	3.46)	1.39	(0.93;	2.02)
Relative decline in the five-repetition chair stand test and ADL incidence						
	<i>SAGE</i>			<i>MAPT</i>		
<i>Contingency table</i>	<i>Decline</i>	<i>No decline</i>	<i>Total</i>	<i>Decline</i>	<i>No decline</i>	<i>Total</i>
Incident ADL	27	19	46	29	96	125
No incident ADL	329	482	811	125	632	757
Total	356	501	857	154	728	882
<i>RR for incident ADLs</i>	<i>aRR*</i>	<i>95%CI</i>		<i>aRR*</i>	<i>95%CI</i>	
Clinically meaningful decline	2.27	(1.22;	4.10)	1.63	(1.08;	2.35)

*aRR: Risk ratio adjusted for age, sex, and baseline chair stand time

Meaningful change according to effect size

The small and moderate effects for the absolute decline were 0.7 s and 1.7 s, respectively. The small and moderate effects for the relative decline were 12.1% and 30.4%, respectively.

Meaningful change according to the standard error of measurement (SEM)

The standard error of measurement was 0.5 s and 9.6% for the absolute and relative declines, respectively.

Meaningful change according to the comparison of means

Small meaningful changes according to anchor-based measurements averaged 3.1 s and 39% respectively for absolute and relative changes (range for absolute change= 3.0 to 3.2 s; range for relative change=32.8 to 45.0%).

Moderate meaningful changes according to anchor-based measurements averaged 3.8 s and 39% respectively for absolute and relative changes (range for absolute change= 3.1 to 4.7 s; range for relative change=32.9 to 46.2%).

Meaningful change derived from ROC analyses

The absolute and relative changes found using Youden's index were 2.6 s and 27.7%.

In SAGE Mexico, older adults with incident ADL disability had a mean decline of 5.1 s and 68.9% from baseline over three years.

External validation

As shown in Table 4.3, MAPT participants with a clinically meaningful absolute worsening of their chair stand time (≥ 2.6 s) during the first three years of follow-up had a 46% higher risk of

incident ADL disability (aHR= 1.46. CI95% 0.95; 2.25). Those with a clinically meaningful relative worsening of their chair stand time ($\geq 27.7\%$ from baseline) had a 74% higher risk of incident ADL disability (aHR= 1.74. CI95% 1.11; 2.72) with a mean follow-up of 58 months.

4.4 Interpretation of main findings

Using a population-based study (SAGE Mexico), we found that absolute meaningful changes for the five-repetition chair stand time ranged from 0.5 s to 1.7 s and from 3.0 s to 4.7 s applying distribution-based and anchor-based methods, respectively. Relative meaningful changes ranged from 9.6% to 30.4% using distribution-based and anchor-based methods, respectively. The results from the ROC analyses showed that ≥ 2.6 s and $\geq 27.7\%$ were coherent with distribution-based and anchor-based methods. Furthermore, we corroborated that older adults with a clinically meaningful decline in the chair stand time were at higher risk of incident ADL disability in an external population (the MAPT study).

A change ≥ 2.6 s (or 27.7%) from baseline over three years was clinically meaningful in our research. This amount could seem substantial for some clinicians but bear in mind that we measured changes over three years. Yet, we found that changes as small as 0.5 s or 9.6% over three years are already meaningful from the statistical point of view. The standard error of measurement (SEM) served as a “bottom line” for the change attributed to other than measurement error. A change ≥ 2.6 s (or 27.7%) from baseline over three years is higher than the minimal detectable change estimated by $1.96 \times \text{SEM}\sqrt{2}$ in our data (1.5 s or 26.6%), and consistent with a previous study in older women(132).

To the best of our knowledge, no other study has estimated the clinically meaningful change for the five-repetition chair stand test using distribution- and anchor-based methods with a population-based sample. In this vein, our study builds on previously published works about

the meaningful change for physical performance measures for older adults, with recommendations for clinically meaningful differences in gait speed and the short physical performance battery (SPPB) through the distribution- and anchor-based methods (124,125). Going beyond previous publications, in addition to distribution- and anchor-based methods, we also used ROC analyses; this approach allowed us to make an objective choice for establishing recommendations on the most appropriate clinically meaningful decline across the range of results (Fig. 4.1). Therefore, we defined the clinically meaningful change in the chair stand test using the Youden's index (2.6 s and 27.7% for the absolute and relative, respectively) because it was coherent and located in an intermediate position between the distribution- and anchor-based methods' results.

Our findings suggest that a difference of one second or ten percent change *per year* in the five-repetition chair stand test would be clinically meaningful, assuming a linear trend. We did not find publications for the clinically meaningful decline in the chair stand test. Still, Onder and co-authors have reported average decreases of 2.2 s or 11.2% and 4.0 s or 21.1% from baseline to one and three years, respectively, for absolute and relative changes in the Women's Health and Aging study (133). Our results are coherent with such rate of decline considering that we are using population-based data with no function-based selection criteria as the ones applied for the WHAS, which is also an older population (mean (SD) age = 78.9 (8.1)) (133). A slight decline of 0.5 s was reported over seven years on high-functioning community-dwelling American adults aged 70- 79 as part of the Mac Arthur study (134). Also, Rosano and co-authors have reported an average decline of 0.5 s/y in people with severe white matter hyperintensities (WMH) (n=2 450, mean age =75 years)(135).

Defining clinically meaningful changes for the chair stand test can empower the healthcare professionals during the follow-up of older adults. Our results on the clinically meaningful

changes add value to the cross-sectional cut points for the chair stand test in the context of ICOPE. For example, a clinician might find a patient has declined from 10 to 13 s in the five-repetition chair stand test over three years. This patient is below the 14 s cut point recommended by the ICOPE handbook (34). However, the patient has already expressed a clinically meaningful change. Thus, clinicians might decide to implement interventions in a higher-risk population even earlier. Furthermore, distribution-based meaningful changes might be applicable for monitoring meaningful changes in lower limb strength and power during/after clinical interventions. For example, improvements of 2.9 and 2.5 s have been reported after six weeks of pre-operative exercise training (136) and after three months of total hip arthroplasty (137), respectively.

To further explore the trajectory of the chair rise time, we were not able to test if the test time changes in a linear or non-linear fashion because data was only available for two time points in SAGE Mexico. However, we used the chair stand test times available in MAPT for several time points, the trade-off being that it is not a population-based study. We modeled the time trajectory for those with and without incident ADL disability which best fitted a quadratic function. (Figures 4.2 and 4.3). Then we retrospectively modeled the time trajectories for those participants who performed better or worse than our recommended clinically meaningful change for a 3-year follow-up. Participants with a clinically meaningful change went from 11 s at baseline to 12, 13, and 14.4 s after 6, 12, and 24 months of follow-up, respectively. MAPT participants with time differences lower than the clinically meaningful roughly maintained their performance throughout the five-year follow-up.

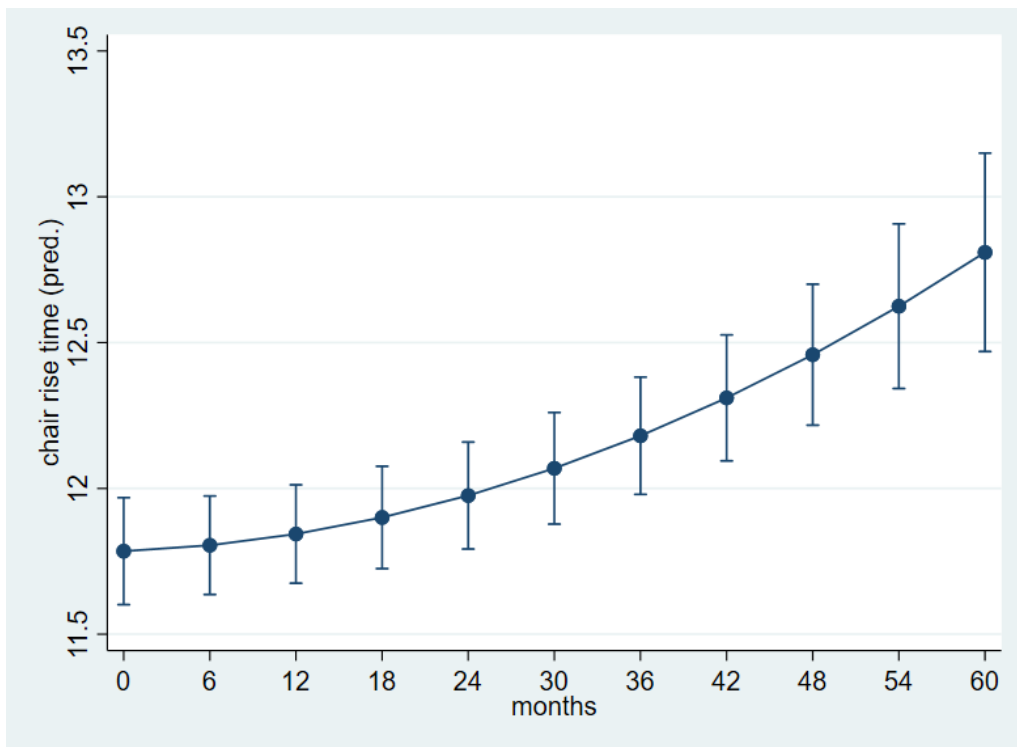
Table 4.3. Adjusted hazard ratio for incident ADL disability in MAPT participants with clinically meaningful decline in the five-repetition chair stand test

n= 872 Events of incident ADL disability= 125 Mean FU time= 58.6 months	aHR*	p	CI95%	
≥ absolute clinically meaningful change	1.46	0.087	(0.95;	2.25)
≥ relative clinically meaningful change	1.74	0.016	(1.11;	2.72)

*Hazard ratio adjusted for age, sex, education level, MAPT allocation group, and baseline chair stand time

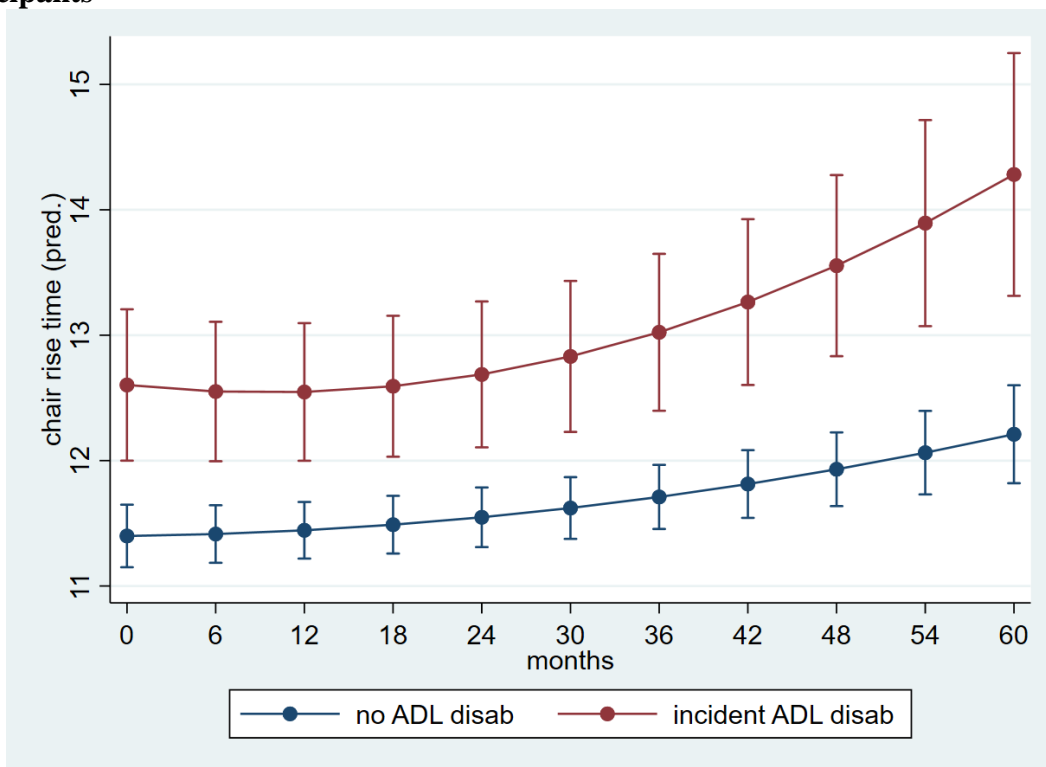
Our work fills the gap regarding the clinically meaningful change for older adults' chair stand test time. The mobility domain can be monitored using other means with established clinically meaningful change, the SPPB, for instance (100). Nevertheless, using the chair stand test brings advantages like shorter application time and feasibility even with spatial room constraints. Furthermore, it is reactive to acute conditions like self-reported dizziness or flu-like symptoms within weeks (138). Offering recommendations for the clinically meaningful change in the chair stand test in older adults might lead to early detection of mobility declines and prevention of disability in older age.

Figure 4.2 Predicted chair rise time with 95% CI in MAPT participants



Y axis: Predicted time to perform the five-repetition chair stand test in seconds adjusted for age and sex and MAPT group.

Figure 4.3 Predicted chair rise time by incident ADL disability with 95% CI in MAPT participants



Y axis: Predicted time to perform the five-repetition chair stand test in seconds adjusted for age and sex and MAPT group.

4.5 Strengths and limitations

Our study has several strengths; for instance, it is the first to provide recommendations for clinically meaningful change in community-dwelling older adults derived from population-based data. In addition to using the conventional methods reported by previous literature (123,124), we applied ROC analyses to obtain a data-driven cut point of the clinically meaningful change. Also, besides reporting the absolute changes like in previous papers(124), we have also attained the relative meaningful changes expressed as a percentage of change. It is possible that relative meaningful changes (%) outperform absolute meaningful changes (seconds) in populations distinct to SAGE Mexico, depending on their distribution of the chair rise time and other markers of physical performance. In very fit populations such as in MAPT, the absolute decline might not be sensitive enough to detect clinically meaningful changes. There was a very low increase in the times of MAPT participants, as can be seen in their five-year performance overall trajectory (~1.5 s). The relative change is useful in these populations.

One limitation of our study is that the external validation was performed in MAPT, which is not a population-based study. MAPT was a randomized controlled trial not designed to test the clinically meaningful changes in the chair stand time. MAPT's population included relatively fit and well-educated older adults (see data sources and Andrieu et al. (139)). The estimates on the adjusted Hazard ratios for incident ADL in MAPT are not directly generalizable to other populations. Despite this limitation, we were able to demonstrate the usefulness of the clinically meaningful change as a risk-stratifying feature in MAPT participants. Future external validation studies using a variety of populations are needed.

This research was published as: Gonzalez-Bautista, E. *et al.* Clinically meaningful change for the chair stand test: monitoring mobility in integrated care for older people. *J. Cachexia. Sarcopenia Muscle* (2022) doi:10.1002/JCSM.13042.

Chapter 5. Integrative discussion.

We have contributed to the validation process of the ICOPE Step 1 screening tool by providing evidence of its properties as a good risk-stratifying tool for functional decline, with a focus on the locomotion domain of intrinsic capacity.

5.1 Summary of main findings

We have contributed to the validation process of the ICOPE Step 1 screening tool by filling in the evidence gap about its properties as a risk-stratifying tool for functional decline.

Each additional IC impairment increased the risk of disability for ADLs by 23% in MAPT participants. (Table 2.2). Participants screened with limited mobility, depressive symptoms, or visual impairment had a higher risk of developing frailty. Limited mobility and depressive symptoms (to a lesser extent) were also associated with incident ADL disability. An adaptation of the ICOPE Step 1 screening tool showed a good predictive ability based on the Harrell C statistic ($0.70 < C < 0.83$) (83).

The cut points found for the chair stand test were 14 seconds for the 70-79 age group and 16 seconds for those aged 80+ for incident ADL disability. Changing the current cut point of 14 seconds to 16 in adults aged 80 and over leads to improvements of up to 42% in specificity.

These cut-offs predicted frailty and ADLs disability in older adults from different clinical settings. Our results showed that slow chair standers had a faster decline in their ADL status and sooner frailty worsening than fast chair standers. Moreover, the cut points discriminated frail from non-frail individuals and ADL disabled from non-disabled people among patients of the frailty day-hospital.

Absolute meaningful changes for the five-repetition chair stand time over three years of follow-

up ranged from 0.5 s to 1.7 s and from 3.0 s to 4.7 s applying distribution-based and anchor-based methods, respectively. Relative meaningful changes ranged from 9.6% to 30.4% using distribution-based and anchor-based methods, respectively. The results from the ROC analyses showed that ≥ 2.6 s and $\geq 27.7\%$ were coherent with distribution-based and anchor-based methods. Furthermore, we corroborated the findings that older adults with a clinically meaningful decline in the chair stand time were at higher risk of incident ADL disability in an external population (the MAPT study).

5.2 Methodological limitations for the studies in this thesis

The studies in this thesis used sound methodology, yet there is room for improvement in the following aspects: a) they are secondary analyses from studies performed before the formal operationalization of the ICOPE screening tool (retrospective), b) the statistical models were not built based on a causal graph to allow for further causal inference, and c) the model parameters were estimated assuming a “missing at random” pattern in the datasets.

In chapter 2 we had to adapt the available items of the MAPT study to get an instrument like the ICOPE step 1 screening tool. This opens the door to misclassification because the resulting “MAPT step 1 screening tool” might classify the same participant under a different category if the ICOPE Step 1 tool was used, specifically in the sensory and psychological domains. (Table 2.1) Misclassification bias is a type of information bias that occurs when the measurement of exposures and/or outcomes is not perfect. (97) In our case, misclassification is non-differential across comparison groups, resulting in estimates biased towards the null value for our ADL incidence models. (97) Ideally, we should have used a study with the exact ICOPE Step 1 items to avoid this error. This bias was impossible to solve because by the time we started this thesis no study designed to investigate IC domains -measured as in ICOPE- was ongoing, as far as we knew.

After an in-depth review of the methodological limitations for this thesis I found two tools that could help to strengthen the analysis in future works: causal networks and shared-parameter models. I do not yet have enough skills to apply these tools. However, I am looking for resources to learn more about them.

In Chapters 2-4 we applied multivariate statistical modelling to measure the strength of the association of our main exposures (ICOPE step 1 items and the chair stand time) with our main outcome (incident disability and incident frailty). To avoid wrong (confounded) estimations, we included covariates in our models. Variables such as age, sex, and education were included in our models based on previous knowledge on how they are associated with our main exposures and outcomes. (140,141) However, the selection of these variables was not based on a structured causal network/causal diagram.

Scientists from other fields may criticize these models because they describe correlations rather than causality. The more often taught framework of the quality in study designs places observational studies as of lower quality than randomized controlled trials. Nevertheless, data from observational studies might be used for causal inference. Causal relations can be represented using Bayesian statistics and Direct Acyclic Graphs (DAGs)(142). The DAGs are convenient tools because they can represent different causal structures (e.g., distinguish mediation from confounding) and they can be translated into structural equations to obtain quantitative parameters. DAGs are also helpful to decide which variables should be included in a statistical multivariate model to avoid confounding. For example, including collider variables in a model introduces collider bias and can lead to wrong estimations. (143) Colliders are variables independently caused by the main exposure and outcome of the model. Drawing a DAG of the candidate variables for a model can clarify the structure of the causal network and identify colliders, mediators and others. (144,145) Judea Pearl has advocated for the increasing

use of DAGs in the era of big data arguing that causal inference can be drawn from observational studies if DAGs and counterfactuals are applied, and not only randomized experiments. (146) Greenland, Hernan and others are applying modern epidemiology approaches in line with this thought. (142,144)

MAPT, SAGE Mexico and the TSHA were our sources of longitudinal data for this thesis. It is known that longitudinal studies might experience attrition of their study sample because of lost to follow-up participants. (147) They will be considered as “missings” in the data jargon. In longitudinal studies with older adults, the probability of “missing” is likely associated with declining health. Thus, missing data is rarely randomly distributed. For example, in Chapter 3 we used linear mixed models under the assumption of data missing at random. According to a study by Griswold et al. our estimates could be inappropriately attenuated between 17-40%. (148) In their study they estimate the association of cognitive decline and dementia with data from the Atherosclerosis Risk in Communities (ARIC) study. They compare the estimates obtained from mixed-effects models with those from shared-parameter models (SPM) and found an attenuation of the effect of cognitive decline in dementia when missing data were incorrectly assumed to have a random distribution. The authors present the shared parameter models as a useful tool to allow for a more accurate parameter estimation under a non-random distribution of missing data.

The use of DAGs and SPM could have strengthened my methodological approach in this thesis. I am currently working to develop the skills needed to apply them in future works.

5.3 Screening for intrinsic capacity impairments aiming at disability prevention: implications for clinical practice

The main objective of the ICOPE strategy is to preserve functionality and prevent disability in older people.(10) This objective along with the conditions of the health system need to be considered when implementing the ICOPE screening tool in a given setting.

The assumption is that low levels of intrinsic capacity are a risk factor for disability in older adults. Then, the ICOPE Step 1 tool would be used as a primary prevention tool. (149) For example, when selecting a cut point for the intrinsic capacity screening tool, the optimal threshold on the ROC curve (Youden index) may be irrelevant and suboptimal from a clinical perspective, or could end up putting too much pressure on the health system's resources if it is too strict. (82)

In reference to severe disease, it is said that sensitivity should be privileged when selecting a cut point for a screening tool.(150) The rationale is that severe disease will kill the patient if the clinician does not timely detect it. So, it makes sense to minimize the risk of "letting go" a true positive case, and thus maximize sensitivity. The scenario is different for the IC screening because frailty or disability (as expressions of low IC) will not directly kill the patient within a short time. In this vein, and in sake of efficiency, health managers might want to screen for older adults with the highest potential to benefit for interventions (e.g., close follow-up with a physical therapist, what can be offered to a large number of people), and those at higher risk of high-impact functional decline.

In the ideal health system, every older adult with at least one IC impairment is conducted to the corresponding clinical pathway for an in-depth assessment and intervention. Such scenario is not possible under current resources constraints. Health systems ought to treat the conditions

which are being screened with a high impact on the user's health. In this vein, our work has shown that changing the cut point from 14 to 16 s for people aged 80+ can lead to improvements in the clinimetric properties of up to 42%, reducing the burden that false positives may carry to the health system.

5.3.1 Limitations faced for the definition of cut points for chair stand test to assess the locomotion domain of IC

In the case presented in Chapter 3 of this thesis, we faced limitations that impede us to obtain the final answer to our research question about the best cut points for the chair stand test. In summary, I think that two additional variables, an indicator of acute health problem and a biomarker of biological age would have helped us to get a more elaborated answer. I explain in the following paragraphs.

The ROC analyses applied to the cut point definition is based on discriminating between two populations. For instance, Figure 5.1 shows the frequency distribution of the chair stand times (seconds in the x-axis). We plotted in blue the distribution for the sample who did not have ADL disability incidence at follow-up, and in red those who did. We noticed that in the merged population of SAGE Mexico and the TSHA, even after stratifying by age group, there were still two potentially distinct populations depicted by the two "humps". The second hump is more evident in the 80+ age group. We can infer there is another potential source of variability in the association of the ADL disability incidence and the chair stand time, after stratifying by age groups.

This distribution plots are used in ROC analyses to see the amount of overlapping area between the two curves. The overlapping area is inversely proportional to the ability of the x-axis variable to discriminate between the two populations. (151) In our case, the areas tend to

intersect at 14 and 16 seconds for the 70-79 and 80+ age groups, which is congruent with our results. Yet, the overlapping area is not small, hence, the low AUROC curve.

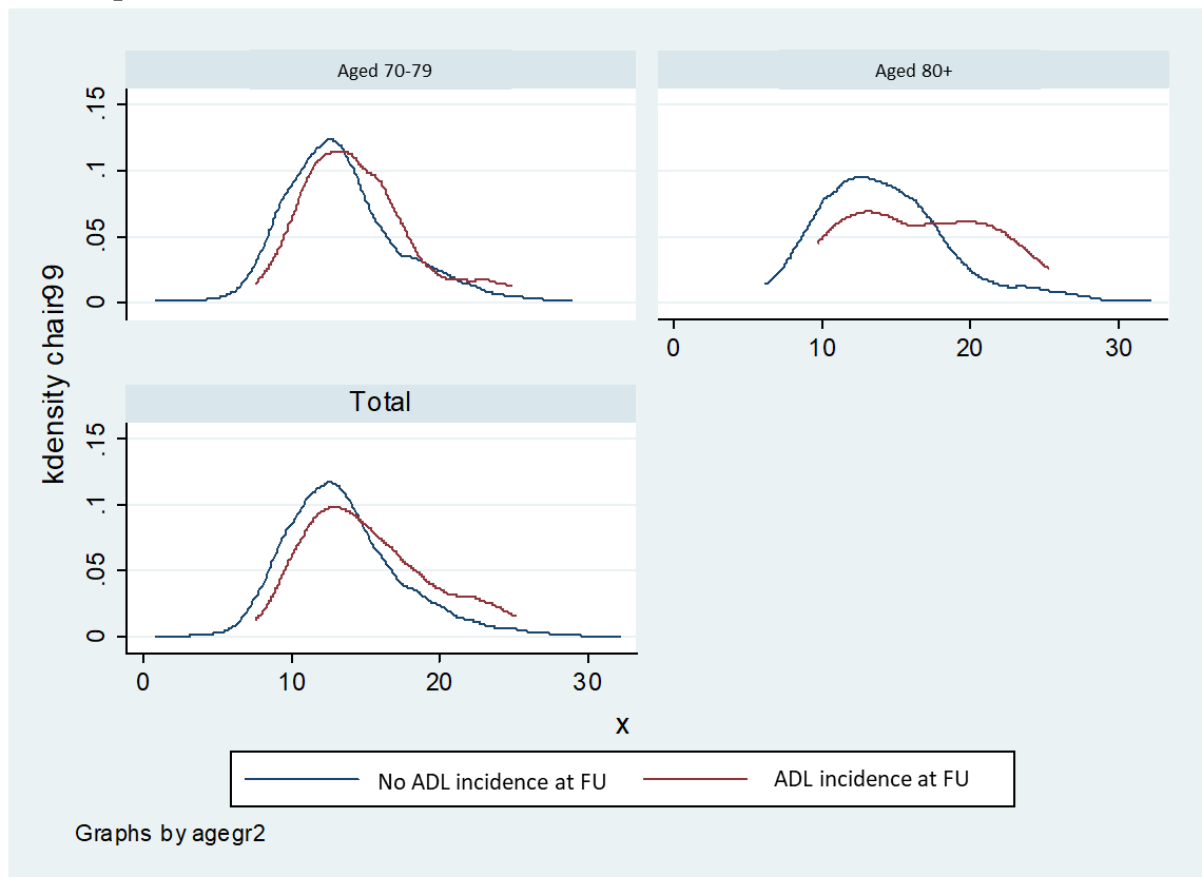
This distribution plot suggests:

- a) The stratification of chronological age in two groups is not enough to distinguish the two sub-populations depicted. In this case we would have needed to stratify using five-year periods, but we did not have enough sample size for this. We looked at the contingency tables and for the 85-90 we got less than 12 stratified observations.
- b) Or there are other determinants of the sub-populations depicted. One possibility is biological age. Maybe “biologically younger” participants are depicted in the first hump than the second. The other determinant can possibly be the occurrence of an acute disease or injury because for those with an acute injury, regardless of their faster or lower chair stand time, they would end up with ADL disability incidence at follow-up.

We did not have enough sample size to go further in age-stratification. For instance, in the merged population of SAGE Mexico and the TSHA, 77% of the participants were younger than 80 (Table 3.1). This limits our ability to further characterize this population, and widened the confidence intervals from the estimates in this age group (Table 3.2). We applied bootstrap for the estimation of cut points and AUROC to compensate this limitation as shown in Table 3.2.

Another limitation was the lack of a biomarker of biological age and an indicator of an acute event or injury in the TSHA. (108) Ideally, we would need to have enough participants in each age five-year age group with data on a biological age biomarker and an indicator of acute injury to test which of these variables allows to better discriminate the incident ADL outcome according to chair stand test.

Figure 5.1 Distributional plots for the chair stand time by ADL incidence status at follow-up



Source: the author. The frequency distribution of the chair stand times is shown in the x axis (seconds needed to perform five-chair stands). The curves reach a high point at the highest frequency in the study sample.

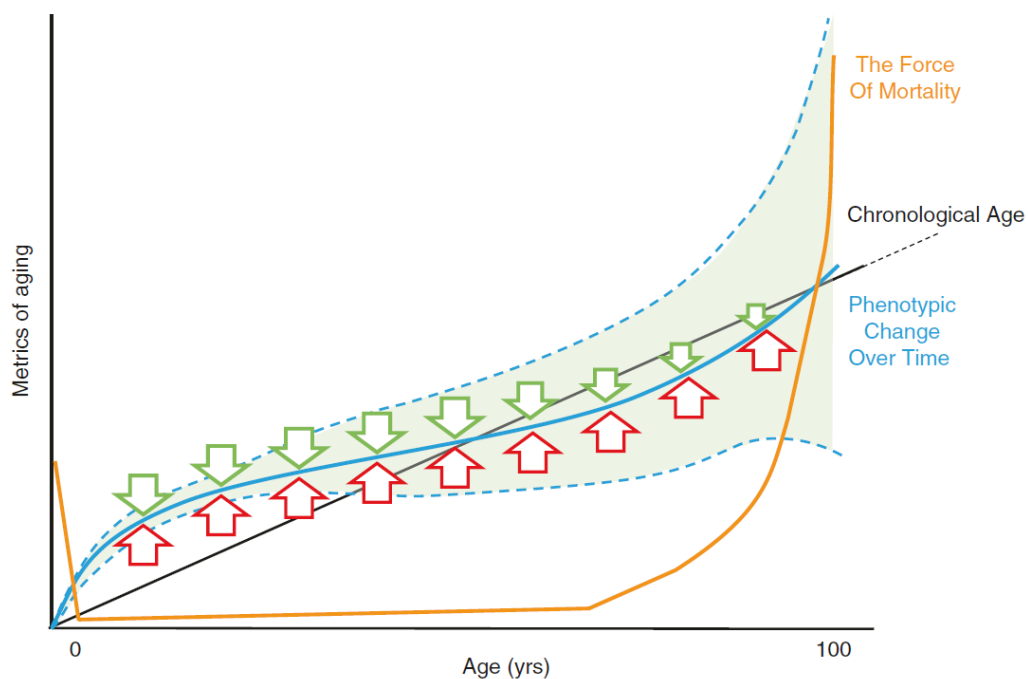
5.4 The interplay of the chronological and phenotypical metrics of aging

The cut points and clinically meaningful changes for the chair stand test to predict disability are an empirical problem implying the interplay of chronological and phenotypical age with a functional outcome. The scope of this thesis was limited because it did not explore the role of biological aging in this relationship.

The interplay of the chronological and phenotypical metrics of aging is represented in Figure 5.2 extracted from a text by Ferrucci and Orini (29). In the figure, we find that chronological age is a linear function of time. Phenotypic age is represented here with a non-linear line to represent the accelerated changes during adolescence followed by a relative stability in young adulthood, and then a second phase of accelerated changes in old age. The heterogeneity in the

phenotypic age (i.e., how different can the phenotypic age be for a same chronological age) widens for older ages. Ferrucci and Orini suggest that the narrow variance in the early life course corresponds to the predominance of a genetic timing. Variability increases for older ages because of the growing influence of stochastic and environmental factors that might pose a challenge to health (red arrows). The homeodynamic mechanisms that build resilience are represented by the green arrows. (152) They tend to be smaller at the end of life, as resilience and physiological reserves waste away. Finally, the force of mortality is represented by an orange line.

Figure 5.2 The interplay of the chronological, biological, and phenotypical metrics of aging



Source: Ferrucci and Orini. Comprehensive geriatric assessment, an updated perspective. (29)

Ferrucci and Orini use this diagram in the context of the comprehensive geriatric assessment (CGA –see chapter 1-). They claim that the CGA aims to capture the green area. Therefore, given the results of older adults CGA, the health care team should be able to know not only their phenotypic age –i.e., the point along the blue line), but also the state of the equilibrium between the challenging and resilience forces, i.e., the size of the green and the red arrows.

Physical resilience measurement is still an incipient issue in Geriatrics. For instance, there is a standardized test to calculate the amount of pancreatic reserve –the glucose tolerance test-. Yet, there is no such test to calculate the amount of physiological reserve, nor physical resilience. (153–157)

The aims and scope of ICOPE Step 1 are not as extended as the CGA. However, it offers a huge potential to go beyond the risk stratification approach described in section 1.6. From a “translational science” point of view, we need to further work on the application of ICOPE Step 1. For example, we could use the chair stand test (as a continuous variable) as an indicator of phenotypic age. The chair stand test captures the locomotion domain of IC with a cardinal role on functional ability as described in section 1.9 of this thesis. Furthermore, in the five-repetition chair stand, people are asked to perform it as fast as possible. It is a submaximal test requiring the integration of several systems (muscle strength and power, bone, proprioception/balance). This provides an indication of the maximum capacity of individual’s body to cope.

5.5 Non-linear functional decline with aging: Implications for health measurement in older people

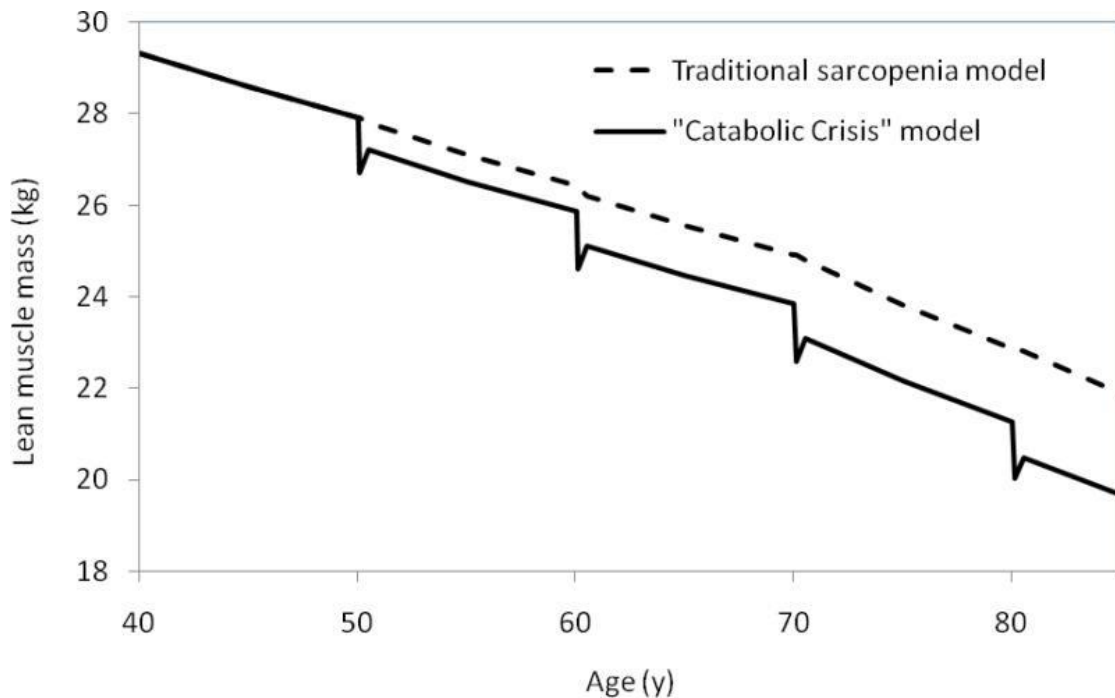
The function-based paradigm, vis a vis the disease-centred paradigm, can have a deeper impact in older people’s reality. Yet, health systems around the globe need information to improve their service to older populations.(158) Better characterising functional loss in older adults provides information useful for designing disability-prevention interventions.

There seems to be a turning point for mobility function around the age of 80 years.

Studies of the loss of muscle mass and function have described a constant and linear decline in muscle mass since the third decade of life. On the other hand, muscle mass might follow a non-linear loss, under the influence of factors like the catabolic crisis or anabolic resistance.

(159,160) Figure 5.4 shows how the catabolic crisis might theoretically diverge from the linear decline in lean muscle mass through the life course.

Figure 5.4 Trajectories of lean muscle mass according to the linear sarcopenia model and the catabolic crisis model



Proposed model of age-related muscle loss punctuated by episodes of acute illness or injury and characterized by accelerated muscle loss and incomplete recovery.

Source: English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. *Curr Opin Clin Nutr Metab Care*. 2010 Jan;13(1):34-9. doi: 10.1097/MCO.0b013e328333aa66. PMID: 19898232; PMCID: PMC3276215.

It might be that around the age of 80, the behavioral and physiological interacting factors contributing to muscle mass loss are more likely to coincide. I.e., resistance to anabolic stimuli, leading to suppressed muscle protein synthesis and inhibited suppression of muscle protein breakdown, plus inactivity and immobilization, exacerbation of atrophic responses and a failure to fully recover from acute insults. (160)

In Hispanic population-based studies, the 80+ age group has shown disproportionately higher frailty index and sarcopenia prevalence compared to the 70-79 age group. (161,162)

Observational studies have shown that muscle mass tends to be rather stable between the third

and the sixth decades of life, with a tipping-point of loss of muscular appendicular mass starting at age 60 with significantly lower values of fat-free mass after age 75. (163)

In the same vein, studies of the functional loss for ADL have found remarkable differences between adults before and after the age of 80. For example, Covinsky and cols. reported that the percentage of older adults with decline in ADL functionality in a hospitalization setting between baseline and discharge was 23%, 28%, 38%, 50%, and 63% in patients aged 70–74, 75–79, 80–84, 85–89, and ≥ 90 , respectively, $P < .001$. (164) The IC mobility domain is particularly sensitive to hospitalization-related bed rest. (165)

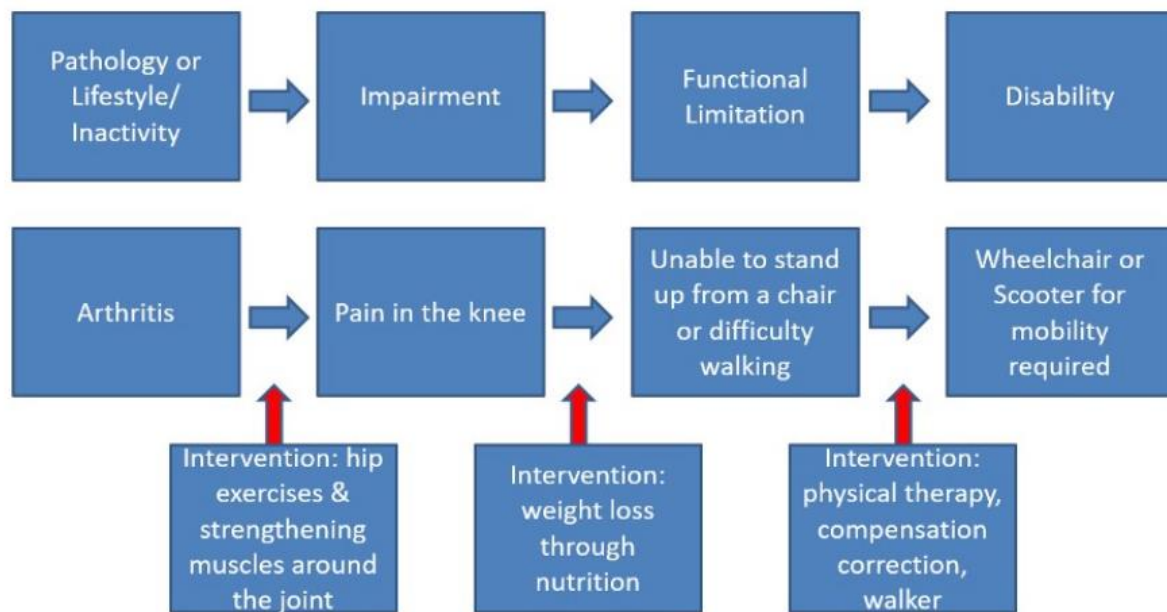
Further research is needed to explore the life course trajectory of IC domains and physical function in older adults, ideally with a continuous measurement. It is not clear whether the domains of intrinsic capacity exhibit an inflexion point around the chronological age of 80 and how the determinants of biological age intertwine in such trajectories.

5.6 The challenges of predicting incident disability based on physical impairments in older adults

The accuracy of our models predicting incident disability is not high. Other authors have reported similar results. (114). Predicting incident disability in older adults entails several challenges because it does not follow a direct causality with a clearly identified necessary cause. (142)

According to the biopsychosocial disablement process model(17), pathologies occurring at one anatomical place/organ or one physiological system might cause impairments (abnormality at the organ, tissue or system level). Those physical impairments would cause functional limitations. (19)

Figure 5.5 The Nagi model applied to optimal aging



Source: Blackburn (2020)(166)

The mechanisms behind the disablement process gain in complexity as we go upstream from pathologies to impairments and limitations. In the disablement process, causality for the first element (pathology) is more well-known as it has been the focus of medical science for hundreds of years. For example, causality in infectious diseases is direct because there is one necessary cause i.e., the biological agent. Other determinants such as the host's immune response are also important but not sufficient causes.

On the other hand, it is troublesome to think of a necessary cause for disability. For the cases of sudden disability, like breaking an ankle while skiing, there might be no background active pathology nor previous functional limitation (a bit of bad luck?). On the other hand, for the type of disability that will be long-lasting, then we might think of two possibilities: a) the abrupt incidence following an acute (worsening of a) pathological event (e.g. stroke) and b) the chronic progression from functional limitations to impairments and disability. In these cases, pathology can be a necessary cause, but in case of b), the presentation or absence of disability will be

mediated by the amount of individual physical reserve. In other words, there direct impact of pathology via impairments can be buffered by compensatory mechanisms. This explains why there are older adults with hypertension or diabetes who have preserved functionality.

Timing is crucial when referring to the chronic progression from limitations to disability. One way of measuring such chronicity is through the aging process. Angioni et al. defined age-related frailty as the occurrence of physical frailty not related to the comorbidities known at baseline or to the clinical events occurring during the follow-up period but occurring with advancing age. (167) They defined frailty related to diseases as the occurrence of physical frailty related to one or more intervening medical events occurring during follow-up. They classified 42% as age-related frailty, 27% as frailty related to diseases, and the rest as frailty from uncertain origin in the MAPT study n=195. Older adults classified as age-related frailty were chronologically younger and showed a lower burden of chronic diseases. They seemed to have undergone lower deficit accumulation. (168)

In this thesis, the ROC AUC of our models in Chapter 3 suggest that lower limb power (along with sex and age) explains 60% of the factors leading to disability. We also found that improvements in strength impact function more in those with low baseline strength than in those with higher baseline strength. (62)

The C statistic of predictive power in the models in Chapter 2 ranged from 0.7 to 0.83. This suggests that including the rest of the intrinsic capacity domains in the model -even if measured with a Step 1 approach- significantly improves the prediction of disability.

Yet, there is 17% of non-explained factors, which could be due to a) physical reserves not measured by intrinsic capacity – step 1- domains, b) biological age -partially captured by

chronological age- and c) environmental factors that can act as buffers of aggravators of the disabling cascade.

To increase the accuracy in incident disability prediction at an individual level, it would be highly recommended to add biomarkers of physiological reserve -grip strength, appendicular muscle mass index DXA-, biological age –e.g., GDF-15- and environmental factors -level of education, wealth-.

Lastly, a relevant factor is the latency between the IC impairments and incident disability. So far, the classical literature on clinimetrics approach the screening tools assuming a cross-sectional design. i.e., there is not time gap between the screening and the diseased/ non-diseases status. In our case, the time gap between the screening and the observed outcome adds a source of variability. Thus the importance of completing the validation of the ICOPE Step 1 tool with a prospective design and the estimation of reliability parameters.

5.7 Future directions

There are pending tasks to complete the evaluation of the clinimetric properties of the ICOPE Step 1 screening tool: examine reliability and responsiveness or sensitiveness to change. Additionally, the validity of the ICOPE Step 1 tool should be assessed using a prospective approach in different populations and settings.

The validation process of the ICOPE Step 1 screening tool is incomplete. “Validation efforts are integrative, subjective, and can be based on different sources of evidence such as theory, logical argument, and empirical evidence”(169). Our results from the study in Chapter 2 suggest that the ICOPE Step 1 tool might serve to identify older adults at higher risk of disability. Yet, we cannot be sure about the validity of the inferences we can obtain from the ICOPE screening

tool because we did not use the exact ICOPE instrument and because we did not use a population-based study.

We envision that the INSPIRE ICOPE care cohort would allow going further in the validity and reliability assessment of the ICOPE Step 1 approach in users of the French health system in Occitanie region. Briefly, this study counts on repeated measures of the ICOPE Step 1 screening in community-dwelling adults who are using the French health system in a regular basis. (12) The INSPIRE ICOPE Care study is a very relevant cohort that applied an ICOPE Step 1 assessment to 10 903 older people between January 1st, 2020, and November 18th, 2021, from who 70.4% had a 6-month follow-up evaluation. Additionally, 9.3% of the baseline sample underwent an in-depth functional assessment corresponding to the ICOPE Step 2. (12) This study offers the opportunity to advance on the validation of the ICOPE Step 1 tool because of its large amount of data and the available variables. For instance, in the subgroup with in-depth evaluations we could estimate not only sensitivity and specificity, but also the predictive ability towards disability and frailty.

In addition, recall our findings in chapter 2 about the locomotion domain of IC being more strongly related to the incident outcomes. This finding triggers a question on the use of weights for the IC domains to obtain an IC score. The aim of the ICOPE Step 1 is not to accurately measure IC. Yet may the use of domain-tailored weights improve its predictive ability for incident disability? We might explore this question using the INSIPRE ICOPE Care cohort, too.

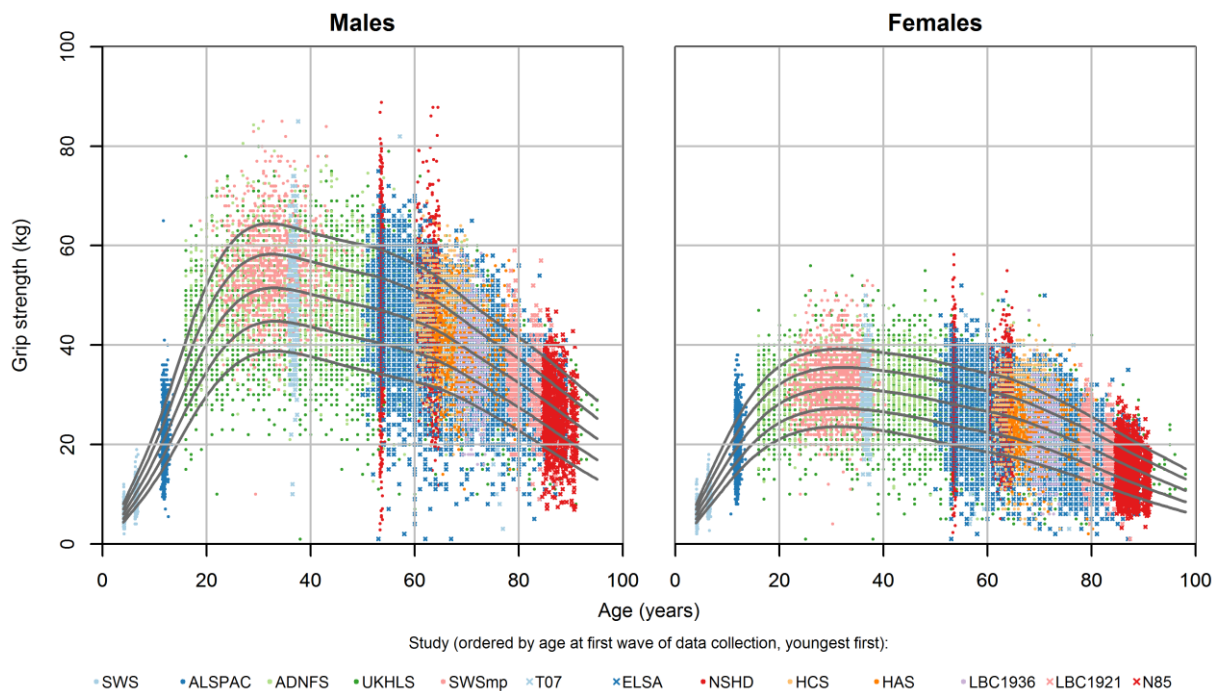
On the other hand, responsiveness to change would need to be measured in a clinical trial to test the responsiveness of the ICOPE Step 1 score to a specific intervention.

From a translational science point of view, there are still potential “upgrades” of ICOPE step 1. Potential future directions for my research career include addressing the methodological prerequisites for further development of the intrinsic capacity assessment. For example, centile curves for intrinsic capacity across the life course.

Dr. Richard Dodds (r.i.p.) and cols. compiled and modelled the centile curves for grip strength from a dozen of British studies for ages 4 to 90. (170) They obtained gender-specific peak means for each age and defined weak grip strength as 2.5 standard deviations below the mean. (Figure 5.6) Their study provided one of the first empirical examples of a measure of a physiological reserve that is feasible across the life course. Grip strength was also used as a marker of the vitality domain by Beard and cols. in the pioneer paper on intrinsic capacity validation. (21)

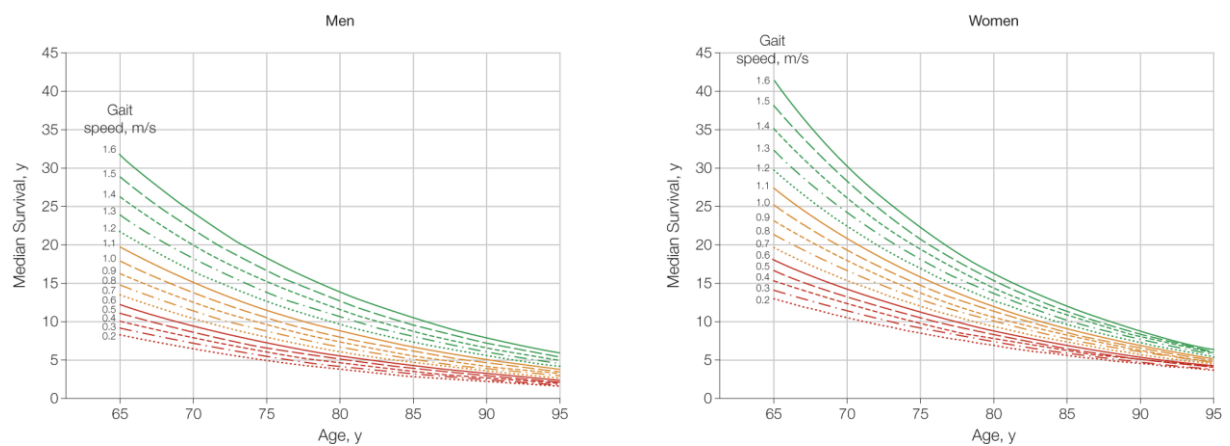
Another example are the centile curves for the walking speed produced by Studenski et al. (171) Using nine cohort studies from the USA, the researchers modelled the centile curves of gait speed by sex for ages 65 to 90. They presented their centile curves in a creative way by linking gait speed with the predicted median survival by age and sex. (Figure 5.7) One limitation of gait speed being the impossibility for immobilized/paraplegic people.

Figure 5.6 Cross-cohort centile curves for grip strength from twelve British studies



Source: Dodds, R. M. *et al.* Grip strength across the life course: Normative data from twelve British studies. *PLoS One* 9, (2014).

Figure 5.7 Centile curves of gait speed and median survival time by sex and age



Source: Studenski, S. *et al.* Gait speed and survival in older adults. *JAMA* 305, 50–58 (2011).

In the future, there will be growing data availability in line with the phenotypical age measurement and/or intrinsic capacity. We will be able to compile several prospective studies from a country or region to produce the centile curves of a validated summary measurement of intrinsic capacity. There is room for improvement in the measurement of domains like vitality.

For example, Kelly Virecoulon et al. have compared different operationalizations of vitality using the MAPT data. (172) Wan Hsuan Lu is working on that question exploring how inflammation biomarkers can represent the vitality domain of IC (internal communication of unpublished work). Both researchers are part of the team of the Institute of Aging and work under the scope of the INSPIRE project of the CHU Toulouse. (173)

On the other hand, some caveats for the life course application of functional tests across the life course are its floor and ceiling effects. (174) In this thesis we have proposed the age-stratified cut points as one solution for this limitation in people aged 80 and over. Alternatively, the test could be adapted for to increase sensitivity in younger population, for instance by using the number of chair stands in 30 seconds. (111) Roberta Rikli et al. developed the 30-seconds chair stand test. According to one of their reports, (175) they aimed at filling in the gap of the lower-limb functional test for older adults and overcoming the ceiling effects of the balance test in the SPPB and the floor effects in the five-repetition chair stand test from the same battery. (100) Normative values have been published for adults aged 60 and older. (176)

We can imagine future person-centred medicine screenings that integrate phenotypical, and potentially self-perceived and biological age. Based on basic screening data transferred to an informatic device, health care providers might offer the best interventions to preserve intrinsic capacity and maintain resilience, anytime along the second half of the life course.

Among the next steps in my career, I would like to use Epidemiological methods to foster healthy aging in the community and hospital contexts. There are some examples already in place: simple tests e.g., the chair stand test have been loaded into a mobile app to calculate more informative variables like the leg power. (177) We could go beyond that by adding multimedia data e.g., a picture of the participant's face or a voice recording (following informed consent).

Integrating a few but very representative markers of the phenotypical and biological age we could give a step forward in the person-centred health care provision.

I would also like to acquire experience on designing and conducting prospective studies. I have taken the first step by writing a grant application on the impact of the ICOPE program in the Occitania region of France for the IRESP (Public Health Research Institute of France).

Overall, the gold standard for healthy aging is what allows older adults to be and do what is meaningful for them. Thus, the dialogue between health care providers and older adults is crucial and cannot be replaced, even by the most sophisticated algorithm.

Conclusions

We have contributed to the validation process of a screening tool for intrinsic capacity impairments in older adults towards the risk of incident disability, with a focus on the locomotion domain.

Each additional IC impairment increased the risk of disability for ADLs by 23% in MAPT participants, with a good predictive ability. Having less than two IC impairments might be a sign of very low risk of incident frailty or disability in the next few years.

The cut points found for the chair stand test were 14 seconds for the 70-79 age group and 16 seconds for those aged 80+ for incident ADL disability. Changing the current cut point of 14 seconds to 16 in adults aged 80 and over leads to improvements of up to 42% in clinimetric parameters.

Absolute meaningful changes for the five-repetition chair stand time ranged from 0.5 s to 1.7 s and from 3.0 s to 4.7 s applying distribution-based and anchor-based methods, respectively. Relative meaningful changes ranged from 9.6% to 30.4% using distribution-based and anchor-based methods, respectively.

Extending the knowledge on the clinimetric properties and clinically meaningful change in the chair stand test can contribute to improve the ICOPE Step 1 screening tool.

References

1. Ham-Chande R, Nava-Bolaños I. Convergence Toward Demographic Aging in Latin America and the Caribbean. *Annu Rev Sociol* [Internet]. 2019 Jul 30;45(1):607–23. Available from: <https://doi.org/10.1146/annurev-soc-073018-022532>
2. United Nations D of E and SA. *World Population Ageing 2019: Highlights*. 2019.
3. Mendenhall E, Weaver LJ. Reorienting women’s health in low- and middle-income countries: The case of depression and Type 2 diabetes. *Glob Health Action*. 2014;7(1):1–4.
4. Gómez-Dantés H, Fullman N, Lamadrid-Figueroa H, Cahuana-Hurtado L, Darney B, Avila-Burgos L, et al. Dissonant health transition in the states of Mexico, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* (London, England). 2016 Nov;388(10058):2386–402.
5. Lozano R, Fullman N, Mumford JE, Knight M, Barthelemy CM, Abbafati C, et al. Measuring universal health coverage based on an index of effective coverage of health services in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* (London, England) [Internet]. 2020 Oct 17 [cited 2022 Jul 17];396(10258):1250–84. Available from: <https://pubmed.ncbi.nlm.nih.gov/32861314/>
6. Rechel B, Doyle Y, Grundy E, Mckee M. How can health systems respond to population ageing? [Internet]. WHO Regional Office for Europe and European Observatory on Health Systems and Policies, Govin Permanand, editors. Copenhagen; 2009 [cited 2022 May 18]. Available from: <http://www.euro.who.int/pubrequest>
7. Organización Panamericana de la Salud/Organización Mundial de la Salud. Portal de Indicadores Básicos. [Internet]. Portal de Indicadores Básicos. 2021 [cited 2022 May 24]. Available from: <https://opendata.paho.org/es/indicadores-basicos/sobre-los-datos>
8. World Health Organization. *World Report on Ageing and Health*. Geneva: WHO Press; 2015.
9. Pan American Health Organization. *Health in the Americas+, 2017 Edition. Summary: Regional Outlook and Country Profiles* [Internet]. Health in the Americas+, 2017 Edition. Summary: Regional Outlook and Country Profiles. 2019 [cited 2021 Jun 3]. Available from: <https://iris.paho.org/handle/10665.2/34321>
10. WHO. WHO | Integrated Care for Older People [Internet]. WHO. World Health Organization; 2018 [cited 2018 Jul 27]. Available from: <http://www.who.int/ageing/health-systems/icope/en/>
11. World Health Organization. *Agenda 2030* [Internet]. 2021 [cited 2022 Apr 26]. (Decade of Healthy Ageing Connection Series No. 2). Report No.: 2. Available from: <https://www.who.int/publications/m/item/decade-of-healthy-ageing-connection-series-no2>
12. Tavassoli N, de Souto Barreto P, Berbon C, Mathieu C, de Kerimel J, Lafont C, et al. Implementation of the WHO integrated care for older people (ICOPE) programme in clinical practice: a prospective study. *Lancet Heal Longev* [Internet]. 2022 Jun 1 [cited 2022 Jul 18];3(6):e394–404. Available from: <http://www.thelancet.com/article/S2666756822000976/fulltext>
13. Beard JR, Officer A, De Carvalho IA, Sadana R, Pot AM, Michel JP, et al. The World report on ageing and health: A policy framework for healthy ageing. Vol. 387, *The Lancet*. Lancet Publishing Group; 2016. p. 2145–54.
14. Beard JR, Jotheeswaran AT, Cesari M, Araujo de Carvalho I. The structure and predictive value of intrinsic capacity in a longitudinal study of ageing. *BMJ Open* [Internet]. 2019 Nov 2 [cited 2019 Nov 7];9(11):e026119. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/31678933>
15. Chatterji S, Ustün BL, Sadana R, Salomon JA, Mathers CD, Murray CJ. The conceptual basis for measuring and reporting on health. Geneva; 2002. (Global Programme on Evidence for Health Policy Discussion Paper No. 45).
16. Cesari M, De Carvalho IA, Thiyagarajan JA, Cooper C, Martin FC, Reginster JY, et al. Evidence for the domains supporting the construct of intrinsic capacity. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2018;73(12):1653–60.
17. OMS. *The International Classification of Functioning, Disability and Health (ICF)*. Vol. 18. Geneva; 2001 Jan.
18. Hall JE, Hall ME. *Guyton and Hall Textbook of Medical Physiology* [Internet]. Elsevier Health

- Sciences; 2020 [cited 2022 Jul 19]. (Guyton Physiology). Available from: <https://books.google.co.id/books?id=H1rrDwAAQBAJ>
19. Verbrugge LM, Jette AM. The disablement process. *Soc Sci Med* [Internet]. 1994 [cited 2020 Nov 3];38(1):1–14. Available from: <https://pubmed.ncbi.nlm.nih.gov/8146699/>
 20. Cesari M, Penninx BWJH, Pahor M, Lauretani F, Corsi AM, Williams GR, et al. Inflammatory markers and physical performance in older persons: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* [Internet]. 2004 [cited 2022 Aug 10];59(3):242–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/15031308/>
 21. Beard JR, Jotheeswaran AT, Cesari M, Araujo De Carvalho I. The structure and predictive value of intrinsic capacity in a longitudinal study of ageing. *BMJ Open*. 2019 Nov 1;9(11).
 22. Araujo De Carvalho I, Martin C, Cesari M, Sumi Y, Thiagarajan JA, Beard J. Operationalising the concept of intrinsic capacity in clinical settings. 2017;(November):31. Available from: <https://www.who.int/ageing/health-systems/clinical-consortium/CCHA2017-backgroundpaper-1.pdf>
 23. Morley JE. A brief history of geriatrics. *J Gerontol A Biol Sci Med Sci*. 2004 Nov;59(11):1132–52.
 24. Matthews DA. Dr. Marjory Warren and the origin of British geriatrics. *J Am Geriatr Soc*. 1984 Apr;32(4):253–8.
 25. Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impacts of geriatric evaluation and management programs on defined outcomes: overview of the evidence. *J Am Geriatr Soc*. 1991 Sep;39(9 Pt 2):8S-16S; discussion 17S-18S.
 26. Stuck AE, Siu AL, Wieland GD, Adams J, Rubenstein LZ. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* (London, England). 1993 Oct;342(8878):1032–6.
 27. Rubenstein LZ, Josephson KR, Wieland GD, English PA, Sayre JA, Kane RL. Effectiveness of a geriatric evaluation unit. A randomized clinical trial. *N Engl J Med*. 1984 Dec;311(26):1664–70.
 28. Wellens NIH, Deschodt M, Flamaing J, Moons P, Boonen S, Boman X, et al. First-generation versus third-generation comprehensive geriatric assessment instruments in the acute hospital setting: a comparison of the Minimum Geriatric Screening Tools (MGST) and the interRAI Acute Care (interRAI AC). *J Nutr Health Aging*. 2011 Aug;15(8):638–44.
 29. Ferrucci L, Orini S. Comprehensive Geriatric Assessment: An Updated Perspective. In: Pilotto A, Martin FC, editors. *Comprehensive Geriatric Assessment* [Internet]. Springer International Publishing; 2018 [cited 2022 Oct 7]. (Practical Issues in Geriatrics). Available from: <http://link.springer.com/10.1007/978-3-319-62503-4>
 30. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen MLG, Extermann M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol Off J Am Soc Clin Oncol*. 2014 Aug;32(24):2595–603.
 31. Pilotto A, Cella A, Pilotto A, Daragjati J, Veronese N, Musacchio C, et al. Three Decades of Comprehensive Geriatric Assessment: Evidence Coming From Different Healthcare Settings and Specific Clinical Conditions. *J Am Med Dir Assoc*. 2017 Feb;18(2):192.e1-192.e11.
 32. Pilotto A, Martin FC, editors. *Comprehensive Geriatric Assessment*. Springer International Publishing; 2018. (Practical Issues in Geriatrics).
 33. Kinsella K, He W. An Aging World: 2008 International Population Reports [Internet]. 2009 [cited 2022 Oct 7]. Report No.: P95/09-1. Available from: <http://envejecimiento.csic.es/documentos/documentos/aging-nia-02.pdf>
 34. World Health Organization. Integrated care for older people (ICOPE): Guidance for person-centred assessment and pathways in primary care. [Internet]. Geneva: WHO; 2019 [cited 2019 Nov 14]. 87 p. Available from: <https://apps.who.int/iris/bitstream/handle/10665/326843/WHO-FWC-ALC-19.1-eng.pdf?sequence=17>
 35. Stolz E, Mayerl H, Freidl W, Roller-Wirnsberger R, Gill TM. Intrinsic Capacity Predicts Negative Health Outcomes in Older Adults. *Journals Gerontol Ser A* [Internet]. 2022 Jan 7 [cited 2022 Feb 3];77(1):101–5. Available from: <https://academic.oup.com/biomedgerontology/article/77/1/101/6375807>
 36. Gutiérrez-Robledo LM, García-Chanes RE, González-Bautista E, Rosas-Carrasco O.

- Validation of Two Intrinsic Capacity Scales and Its Relationship With Frailty And Other Outcomes In Mexican Community-Dwelling Older Adults. *J Nutr Health Aging* [Internet]. 2020 Dec 23 [cited 2021 Jan 19];25(1):33–40. Available from: <https://link.springer.com/article/10.1007/s12603-020-1555-5>
37. Salinas-Rodríguez A, González-Bautista E, Rivera-Almaraz A, Manrique-Espinoza B. Longitudinal trajectories of intrinsic capacity and their association with quality of life and disability. *Maturitas*. 2022 Jul;161:49–54.
 38. Beard JR, Si Y, Liu Z, Chenoweth L, Hanewald K. Intrinsic Capacity: Validation of a New WHO Concept for Healthy Aging in a Longitudinal Chinese Study. *Journals Gerontol Ser A* [Internet]. 2022 Jan 7 [cited 2022 May 6];77(1):94–100. Available from: <https://academic.oup.com/biomedgerontology/article/77/1/94/6338147>
 39. World Health Organization. Clinical Consortium on Healthy Ageing [Internet]. 2022 [cited 2022 Jul 19]. Available from: <https://www.who.int/groups/clinical-consortium-on-healthy-ageing>
 40. Streiner D, Norman G. *Health Measurement Scales*. 2nd ed. Great Britain: Oxford; 2001.
 41. Ma L, Chhetri JK, Zhang Y, Liu P, Chen Y, Li Y, et al. Integrated Care for Older People Screening Tool for Measuring Intrinsic Capacity: Preliminary Findings From ICOPE Pilot in China. *Front Med*. 2020;7:576079.
 42. Leung AYM, Su JJ, Lee ESH, Fung JTS, Molassiotis A. Intrinsic capacity of older people in the community using WHO Integrated Care for Older People (ICOPE) framework: a cross-sectional study. *BMC Geriatr* [Internet]. 2022;22(1):304. Available from: <https://doi.org/10.1186/s12877-022-02980-1>
 43. Cheng YC, Kuo YC, Chang PC, Li YC, Huang WT, Chen W, et al. Geriatric Functional Impairment Using the Integrated Care for Older People (ICOPE) Approach in Community-Dwelling Elderly and Its Association with Dyslipidemia. *Vasc Health Risk Manag* [Internet]. 2021 [cited 2022 Jul 18];17:389. Available from: [/pmc/articles/PMC8274513/](https://pubmed.ncbi.nlm.nih.gov/35274513/)
 44. Tavassoli N, Piau A, Berbon C, De Kerimel J, Lafont C, De Souto Barreto P, et al. Framework Implementation of the INSPIRE ICOPE-CARE Program in Collaboration with the World Health Organization (WHO) in the Occitania Region. *J frailty aging*. 2021;10(2):103–9.
 45. Liu S, Yu XX, Wang XP, Li JJ, Jiang S, Kang L, et al. Intrinsic Capacity predicts adverse outcomes using Integrated Care for Older People screening tool in a senior community in Beijing. *Arch Gerontol Geriatr*. 2021 May 1;94:104358.
 46. Liu S, Kang L, Liu XH, Zhao SQ, Wang XP, Li JJ, et al. Trajectory and Correlation of Intrinsic Capacity and Frailty in a Beijing Elderly Community. *Front Med*. 2021 Dec 9;8:2456.
 47. Zeng X, Shen S, Xu L, Wang Y, Yang Y, Chen L, et al. The Impact of Intrinsic Capacity on Adverse Outcomes in Older Hospitalized Patients: A One-Year Follow-Up Study. *Gerontology* [Internet]. 2021 Jun 1 [cited 2022 Jul 27];67(3):267–75. Available from: <https://www.karger.com/Article/FullText/512794>
 48. González-Bautista E, Barreto PDS, Giudici KV, Andrieu S, Rolland Y, Vellas B. Frequency of Conditions Associated with Declines in Intrinsic Capacity According to a Screening Tool in the Context of Integrated Care for Older People. *J Frailty Aging* 2020 [Internet]. 2020 Aug 7 [cited 2020 Aug 10];1–9. Available from: <https://link.springer.com/article/10.14283/jfa.2020.42>
 49. Ma L, Chhetri JK, Zhang L, Sun F, Li Y, Tang Z. Cross-sectional study examining the status of intrinsic capacity decline in community-dwelling older adults in China: prevalence, associated factors and implications for clinical care. *BMJ Open* [Internet]. 2021 Jan 1 [cited 2022 Jul 27];11(1):e043062. Available from: <https://bmjopen.bmj.com/content/11/1/e043062>
 50. Ramírez-Vélez R, Correa-Bautista JE, García-Hermoso A, Cano CA, Izquierdo M. Reference values for handgrip strength and their association with intrinsic capacity domains among older adults. *J Cachexia Sarcopenia Muscle* [Internet]. 2019 Apr 6 [cited 2019 Nov 14];10(2):278–86. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/jcsm.12373>
 51. Prince MJ, Acosta D, Guerra M, Huang Y, Jacob KS, Jimenez-Velazquez IZ, et al. Intrinsic capacity and its associations with incident dependence and mortality in 10/66 Dementia Research Group studies in Latin America, India, and China: A population-based cohort study. *PLoS Med*. 2021 Sep 1;18(9).
 52. Zhao J, Chhetri JK, Chang Y, Zheng Z, Ma L, Chan P. Intrinsic Capacity vs. Multimorbidity:

- A Function-Centered Construct Predicts Disability Better Than a Disease-Based Approach in a Community-Dwelling Older Population Cohort. *Front Med*. 2021 Sep 28;8:1656.
53. López-Ortiz S, Lista S, Peñín-Grandes S, Pinto-Fraga J, Valenzuela PL, Nisticò R, et al. Defining and assessing intrinsic capacity in older people: A systematic review and a proposed scoring system. *Ageing Res Rev*. 2022 Aug 1;79:101640.
 54. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of Illness in the Aged: The Index of ADL: A Standardized Measure of Biological and Psychosocial Function. *JAMA* [Internet]. 1963 Sep 21 [cited 2022 Jul 25];185(12):914–9. Available from: <https://jamanetwork.com/journals/jama/fullarticle/666768>
 55. Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *J Am Geriatr Soc* [Internet]. 1983 [cited 2022 Jul 25];31(12):721–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/6418786/>
 56. Villalobos Dintrans P, González Bautista E. Functional Dependency in Mexico: Measurement Issues and Policy Challenges. *Int J Heal policy Manag*. 2020 Dec;
 57. Jette AM. Toward a Common Language for Function, Disability, and Health. *Phys Ther* [Internet]. 2006 May 1 [cited 2022 Jul 26];86(5):726–34. Available from: <https://academic.oup.com/ptj/article/86/5/726/2857468>
 58. NAGI SZ. A Study in the Evaluation of Disability and Rehabilitation Potential: CONCEPTS, METHODS, AND PROCEDURES. *Am J Public Heal Nations Heal* [Internet]. 1964 [cited 2022 Jul 26];54(9):1568. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1255011/>
 59. Jung H, Tanaka S, Iwamoto Y, Kawano T, Yamasaki M, Tanaka R. Reductions in Muscle Strength and Range of Motion Cause Locomotion Disability via Locomotion-Related Functional Limitation in Japanese Older Adults: A Cross-Sectional Study. *J Aging Res* [Internet]. 2021 [cited 2022 Aug 9];2021. Available from: [/pmc/articles/PMC8282387/](https://pubmed.ncbi.nlm.nih.gov/pmc/articles/PMC8282387/)
 60. Dodds RM, Murray JC, Granic A, Hurst C, Uwimpuhwe G, Richardson S, et al. Prevalence and factors associated with poor performance in the 5-chair stand test: findings from the Cognitive Function and Ageing Study II and proposed Newcastle protocol for use in the assessment of sarcopenia. *J Cachexia Sarcopenia Muscle*. 2021;12(2):308–18.
 61. BOHANNON RW. Reference Values for the Five-Repetition Sit-To-Stand Test: a Descriptive Meta-Analysis of Data From Elders. *Percept Mot Skills*. 2006;103(5):215.
 62. Ferrucci L, Guralnik JM, Buchner D, Kasper J, Lamb SE, Simonsick EM, et al. Departures From Linearity in the Relationship Between Measures of Muscular Strength and Physical Performance of the Lower Extremities: The Women’s Health and Aging Study. *Journals Gerontol Ser A* [Internet]. 1997 Sep 1 [cited 2022 Jul 26];52A(5):M275–85. Available from: <https://academic.oup.com/biomedgerontology/article/52A/5/M275/617519>
 63. Alcazar J, Losa-Reyna J, Rodriguez-Lopez C, Alfaro-Acha A, Rodriguez-Mañas L, Ara I, et al. The sit-to-stand muscle power test: An easy, inexpensive and portable procedure to assess muscle power in older people. *Exp Gerontol*. 2018 Oct 2;112:38–43.
 64. Bean JF, Kiely DK, Herman S, Leveille SG, Mizer K, Frontera WR, et al. The Relationship Between Leg Power and Physical Performance in Mobility-Limited Older People. *J Am Geriatr Soc* [Internet]. 2002 Mar 1 [cited 2022 Jul 26];50(3):461–7. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1046/j.1532-5415.2002.50111.x>
 65. Evans WJ. Exercise Strategies Should Be Designed to Increase Muscle Power. *Journals Gerontol Ser A* [Internet]. 2000 Jun 1 [cited 2022 Jul 26];55(6):M309–10. Available from: <https://academic.oup.com/biomedgerontology/article/55/6/M309/2948065>
 66. Brown M, Fisher JS, Salsich G. Stiffness and muscle function with age and reduced muscle use. *J Orthop Res* [Internet]. 1999 [cited 2022 Jul 26];17(3):409–14. Available from: <https://pubmed.ncbi.nlm.nih.gov/10376731/>
 67. Hardy R, Cooper R, Shah I, Harridge S, Guralnik J, Kuh D. Is chair rise performance a useful measure of leg power? *Aging Clin Exp Res*. 2010;22(5–6):412–8.
 68. Gonzalez-Bautista E, Andrieu S, Gutiérrez-Robledo LM, García-Chanes RE, De Souto Barreto P. In the Quest of a Standard Index of Intrinsic Capacity. A Critical Literature Review. *J Nutr Health Aging* [Internet]. 2020;(5). Available from: <https://doi.org/10.1007/s12603-020-1394-4>
 69. Rösslein R, Dressel H. [Causes for care dependency in the context of long-term care

- insurance]. *Pflege Z.* 2014 Sep;67(9):558–61.
70. Thiagarajan JA, Araujo de Carvalho I, Peña-Rosas JP, Chadha S, Mariotti SP, Dua T, et al. Redesigning care for older people to preserve physical and mental capacity: WHO guidelines on community-level interventions in integrated care. *PLOS Med* [Internet]. 2019 Oct 18 [cited 2020 Jan 8];16(10):e1002948. Available from: <http://dx.plos.org/10.1371/journal.pmed.1002948>
 71. Vellas B, Carrie I, Gillette-Guyonnet S, Touchon J, Dantoine T, Dartigues JF, et al. MAPT study: A multidomain approach for preventing Alzheimer's disease: design and baseline data. *J Prev Alzheimer's Dis* [Internet]. 2014 Jun [cited 2020 Feb 5];1(1):13–22. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26594639>
 72. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol.* 2017 May 1;16(5):377–89.
 73. Ventry IM, Weinstein BE. The hearing handicap inventory for the elderly: A new tool. *Ear Hear.* 1982;3(3):128–34.
 74. Bagai A. Does This Patient Have Hearing Impairment? *JAMA.* 2008;295(4):416–28.
 75. Yesavage JA, Sheikh JI. Geriatric Depression Scale (GDS). *Clin Gerontol* [Internet]. 1986 Nov 18;5(1–2):165–73. Available from: https://doi.org/10.1300/J018v05n01_09
 76. Fried L, Tangen C. Frailty in older adults evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* [Internet]. 2001 [cited 2014 Jun 11];56A(3):M146–56. Available from: <http://biomedgerontology.oxfordjournals.org/content/56/3/M146.short>
 77. Lawton MP, Brody EM. Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living1. *Gerontologist* [Internet]. 1969 Oct 1;9(3_Part_1):179–86. Available from: https://doi.org/10.1093/geront/9.3_Part_1.179
 78. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist.* 1970;10(1):20–30.
 79. Altman DG, Bland JM. Diagnostic tests. 1: Sensitivity and specificity. *BMJ* [Internet]. 1994 Jun 11 [cited 2022 Aug 24];308(6943):1552. Available from: <https://pubmed.ncbi.nlm.nih.gov/8019315/>
 80. Altman DG, Bland j. M. Diagnostic tests 2: Predictive values. *BMJ* [Internet]. 1994 Jul 9 [cited 2022 Aug 24];309(6947):102. Available from: <https://pubmed.ncbi.nlm.nih.gov/8038641/>
 81. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ.* 2004 Jul 17;329(7458):168–9.
 82. Janssens ACJW, Martens FK. Reflection on modern methods: Revisiting the area under the ROC Curve. *Int J Epidemiol* [Internet]. 2020 Aug 1 [cited 2022 Aug 25];49(4):1397–403. Available from: <https://pubmed.ncbi.nlm.nih.gov/31967640/>
 83. Harrell FEJ, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA.* 1982 May;247(18):2543–6.
 84. Hernán MA. The hazards of hazard ratios. *Epidemiology* [Internet]. 2010 Jan;21(1):13–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/20010207>
 85. Youden WJ. Index for rating diagnostic tests. *Cancer.* 1950;3(1):32–5.
 86. Chaudhry SI, McAvay G, Ning Y, Allore HG, Newman AB, Gill TM. Geriatric impairments and disability: The cardiovascular health study. *J Am Geriatr Soc.* 2010;58(9):1686–92.
 87. Fried LP, Xue Q-L, Cappola AR, Ferrucci L, Chaves P, Varadhan R, et al. Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *J Gerontol A Biol Sci Med Sci* [Internet]. 2009 Oct [cited 2014 Jul 11];64(10):1049–57. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2737590&tool=pmcentrez&rendertype=abstract>
 88. Kuzuya M. Process of physical disability among older adults--contribution of frailty in the super-aged society. *Nagoya J Med Sci* [Internet]. 2012 Feb;74(1–2):31–7. Available from: <https://pubmed.ncbi.nlm.nih.gov/22515109>
 89. Vermeulen J, Neyens JCL, van Rossum E, Spreeuwenberg MD, de Witte LP. Predicting ADL

- disability in community-dwelling elderly people using physical frailty indicators: a systematic review. *BMC Geriatr*. 2011 Jul;11:33.
90. Feng Z, Lugtenberg M, Franse C, Fang X, Hu S, Jin C, et al. Risk factors and protective factors associated with incident or increase of frailty among community-dwelling older adults: A systematic review of longitudinal studies. *PLoS One*. 2017;12(6):e0178383.
 91. Morley JE. Frailty screening comes of age. *J Nutr Health Aging [Internet]*. 2014;18(5):453–4. Available from: <https://doi.org/10.1007/s12603-014-0457-9>
 92. Swenor BK, Lee MJ, Tian J, Varadaraj V, Bandeen-Roche K. Visual Impairment and Frailty: Examining an Understudied Relationship. Magaziner J, editor. *Journals Gerontol Ser A [Internet]*. 2020 Feb 14 [cited 2021 Jan 21];75(3):596–602. Available from: <https://academic.oup.com/biomedgerontology/article/75/3/596/5550824>
 93. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. *J Clin Psychol*. 1986 Jan;42(1):28–33.
 94. Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. *Clin Gerontol*. 1986;5:165–173.
 95. Guerville F, Souto Barreto P, Giudici KV, Rolland Y, Vellas B. Association of 3-Year Multidomain Intervention and Omega-3 Supplementation with Frailty Incidence. *J Am Geriatr Soc [Internet]*. 2019 Aug 6 [cited 2020 Jun 16];67(8):1700–6. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/jgs.15994>
 96. Ávila-Funes JA, Helmer C, Amieva H, Barberger-Gateau P, Le Goff M, Ritchie K, et al. Frailty among community-dwelling elderly people in france: The three-city study. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2008;63(10):1089–96.
 97. Delgado-Rodríguez M, Llorca J. Bias. *J Epidemiol Community Heal [Internet]*. 2004 Aug 1 [cited 2022 Aug 25];58(8):635–41. Available from: <https://jech.bmj.com/content/58/8/635>
 98. Pinsky PF, Miller A, Kramer BS, Church T, Reding D, Prorok P, et al. Evidence of a healthy volunteer effect in the prostate, lung, colorectal, and ovarian cancer screening trial. *Am J Epidemiol [Internet]*. 2007 Apr [cited 2022 Aug 25];165(8):874–81. Available from: <https://pubmed.ncbi.nlm.nih.gov/17244633/>
 99. Froom P, Melamed S, Kristal-Boneh E, Benbassat J, Ribak J. Healthy volunteer effect in industrial workers. *J Clin Epidemiol [Internet]*. 1999 Aug [cited 2022 Aug 25];52(8):731–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/10465317/>
 100. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. *Journals Gerontol*. 1994;49(2).
 101. Seino S, Yabushita N, Kim M-J, Nemoto M, Jung S, Osuka Y, et al. Physical performance measures as a useful indicator of multiple geriatric syndromes in women aged 75 years and older. *Geriatr Gerontol Int*. 2013 Oct;13(4):901–10.
 102. Pinheiro PA, Carneiro JAO, Coqueiro RS, Pereira R, Fernandes MH. “Chair Stand Test” as Simple Tool for Sarcopenia Screening in Elderly Women. *J Nutr Health Aging*. 2016 Jan;20(1):56–9.
 103. Nishimura T, Arima K, Okabe T, Mizukami S, Tomita Y, Kanagae M, et al. Usefulness of chair stand time as a surrogate of gait speed in diagnosing sarcopenia. *Geriatr Gerontol Int*. 2017 Apr;17(4):659–61.
 104. Shimada H, Suzukawa M, Tiedemann A, Kobayashi K, Yoshida H, Suzuki T. Which neuromuscular or cognitive test is the optimal screening tool to predict falls in frail community-dwelling older people? *Gerontology*. 2009;55(5):532–8.
 105. Velazquez-Alva MC, Irigoyen Camacho ME, Lazarevich I, Delgadillo Velazquez J, Acosta Dominguez P, Zepeda Zepeda MA. Comparison of the prevalence of sarcopenia using skeletal muscle mass index and calf circumference applying the European consensus definition in elderly Mexican women. *Geriatr Gerontol Int*. 2017 Jan;17(1):161–70.
 106. Santos KT, Fernandes MH, Carneiro JA, da Silva Coqueiro R. Motor performance tests as screening instruments for frailty in the older adults. *Appl Nurs Res*. 2016 Nov;32:80–4.
 107. Kowal P, Chatterji S, Naidoo N, Biritwum R, Fan W, Lopez Ridaura R, et al. Data resource profile: the World Health Organization Study on global AGEing and adult health (SAGE). *Int J*

- Epidemiol [Internet]. 2012 Dec [cited 2014 Oct 22];41(6):1639–49. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3535754&tool=pmcentrez&rendertype=abstract>
108. Garcia-Garcia FJ, Gutierrez Avila G, Alfaro-Acha A, Amor Andres MS, De Los Angeles de la Torre Lanza M, Escribano Aparicio M V, et al. The prevalence of frailty syndrome in an older population from Spain. The Toledo study for healthy aging. *J Nutr Health Aging* [Internet]. 2011;15(10):852–6. Available from: <https://doi.org/10.1007/s12603-011-0075-8>
 109. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–98.
 110. StataCorp LLC. The Stata Blog » Using Stata’s random-number generators, part 2, drawing without replacement [Internet]. 2012 [cited 2021 May 20]. Available from: <https://blog.stata.com/2012/08/03/using-statas-random-number-generators-part-2-drawing-without-replacement/>
 111. Cesari M, Kritchevsky SB, Newman AB, Simonsick EM, Harris TB, Penninx BW, et al. Added value of physical performance measures in predicting adverse health-related events: Results from the health, aging and body composition study. *J Am Geriatr Soc* [Internet]. 2009 Feb 1 [cited 2021 Jun 25];57(2):251–9. Available from: <https://agsjournals.onlinelibrary.wiley.com/doi/full/10.1111/j.1532-5415.2008.02126.x>
 112. Dodds RM, Murray JC, Granic A, Hurst C, Uwimpuhwe G, Richardson S, et al. Prevalence and factors associated with poor performance in the 5-chair stand test: findings from the Cognitive Function and Ageing Study II and proposed Newcastle protocol for use in the assessment of sarcopenia. *J Cachexia Sarcopenia Muscle* [Internet]. 2021 Apr 1 [cited 2021 Jun 25];12(2):308–18. Available from: <http://www.cfas.ac.uk/>.
 113. Staartjes VE, Schröder ML. The five-repetition sit-to-stand test: evaluation of a simple and objective tool for the assessment of degenerative pathologies of the lumbar spine. *J Neurosurg Spine*. 2018 Oct;29(4):380–7.
 114. Makizako H, Shimada H, Doi T, Tsutsumimoto K, Nakakubo S, Hotta R, et al. Predictive cutoff values of the five-times Sit-to-Stand Test and the Timed “Up & Go” test for disability incidence in older people dwelling in the community. *Phys Ther* [Internet]. 2017 Apr 1 [cited 2020 Oct 23];97(4):417–24. Available from: <https://pubmed.ncbi.nlm.nih.gov/28371914/>
 115. Santos KT, Fernandes MH, Carneiro JA, da Silva Coqueiro R. Motor performance tests as screening instruments for frailty in the older adults. *Appl Nurs Res*. 2016 Nov 1;32:80–4.
 116. Shimada H, Suzukawa M, Tiedemann A, Kobayashi K, Yoshida H, Suzuki T. Which Neuromuscular or Cognitive Test Is the Optimal Screening Tool to Predict Falls in Frail Community-Dwelling Older People? *Gerontology* [Internet]. 2009 Sep [cited 2021 Mar 18];55(5):532–8. Available from: <https://www.karger.com/Article/FullText/236364>
 117. Velazquez-Alva MC, Irigoyen Camacho ME, Lazarevich I, Delgadillo Velazquez J, Acosta Dominguez P, Zepeda Zepeda MA. Comparison of the prevalence of sarcopenia using skeletal muscle mass index and calf circumference applying the European consensus definition in elderly Mexican women. *Geriatr Gerontol Int* [Internet]. 2017 Jan 1 [cited 2021 Mar 18];17(1):161–70. Available from: <http://doi.wiley.com/10.1111/ggi.12652>
 118. Gunasekaran V, Banerjee J, Dwivedi SN, Upadhyay AD, Chatterjee P, Dey AB. Normal gait speed, grip strength and thirty seconds chair stand test among older Indians. *Arch Gerontol Geriatr*. 2016 Nov 1;67:171–8.
 119. Nielsen LM, Maribo T, Kirkegaard H, Bjerregaard MK, Oestergaard LG. Identifying elderly patients at risk of readmission after discharge from a short-stay unit in the emergency department using performance-based tests of daily activities. *BMC Geriatr* [Internet]. 2020 Jun 22 [cited 2021 Mar 18];20(1):217. Available from: <https://bmgeriatr.biomedcentral.com/articles/10.1186/s12877-020-01591-y>
 120. Chen R, Zhao WB, Zhang XP, Liang H, Song NN, Liu ZY, et al. Relationship between frailty and long-term care needs in Chinese community-dwelling older adults: a cross-sectional study. *BMJ Open* [Internet]. 2022 Apr 1 [cited 2022 Aug 29];12(4):e051801. Available from: <https://bmjopen.bmj.com/content/12/4/e051801>
 121. Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Treatment. *J Am*

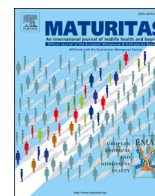
- Med Dir Assoc [Internet]. 2020 Mar 1 [cited 2022 Aug 29];21(3):300-307.e2. Available from: <http://www.jamda.com/article/S1525861019308722/fulltext>
122. González-Bautista E, de Souto Barreto P, Andrieu S, Rolland Y, Vellas B. Screening for intrinsic capacity impairments as markers of increased risk of frailty and disability in the context of integrated care for older people: Secondary analysis of MAPT. *Maturitas* [Internet]. 2021 Aug 1 [cited 2021 Jun 14];150:1–6. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0378512221000815>
 123. Guralnik J, Bandeen-Roche K, Bhasin SAR, Eremenco S, Landi F, Muscedere J, et al. Clinically Meaningful Change for Physical Performance: Perspectives of the ICFSR Task Force. *J frailty aging*. 2020;9(1):9–13.
 124. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc*. 2006 May;54(5):743–9.
 125. Kwon S, Perera S, Pahor M, Katula JA, King AC, Groessl EJ, et al. What is a meaningful change in physical performance? Findings from a clinical trial in older adults (the LIFE-P study). *J Nutr Health Aging* [Internet]. 2009 Jun;13(6):538–44. Available from: <https://pubmed.ncbi.nlm.nih.gov/19536422>
 126. Perera S, Studenski S, Chandler JM, Guralnik JM. Magnitude and patterns of decline in health and function in 1 year affect subsequent 5-year survival. *J Gerontol A Biol Sci Med Sci*. 2005 Jul;60(7):894–900.
 127. Perera S, Studenski S, Newman A, Simonsick E, Harris T, Schwartz A, et al. Are Estimates of Meaningful Decline in Mobility Performance Consistent Among Clinically Important Subgroups? (Health ABC Study). *Journals Gerontol Ser A* [Internet]. 2014 Oct 1;69(10):1260–8. Available from: <https://doi.org/10.1093/gerona/glu033>
 128. Guyatt G, Walter S, Norman G. Measuring change over time: Assessing the usefulness of evaluative instruments. *J Chronic Dis*. 1987 Jan 1;40(2):171–8.
 129. Wywich KW, Bullinger M, Aaronson N, Hays RD, Patrick DL. Estimating clinically significant differences in quality of life outcomes. 2005;285–95.
 130. Wywich KW, Nienaber NA, Tierney WM, Wolinsky FD. Linking Clinical Relevance and Statistical significance in Evaluating Intra-Individual Changes in Health-Related Quality of Life. *Med Care* [Internet]. 1999;37(5). Available from: https://journals.lww.com/lww-medicalcare/Fulltext/1999/05000/Linking_Clinical_Relevance_and_Statistical.6.aspx
 131. Norman GR, Gwadry Sridhar F, Guyatt GH, Walter SD. Relation of Distribution- and Anchor-Based Approaches in Interpretation of Changes in Health-Related Quality of Life. *Med Care* [Internet]. 2001;39(10). Available from: https://journals.lww.com/lww-medicalcare/Fulltext/2001/10000/Relation_of_Distribution__and_Anchor_Based.2.aspx
 132. Goldberg A, Chavis M, Watkins J, Wilson T. The five-times-sit-to-stand test: Validity, reliability and detectable change in older females. *Aging - Clin Exp Res*. 2012;24(4):339–44.
 133. Onder G, Penninx BWJH, Lapuerta P, Fried LP, Ostir G V, Guralnik JM, et al. Change in physical performance over time in older women: the Women’s Health and Aging Study. *J Gerontol A Biol Sci Med Sci*. 2002 May;57(5):M289-93.
 134. Tabbarah M, Crimmins EM, Seeman TE. The relationship between cognitive and physical performance: MacArthur Studies of Successful Aging. *J Gerontol A Biol Sci Med Sci*. 2002 Apr;57(4):M228-35.
 135. Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc*. 2005;53(4):649–54.
 136. Hoogeboom TJ, Dronkers JJ, van den Ende CHM, Oosting E, van Meeteren NLU. Preoperative therapeutic exercise in frail elderly scheduled for total hip replacement: a randomized pilot trial. *Clin Rehabil*. 2010 Oct;24(10):901–10.
 137. de Groot IB, Bussmann HJ, Stam HJ, Verhaar JA. Small increase of actual physical activity 6 months after total hip or knee arthroplasty. *Clin Orthop Relat Res*. 2008 Sep;466(9):2201–8.
 138. Guralnik JM, Ferrucci L, Penninx BWJH, Kasper JD, Leveille SG, Bandeen-Roche K, et al. New and Worsening Conditions and Change in Physical and Cognitive Performance During Weekly Evaluations Over 6 Months: The Women’s Health and Aging Study. *Journals Gerontol*

- Ser A [Internet]. 1999 Aug 1;54(8):M410–22. Available from: <https://doi.org/10.1093/gerona/54.8.M410>
139. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol*. 2017;16(5):377–89.
 140. Hosseinpoor AR, Williams JS, Jann B, Kowal P, Officer A, Posarac A, et al. Social determinants of sex differences in disability among older adults: a multi-country decomposition analysis using the World Health Survey. *Int J Equity Health*. 2012 Sep;11:52.
 141. Gill TM, Gahbauer EA, Lin H, Han L, Allore HG. Comparisons between older men and women in the trajectory and burden of disability over the course of nearly 14 years. *J Am Med Dir Assoc*. 2013 Apr;14(4):280–6.
 142. Rothman K, Greenland S, Lash T. *Modern Epidemiology*. Wolters Kluwer; 2013.
 143. Lee H, Aronson J, Nunan D. Collider bias - Catalog of Bias [Internet]. Oxford University. 2019 [cited 2022 Oct 12]. Available from: <https://catalogofbias.org/biases/collider-bias/>
 144. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol*. 2002 Jan;155(2):176–84.
 145. Greenland S, Brumback B. An overview of relations among causal modelling methods. *Int J Epidemiol*. 2002 Oct;31(5):1030–7.
 146. JUDEA PEARL J, MACKENZIE D. *THE BOOK OF WHY: THE NEW SCIENCE OF CAUSE AND EFFECT* [Internet]. New York: Basic Books; 2018 [cited 2022 Oct 12]. Available from: <http://bayes.cs.ucla.edu/WHY/>
 147. Eekhout I, de Boer RM, Twisk JWR, de Vet HCW, Heymans MW. Missing data: a systematic review of how they are reported and handled. *Epidemiology*. 2012 Sep;23(5):729–32.
 148. Griswold ME, Talluri R, Zhu X, Su D, Tingle J, Gottesman RF, et al. Reflection on modern methods: shared-parameter models for longitudinal studies with missing data. *Int J Epidemiol*. 2021 Aug;50(4):1384–93.
 149. Fletcher R, Fletcher S, Wagner E. *Epidemiología clínica*. 2nd ed. Barcelona: Masson; 1998. 22–24 p.
 150. Trevethan R. Sensitivity, Specificity, and Predictive Values: Foundations, Pliabilities, and Pitfalls in Research and Practice. *Front Public Heal* [Internet]. 2017 Nov 20 [cited 2022 Sep 2];5:307. Available from: [/pmc/articles/PMC5701930/](https://pubmed.ncbi.nlm.nih.gov/30701930/)
 151. Altman DG, Bland JM. Statistics Notes: Diagnostic tests 3: receiver operating characteristic plots. *BMJ* [Internet]. 1994 Jul 16 [cited 2022 Oct 11];309(6948):188. Available from: <https://www.bmj.com/content/309/6948/188>
 152. Yates FE. Order and complexity in dynamical systems: Homeodynamics as a generalized mechanics for biology. *Math Comput Model* [Internet]. 1994 Mar;19(6–8):49–74. Available from: <http://linkinghub.elsevier.com/retrieve/pii/0895717794901899>
 153. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical resilience in older adults: Systematic review and development of an emerging construct. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2016;71(4):489–95.
 154. Varadhan R, Walston JD, Bandeen-Roche K. Can a Link Be Found Between Physical Resilience and Frailty in Older Adults by Studying Dynamical Systems? *J Am Geriatr Soc* [Internet]. 2018 Aug [cited 2019 Dec 13];66(8):1455–8. Available from: <http://doi.wiley.com/10.1111/jgs.15409>
 155. Colón-Emeric C, Pieper CF, Schmader KE, Sloane R, Bloom A, McClain M, et al. Two approaches to classifying and quantifying physical resilience in longitudinal data. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2020;75(4):731–8.
 156. Scheffer M, Elizabeth Bolhuis J, Borsboom D, Buchman TG, Gijzel SMW, Goulson D, et al. Quantifying resilience of humans and other animals. Vol. 115, *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences; 2018. p. 11883–90.
 157. Gijzel SMW, Van De Leemput IA, Scheffer M, Roppolo M, Olde Rikkert MGM, Melis RJF. Dynamical Resilience Indicators in Time Series of Self-Rated Health Correspond to Frailty

- Levels in Older Adults. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2017 Jul 1;72(7):991–6.
158. Gonzalez-Bautista E, Morsch P, Mathur M, Goncalves Bos A, Hommes C, Vega E. Assessing health system responsiveness to the needs of older people. *Rev Panam Salud Pública*. 2021;45:1–7.
 159. English KL, Paddon-Jones D. Protecting muscle mass and function in older adults during bed rest. *Curr Opin Clin Nutr Metab Care* [Internet]. 2010 Jan [cited 2022 Aug 29];13(1):34. Available from: [/pmc/articles/PMC3276215/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3276215/)
 160. Wilkinson DJ, Piasecki M, Atherton PJ. The age-related loss of skeletal muscle mass and function: Measurement and physiology of muscle fibre atrophy and muscle fibre loss in humans. *Ageing Res Rev*. 2018 Nov 1;47:123–32.
 161. García-González JJ, García-Peña C, Franco-Marina F, Gutiérrez-Robledo LM. A frailty index to predict the mortality risk in a population of senior Mexican adults. *BMC Geriatr* [Internet]. 2009 Jan [cited 2014 Jun 3];9:47. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2776593&tool=pmcentrez&rendertype=abstract>
 162. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol*. 1998 Apr;147(8):755–63.
 163. Kyle UG, Genton L, Hans D, Karsegard L, Slosman DO, Pichard C. Age-related differences in fat-free mass, skeletal muscle, body cell mass and fat mass between 18 and 94 years. *Eur J Clin Nutr*. 2001 Aug;55(8):663–72.
 164. Covinsky KE, Palmer RM, Fortinsky RH, Counsell SR, Stewart AL, Kresevic D, et al. Loss of Independence in Activities of Daily Living in Older Adults Hospitalized with Medical Illnesses: Increased Vulnerability with Age. *J Am Geriatr Soc* [Internet]. 2003 Apr 1 [cited 2022 Aug 29];51(4):451–8. Available from: <https://onlinelibrary.wiley.com/doi/full/10.1046/j.1532-5415.2003.51152.x>
 165. Hirsch CH, Sommers L, Olsen A, Mullen L, Winograd CH. The natural history of functional morbidity in hospitalized older patients. *J Am Geriatr Soc*. 1990 Dec;38(12):1296–303.
 166. Blackburn A. The Nagi Model Applied for Optimum Aging [Internet]. 2020 [cited 2022 Oct 10]. Available from: <https://medium.com/selfcaregiver/the-nagi-model-applied-for-optimum-aging-d5694150f3ae>
 167. Angioni D, Macaron T, Takeda C, Sourdet S, Cesari M, Giudici KV, et al. Can We Distinguish Age-Related Frailty from Frailty Related to Diseases ? Data from the MAPT Study. *J Nutr Health Aging* [Internet]. 2020 Dec 1 [cited 2022 Oct 10];24(10):1144–51. Available from: <https://pubmed.ncbi.nlm.nih.gov/33244575/>
 168. Mitnitski A, Song X, Rockwood K. Assessing biological aging: the origin of deficit accumulation. *Biogerontology* [Internet]. 2013 Dec [cited 2014 Jun 3];14(6):709–17. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3847281&tool=pmcentrez&rendertype=abstract>
 169. Cizek GJ. Defining and distinguishing validity: Interpretations of score meaning and justifications of test use. *Psychol Methods*. 2012 Mar;17(1):31–43.
 170. Dodds RM, Syddall HE, Cooper R, Benzeval M, Deary IJ, Dennison EM, et al. Grip strength across the life course: Normative data from twelve British studies. *PLoS One*. 2014 Dec 4;9(12).
 171. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. *JAMA*. 2011 Jan;305(1):50–8.
 172. Giudici KV, de Souto Barreto P, Soriano G, Rolland Y, Vellas B. Defining Vitality: Associations of Three Operational Definitions of Vitality with Disability in Instrumental Activities of Daily Living and Frailty among Elderly Over a 3-Year Follow-Up (MAPT Study). *J Nutr Heal Aging*. 2019 Apr 1;23(4):386–92.
 173. Guyonnet S, Rolland Y, Takeda C, Ousset PJ, Ader I, Davezac N, et al. The INSPIRE Bio-Resource Research Platform for Healthy Aging and Geroscience: Focus on the Human Translational Research Cohort (The INSPIRE-T Cohort). *J frailty aging* [Internet]. 2021 Feb 1 [cited 2022 Apr 22];10(2):110–20. Available from:

- <https://pubmed.ncbi.nlm.nih.gov/33575699/>
174. Francis P, Lyons M, Piasecki M, Mc Phee J, Hind K, Jakeman P. Measurement of muscle health in aging. *Biogerontology*. 2017 Dec 1;18(6):901–11.
 175. Rikli RE, Jones CJ. Development and Validation of a Functional Fitness Test for Community-Residing Older Adults. *J Aging Phys Act* [Internet]. 1999;7(2):129–61. Available from: <https://journals.humankinetics.com/view/journals/japa/7/2/article-p129.xml>
 176. Rikli RE, Jones CJ. Functional Fitness Normative Scores for Community-Residing Older Adults, Ages 60-94. *J Aging Phys Act* [Internet]. 1999;7(2):162–81. Available from: <https://journals.humankinetics.com/view/journals/japa/7/2/article-p162.xml>
 177. Alcazar J, Lopez-Moranchel I, Losa-Reyna J, Baltasar-Fernandez I, Garcia-Garcia F, Alegre L, et al. App Review: PowerFrail for the assessment of relative muscle power and frailty in older people | BJSM blog - social media's leading SEM voice [Internet]. *Blog of the British Journal of Sports Medicine*. 2021 [cited 2022 Feb 1]. Available from: <https://blogs.bmj.com/bjbm/2021/02/04/app-review-powerfrail-for-the-assessment-of-relative-muscle-power-and-frailty-in-older-people/>

ANNEXE. Published articles



Screening for intrinsic capacity impairments as markers of increased risk of frailty and disability in the context of integrated care for older people: Secondary analysis of MAPT

Emmanuel González-Bautista^{a,b,*}, Philippe de Souto Barreto^{a,b}, Sandrine Andrieu^{a,b}, Yves Rolland^{a,b}, Bruno Vellas^{a,b}, for the MAPT/DSA group (members are listed under ‘Contributors’)

^a Gerontopole of Toulouse, Institute of Aging, Toulouse University Hospital (CHU Toulouse), Toulouse, France

^b UPS/Inserm UMR1027, University of Toulouse III, Toulouse, France

ARTICLE INFO

Keywords:

Functional performance
Intrinsic capacity
Frailty
Disability
Screening
ICOPE
Integrated Care of Older People

ABSTRACT

Aim: This longitudinal secondary analysis of the Multidomain Alzheimer Preventive Trial (MAPT) aimed to test whether the Integrated Care for Older People (ICOPE) Step 1 screening tool is able to identify people at risk of developing frailty and disability in basic (ADL) and instrumental (IADL) activities of daily living among community-dwelling older adults.

Participants and setting: Seven hundred and fifty-nine ($n = 759$) non-demented participants of the MAPT aged 70–89 years were assessed in memory clinics in France between 2008 and 2013.

Methods: We measured six intrinsic capacity (IC) impairments, adapted from the ICOPE screening tool. We used Cox models to estimate the adjusted hazard ratios of incident frailty and IADL/ADL disability. Incident frailty was defined by Fried’s phenotype, and incident disability was measured according to Lawton and Katz for IADLs and ADLs.

Results: Limited mobility (HR= 2.97, 95%CI= 1.85–4.76), depressive symptoms (HR= 2.07, 95%CI= 1.03–4.19), and visual impairment (HR= 1.70, 95%CI 1.01–2.86) were associated with a higher incidence of frailty over 5 years. Each additional IC condition demonstrated a positive association with a higher risk of incident frailty, IADL, ADL disability, with risk increased by 47%, 27%, and 23% over 5 years, respectively.

Conclusion: Screening for IC impairments identifies older adults at higher risk of incident frailty and incident IADL/ADL disability. It is relevant to screen for these impairments together because the risk of frailty and disability increases with each additional one.

ClinicalTrials.gov identifier: NCT00672685

1. Background

The Integrated Care for Older People (ICOPE) approach, launched by the World Health Organisation (WHO), provides a function and person-centered model to adapt health systems for population aging. The main goal of the ICOPE strategy is to maintain optimal functional levels in older adults and avoid or delay care dependency as much as possible [1]. Intrinsic capacity (IC), a crucial element to promote healthy aging, is the composite of an individual’s physical and mental capacities. To identify

people at risk for care dependency, the ICOPE health care pathway starts by screening for impairments in five IC domains (ICOPE Step 1): cognitive decline, limited mobility, malnutrition, visual impairment, hearing loss, and depressive symptoms [1–3]. These IC impairments do not represent clinical diagnoses, rather, they may be attributable to underlying health conditions. The screening results will trigger the next steps in the ICOPE healthcare pathway (i.e., in-depth assessments, looking for the causes of IC decline, establishing the care plan). The added value of this screening is its balance between comprehensiveness

* Corresponding author at: Gerontopole of Toulouse, Institute of Ageing, Toulouse University Hospital (CHU Toulouse), 37 Allée Jules Guesde, 31000 Toulouse, France.

E-mail addresses: emmanuel.gonzalez-bautista@univ-tlse3.fr (E. González-Bautista), philipebarreto81@yahoo.com.br (P. de Souto Barreto), sandrine.andrieu@univ-tlse3.fr (S. Andrieu), rolland.y@chu-toulouse.fr (Y. Rolland), vellas.b@chu-toulouse.fr (B. Vellas).

<https://doi.org/10.1016/j.maturitas.2021.05.011>

Received 21 September 2020; Received in revised form 29 April 2021; Accepted 31 May 2021

Available online 4 June 2021

0378-5122/© 2021 Elsevier B.V. All rights reserved.

and feasibility. It can be applied in a few minutes by health workers, trained community agents, or, in some cases, by the older adults themselves. [1,4]

The ICOPE approach and the IC framework are supposed to identify people at-risk for care dependency. To the best of our knowledge, there are no reports of a screening tool for IC impairments to detect people at higher risk of events in the disabling cascade (frailty/disability). [2,3,5]. The ICOPE screening is easy-to-use (i.e., composed of a few simple questions and one test) and not time-consuming. The ICOPE screening tool's main goal is to identify IC impairments, and to act as a trigger for more comprehensive assessment where IC losses are identified. It is essential to investigate if the ICOPE screening can detect people at high risk for clinically meaningful adverse health events [4,6]. The ICOPE screening tool tested in this study and the ICOPE clinical pathways are expected to help the health systems transition to a function- and person-centered care approach.

Therefore, our study aims to evaluate the ICOPE screening tool's ability to identify people at risk of developing frailty and disability in basic (ADL) and instrumental (IADL) activities of daily living among community-dwelling older adults.

2. Methods

This study uses longitudinal data of the Multidomain Alzheimer Preventive Trial (MAPT). The detailed methodology of MAPT has been described elsewhere [7,8]. In summary, MAPT was a randomized controlled trial (RCT) testing the effect of a multidomain intervention (nutritional counseling, physical exercise, and cognitive stimulation) with and without supplementation of omega-3 polyunsaturated fatty acids (PUFA) versus usual care on the prevention of cognitive decline among community-dwelling adults aged 70 years and older recruited in memory clinics in France. The Ethical Committee (CPP SOOM II) based in Toulouse approved the study (ClinicalTrials.gov identifier: NCT00672685). All participants signed a consent form before study assessments. After a three-yearlong RTC period, MAPT continued as an observational study for an additional 2 years.

2.1. Participants

MAPT inclusion criteria were meeting at least one of a) spontaneous memory complaints expressed to their physician, b) limitation in one instrumental activity of daily living (IADL), or c) slow gait speed (≤ 0.8 m/s). Exclusion criteria comprised: a) participants with a Mini-Mental State Examination (MMSE) score < 24 , b) diagnosis of dementia, c) limitation for one or more basic activities of daily living (ADLs), and d) those taking PUFA supplements at baseline.

Of the 1679 participants enrolled, 759 had complete information for the IC domains since they received a preventive consultation as part of the multidomain intervention. A physician assessed their hearing and vision. The differences in sample size across the three tested outcomes are accounted for in Fig S1.

2.2. IC domains assessment – step 1 (screening)

Using a retrospective approach, we operationalized an IC screening tool similar to the ICOPE Step 1, based on the detection of IC impairments. We follow the exact definition of the ICOPE Step 1 tool [1] for three domains: cognition (time and space orientation plus word recall), locomotion (perform five chair rises within 14 s), and vitality/nutrition (self-reported weight loss or appetite loss). Due to data availability, we had to adapt the operationalization of *vision*: answering "yes" to any of: "Even if wearing glasses, do you have visual problems to a) distinguish the faces of people in the same room? b) move indoors/outdoors? c) other activities (reading a paper, watching television)?"; *hearing*: answering "sometimes" or "yes" to the question "Do you have difficulty hearing when someone speaks in a whisper?" (HHSE-S [9,10]);

psychological function: answering "yes" to the item 2 of Geriatric Depression Scale (GDS-15) "Have you dropped many of your activities and interests?", or responding "no" to the item 7 of the GDS-15 "Do you feel happy most of the time?" [11]. Three experts (one geriatrician, one general practitioner, and one researcher in clinical gerontology) judged these GDS items as the closest ones to the ICOPE screening [1]. The resulting set of items was called "MAPT Step 1" (Supplementary Table 1).

Besides, we calculated a "total score" by adding the number of IC impairments found by the MAPT Step 1 (score range 0–6, higher is worst) (Table 1).

2.3. Incident frailty

Participants were assessed for frailty at baseline and 6, 12, 24, 36, 48, and 60 months of follow-up. We used the phenotype criteria of frailty proposed by L. Fried and cols [12]: reported unintentional weight loss, slowness, low physical activity, weakness, and exhaustion. Participants who met ≥ 3 criteria were classified as frail, with one or two criteria, pre-frail, and otherwise, robust. We excluded participants frail at baseline.

2.4. Incident disability

Disability for IADL was assessed according to Lawton [13] (baseline, 36, 48, and 60 months from follow-up). IADLs included were: use the phone, do the grocery, cooking, housekeeping, laundry, use of means of transportation, handle own medication and manage finances. Incident disability for IADLs was defined if the participant had an increase in the number of IADLs during follow-up, compared to the baseline status. We defined incident IADL disability whenever participants developed disability for a new IADL, regardless the baseline number of IADLs affected. ADL disability was assessed according to Katz [14] at baseline and 48 and 60 months of follow-up. ADLs included were: showering, getting dressed, using the toilet, displacing inside a room, continence, and self-feeding. Incident ADL disability was registered if the participant reported needing help or being care dependant for at least one of the ADLs.

2.5. Statistical analysis

Besides descriptive statistics, we used Cox's proportional hazards models for non-recurrent events to estimate the hazard ratios for frailty, IADL, and ADL disability incidence. For each outcome, we ran one separate model testing each condition of interest. (Model 1), another mutually adjusted model including the six IC impairments simultaneously to detect which were the strongest predictors (Model 2), and one model with the "total score" to see if the risk increased with each additional condition (Model 3). We adjusted the frailty models for pre-frail/robust baseline status and the IADL models for baseline IADL to account for different baseline risks. All models were adjusted for age, sex, level of education, MAPT group (multidomain intervention, multidomain intervention + omega 3 supplementation), and multimorbidity (defined as self-reporting 2 or more of COPD/asthma, stroke, active cancer, ischemic heart disease, diabetes, hypertension or heart failure). The proportionality assumption was confirmed by plotting the cumulative risk function against the analysis time and verifying that the predictor-time interactions were not statistically significant at $\alpha=0.05$. We estimated the predictive ability of models 2 and 3 using Harrell's C ($C > 0.5$ and close to 1.0 indicate higher discrimination [15]). We compared the characteristics of the participants lost to follow-up, looking for any differences that could impact our modeling of the outcomes (t -test or χ^2 as appropriate). Receiver operator characteristic (ROC) analyses were performed *vis à vis* the three outcomes of interest. Data were analyzed using STATA 14®.

Table 1

Description of the population according to incident frailty, IADL and ADL disability in MAPT participants over 5 years.

n(%) or mean (SD)	Total n = 759		Incident frailty No=591			Incident IADL disability No=524 ^a			Incident ADL disability No=398			Yes=70		
Age	75.2	(4.3)	74.8	(4.1)	78	(4.6)*	74.7	(4.0)	77.2	(4.9)*	74.3	(4.0)	76.2	(4.2)*
Sex (female)	483	(63.6)	372	(87.5)	53	(12.5)	342	(87.2)	50	(12.8)	251	(81.5)	57	(18.5)*
Education														
Less than primary	31	(4.1)	20	(3.4)	8	(9.6)*	23	(4.4)	2	(2.2)	14	(3.6)	4	(5.8)
Primary	122	(16.2)	85	(14.5)	17	(20.5)	72	(13.9)	22	(24.4)	52	(13.2)	8	(11.6)
Secondary	271	(36.1)	219	(37.4)	21	(25.3)	194	(37.4)	30	(33.3)	141	(35.9)	27	(39.1)
High-school	111	(14.8)	88	(15.0)	12	(14.5)	69	(13.3)	15	(16.7)	54	(13.7)	12	(17.4)
Graduate or higher	216	(28.8)	174	(29.7)	25	(30.1)	161	(31.0)	21	(23.3)	132	(33.6)	18	(26.1)
Multimorbidity ^c (yes)	128	(16.9)	90	(15.2)	20	(24.1)*	75	(14.3)	29	(31.9)*	57	(14.3)	14	(20.0)
Frailty														
Robust	409	(56.5)	373	(94.9)	20	(5.1)*	312	(92.0)	27	(8.0)*	242	(89.6)	28	(10.4)*
Pre-frail	292	(40.3)	218	(77.6)	63	(22.4)	178	(76.7)	54	(23.3)	129	(78.2)	36	(21.8)
Frail	23	(3.2)	^b	^b	^b	^b	9	(52.9)	8	(47.1)	9	(69.2)	4	(30.8)
Intrinsic capacity impairments														
Cognitive decline	396	(52.2)	301	(86.0)	49	(14.0)	257	(82.1)	56	(17.9)*	201	(87.0)	30	(13.0)
Limited mobility	146	(20.2)	84	(71.2)	34	(28.8)*	82	(75.9)	26	(24.1)*	59	(74.7)	20	(25.3)*
Malnutrition	50	(6.6)	35	(85.4)	6	(14.6)	32	(82.1)	7	(17.9)	23	(79.3)	6	(20.7)
Visual impairment	137	(18.1)	90	(77.6)	26	(22.4)*	79	(79.0)	21	(21.0)	57	(79.2)	15	(20.8)
Hearing loss	426	(56.2)	332	(87.4)	48	(12.6)	282	(82.5)	60	(17.5)*	218	(84.5)	40	(15.5)
Depressive symptoms	296	(39.0)	216	(83.1)	44	(16.9)*	183	(81.0)	43	(19.0)*	129	(81.1)	30	(18.9)
IC impairment sum score														
0	81	(10.7)	69	(93.2)	5	(6.8)*	67	(93.1)	5	(6.9)*	50	(86.2)	8	(13.8)*
1	210	(27.7)	179	(93.2)	13	(6.8)	168	(92.8)	13	(7.2)	124	(85.5)	21	(14.5)
2	248	(32.7)	199	(90.0)	22	(10.0)	167	(83.9)	32	(16.1)	136	(91.3)	13	(8.7)
3	149	(19.6)	103	(81.1)	24	(18.9)	80	(72.7)	30	(27.3)	63	(76.8)	19	(23.2)
4	58	(7.6)	34	(66.7)	17	(33.3)	37	(80.4)	9	(19.6)	23	(74.2)	8	(25.8)
5	12	(1.6)	6	(75.0)	2	(25.0)	5	(71.4)	2	(28.6)	2	(66.7)	1	(33.3)
6	1	(0.1)	1	(100.0)	0	(0.0)	524	(85.2)	91	(14.8)	398	(85.0)	70	(15.0)

Abbreviations: MAPT= Multidomain Alzheimer Preventive Trial; IADLs= instrumental activities of daily living; ADL= basic activities of daily living.

^a We included the participants with any number of IADL at baseline for consistency with the population in the models.^b Excluded because they already had the event of interest at baseline.^c Self-reporting 2 or more of COPD/asthma, stroke, active cancer, ischemic heart disease, diabetes, hypertension, or heart failure.* Bivariate *t*-test for continuous or χ^2 for categorical variables, *p*-value <0.05.

3. Results

The baseline characteristics and sample size are described in Table 1 and Supplementary Figure 1, respectively. Briefly, the baseline frailty status of participants with complete data on frailty and IC domains was: robust 56.5% (*n* = 409), pre-frail 40.3% (*n* = 292) and frail 3.2% (*n* = 23).

On average, participants lost to follow-up had a significantly higher number of deficits in IC domains, were older, and had a worst physical performance (chair-rise test) than the ones retained (data not shown). However, obtaining the adjusted Kaplan- Meier curves helped us rule out the impact of informative censoring on our results [16] (Figs. 1 and S2). We decided not to perform a competing risk approach because we observed a mean follow-up period of 4.8 years and low cumulative mortality (*n* = 14, 1.8% of the study sample).

In model 1, we found an association of limited mobility, depressive symptoms, and visual impairment with an increased risk of frailty. Model 2 showed that limited mobility imposed a three-fold risk, depressive symptoms a two-fold risk, and visual impairment a 70% higher risk of incident frailty over five years, after adjusting for covariates and the other five IC impairments. Each additional condition associated with IC declines increased the risk of becoming frail by 47% (model 3).

Each additional condition increased the risk of incident IADL disability in the next five years by 27% (model 3). Limited mobility and depressive symptoms (marginally, *p* = 0.055) increased the risk of incident ADL disability (model 1). Each additional IC condition increased the risk of becoming disabled for ADLs by 23% (Table 2). All

models showed a good predictive ability based on the Harrell C statistic (0.70 < *C* < 0.83) [15]. Cut points for the ICOPE sum score were ≥ 3 for incident frailty and incident ADL disability and ≥ 2 for incident IADL, according to Youden's index [17]. (Supplementary Table 3).

4. Discussion

Our adapted version of the ICOPE screening tool (MAPT Step 1) demonstrated a noteworthy ability to identify older adults at higher risk of incident frailty and disability at a five-year follow-up among the MAPT study participants. Participants screened with limited mobility, depressive symptoms, or visual impairment had a higher risk of developing frailty. Limited mobility and depressive symptoms (to a lesser extent) were also associated with incident ADL disability. Furthermore, each additional domain impairment identified by the screening tool increased the risk of incident frailty by 47% and of incident disability and by 27% (IADL) and 23% (ADL).

The studies reporting the association between IC domains and functional outcomes have not used a screening tool [3,5]. Our findings suggest that using a screening tool to detect impairments in IC might help the primary care providers to identify older adults at higher risk of frailty and disability, for example, those who had limited mobility, visual impairment, and depressive symptoms. Thus, primary care providers can follow at-risk individuals more closely as part of an integrated care plan. Adopting a pro-active screening approach might foster early interventions, even if the older adults do not expressly complain about impairment in the IC domains.

Chaudhry and cols. showed that an increasing number of geriatric

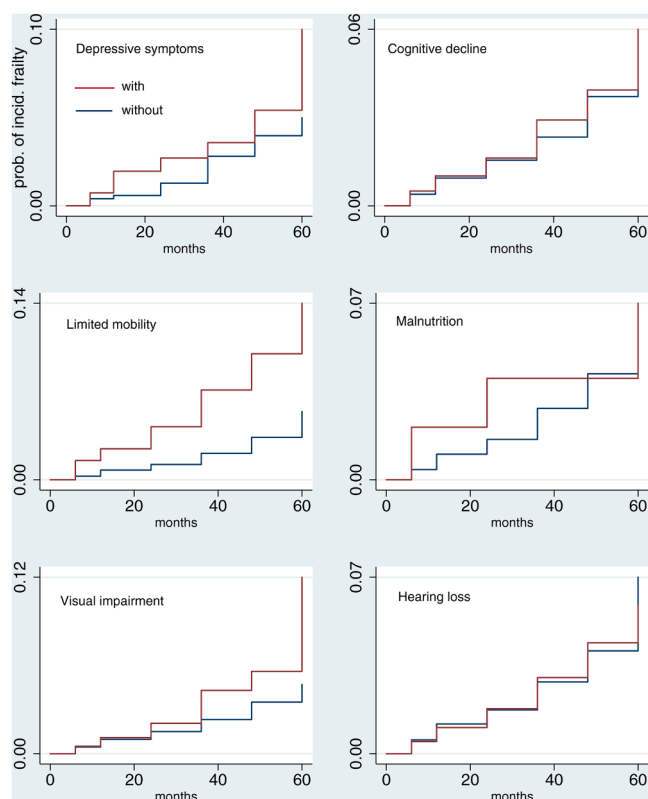


Fig. 1. Kaplan-Meier failure function for incident frailty in each of the intrinsic capacity domains, adjusted for standardized baseline covariates in MAPT participants during a five-year follow-up.

Failure functions for incident frailty were estimated adjusting for standardized baseline covariates: age, sex, education and MAPT group. The y axis represents the Kaplan-Meier failure function for the outcome in each measured time point.

impairments (corresponding to some of the IC domains) was associated with a higher risk of ADL and mobility disability [18]. Also, locomotion and psychological domains play a role in the multisystem dysregulation underlying frailty and disability [19–21]. Low physical performance leads to mobility difficulty and disability [22–24]. Mobility impairments can cause or result from low levels of physical activity and sarcopenia, which are hallmarks of frailty [20,25,26].

Recently, Swenor and cols. have reported that older adults with objectively measured vision impairment are more likely to progress to frailty than their counterparts due to its direct and indirect effects on physical functioning [27]. On the other hand, exhaustion might explain the overlapping of the psychological domain and the disability cascade. Exhaustion is an indicator of poor endurance within the frailty phenotype [12]. In parallel, studies recognize it as a depressive symptom in the psychological domain [12,28].

Cognitive decline, malnutrition, and hearing loss were not significant predictors of frailty or disability in our study. This does not mean these IC domains are not involved in the disabling cascade. Potential explanations are the potential effects of cognitive training in the MAPT study, the exclusion of individuals with a MMSE <24 at baseline and prioritizing sensitivity over specificity to measure the IC domains.

For example, nutritional status is core for preserving function [29] given the influence of diet in functionality, possibly mediated by the gut microbiota [30]. A very low prevalence of malnutrition among MAPT participants (6.6%) [31] might hinder the detection of a significant association of malnutrition with our outcomes of interest. On the other hand, hearing and vision provide peripheral inputs to the central nervous system to allow interaction with the environment. Screening for vision and hearing impairments is helpful because there are quick and relatively cheap interventions to improve the sensory domain, resulting

in a delay of cognitive impairment [32,33].

Our study has several strengths: this is the first study to use a screening tool adapted from the ICOPE Step 1 [1] to identify older adults at higher risk of functional decline; longitudinal design with a reasonably long follow-up period; the use of clinical outcomes relevant from the geriatric standpoint. Limitations in our study include the following: reduction of the sample size due to incomplete data on IC domains and losses to follow-up; this is a secondary analysis using data from a clinical trial, in which all participants received advice on exercise and nutrition and cognitive training [34] however, we adjusted for the intervention group in the multivariable analysis.

4.1. Conclusion

Screening for IC declines using a simple-to-use tool like the ICOPE Step 1 is useful to identify community-dwelling older adults at higher risk of functional decline (incident frailty and incident IADL/ ADL disability) even after adjustments for comorbidity and personal characteristics. Limited mobility, vision impairment, and depressive symptoms were the strongest predictors of adverse health outcomes. Each additional decline in the IC screening significantly increased the risk of adverse functional outcomes. Therefore, screening for IC impairments is a time-effective strategy with important clinical implications for identifying older adults at higher risk of adverse health outcomes who would benefit from a comprehensive assessment.

Contributors

Emmanuel González-Bautista contributed to conception and design, analysis and interpretation of data, statistics and manuscript writing.

Philippe de Souto Barreto contributed to conception and design, analysis and interpretation of data, statistics and manuscript writing.

Sandrine Andrieu contributed to conception and design, analysis and interpretation of data.

Yves Rolland contributed to conception and design, analysis and interpretation of data.

Bruno Vellas contributed to conception and design, analysis and interpretation of data.

All authors provided valuable intellectual input, reviewed the manuscript and approved the version to be published.

MAPT study group

Principal investigator: Bruno Vellas (Toulouse); Coordination: Sophie Guyonnet; Project leader: Isabelle Carrié; CRA: Lauréane Brigitte; Investigators: Catherine Faisant, Françoise Lala, Julien Delrieu, Hélène Villars; Psychologists: Emeline Combrouze, Carole Badufle, Audrey Zuerras; Methodology, statistical analysis and data management: Sandrine Andrieu, Christelle Cantet, Christophe Morin; Multidomain group: Gabor Abellan Van Kan, Charlotte Dupuy, Yves Rolland (physical and nutritional components), Céline Caillaud, Pierre-Jean Ousset (cognitive component), Françoise Lala (preventive consultation) (Toulouse). The cognitive component was designed in collaboration with Sherry Willis from the University of Seattle, and Sylvie Belleville, Brigitte Gilbert and Francine Fontaine from the University of Montreal.

Co-Investigators in associated centres: Jean-François Dartigues, Isabelle Marcet, Fleur Delva, Alexandra Foubert, Sandrine Cerda (Bordeaux); Marie-Noëlle-Cuffi, Corinne Costes (Castres); Olivier Rouaud, Patrick Manckoundia, Valérie Quipourt, Sophie Marilier, Evelyne Franon (Dijon); Lawrence Bories, Marie-Laure Pader, Marie-France Basset, Bruno Lapoujade, Valérie Faure, Michael Li Yung Tong, Christine Malick-Loiseau, Evelyne Cazaban-Campiron (Foix); Françoise Desclaux, Colette Blatge (Lavaur); Thierry Dantoine, Cécile Laubarie-Mouret, Isabelle Saulnier, Jean-Pierre Clément, Marie-Agnès Picat, Laurence Bernard-Bourzeix, Stéphanie Willebois, Iléana Désormais, Noëlle Cardinaud (Limoges); Marc Bonnefoy, Pierre Livet, Pascale

Table 2

Adjusted hazard ratios for the Cox's models linking intrinsic capacity declines and incident frailty and Disability during a five years follow-up among MAPT participants.

	Hazard ratio	CI 95%		p value	Hazard ratio	CI 95%		p value
Frailty (n = 674)	Model 1 ^a				Model 2 ^a			
Depressive symptoms	1.88	1.20 – 2.92		0.005	2.07	(1.03 – 4.19)		0.042
Cognitive decline	1.12	0.71 – 1.76		0.620	1.38	(0.70 – 2.74)		0.345
Limited mobility	2.80	1.76 – 4.44		<0.001	2.97	(1.85 – 4.74)		0.000
Malnutrition	1.45	0.63 – 3.35		0.365	0.97	(0.41 – 2.32)		0.954
Visual impairment	1.95	1.20 – 3.17		0.007	1.70	(1.01 – 2.86)		0.044
Hearing loss	0.92	0.58 – 1.43		0.701	0.81	(0.52 – 1.31)		0.430
Total IC score	1.47	(1.22 – 1.78)		0.000				
IADL disability (n = 615)	Model 1				Model 2 ^b			
Depressive symptoms	1.47	(0.96 – 2.23)		0.071	1.47	(0.94 – 2.27)		0.089
Cognitive decline	1.19	(0.76 – 1.85)		0.431	1.25	(0.78 – 2.00)		0.347
Limited mobility	1.39	(0.85 – 2.30)		0.193	1.42	(0.86 – 2.35)		0.169
Malnutrition	1.05	(0.49 – 2.29)		0.888	0.75	(0.30 – 1.86)		0.533
Visual impairment	1.45	(0.88 – 2.38)		0.140	1.25	(0.73 – 2.12)		0.408
Hearing loss	1.30	(0.83 – 2.02)		0.250	1.25	(0.78 – 1.98)		0.356
Total IC score	1.27	(1.06 – 1.53)		0.010				
ADL disability (n = 468)	Model 1				Model 2			
Depressive symptoms	1.60	(0.98 – 2.53)		0.055	1.60	(0.98 – 2.64)		0.060
Cognitive decline	0.73	(0.45 – 1.18)		0.199	0.72	(0.44 – 1.18)		0.202
Limited mobility	1.92	(1.12 – 3.30)		0.021	1.82	(1.06 – 3.15)		0.029
Malnutrition	1.36	(0.59 – 3.17)		0.464	1.22	(0.52 – 2.91)		0.643
Visual impairment	1.49	(0.84 – 2.64)		0.177	1.40	(0.78 – 2.52)		0.301
Hearing loss	1.14	(0.70 – 1.84)		0.597	1.14	(0.70 – 1.87)		0.595
Total IC score	1.23	(1.00 – 1.52)		0.051				

All models were adjusted for age, sex, education, MAPT group and multimorbidity. Model 1 shows the HR for the intrinsic capacity declines assessed separately. Model 2 shows HR for intrinsic capacity declines mutually-adjusted. Model 3 shows the HR according to the IC sum score.

Abbreviations: CI= confidence interval; MAPT= Multidomain Alzheimer Preventive Trial; MI=multidomain intervention; IADLs= instrumental activities of daily living; ADL= basic activities of daily living.

^a Adjusted for baseline frailty status.

^b Adjusted for baseline IADL disability.

Rebaudet, Claire Gédéon, Catherine Burdet, Flavien Terracol (Lyon), Alain Pesce, Stéphanie Roth, Sylvie Chaillou, Sandrine Louchart (Monaco); Kristel Sudres, Nicolas Lebrun, Nadège Barro-Belaygues (Montauban); Jacques Touchon, Karim Bennys, Audrey Gabelle, Aurélie Romano, Lynda Touati, Cécilia Marelli, Cécile Pays (Montpellier); Philippe Robert, Franck Le Duff, Claire Gervais, Sébastien Gonfrier (Nice); Yannick Gasnier and Serge Bordes, Danièle Begorre, Christian Carpuat, Khaled Khaled, Jean-François Lefebvre, Samira Misbah El Idrissi, Pierre Skolil, Jean-Pierre Salles (Tarbes).

MRI group: Carole Dufouil (Bordeaux), Stéphane Lehericy, Marie Chupin, Jean-François Mangin, Ali Bouhayia (Paris); Michèle Allard (Bordeaux); Frédéric Ricolfi (Dijon); Dominique Dubois (Foix); Marie Paule Bonceour Martel (Limoges); François Cotton (Lyon); Alain Bonafé (Montpellier); Stéphane Chanalet (Nice); Françoise Hugon (Tarbes); Fabrice Bonneville, Christophe Cognard, François Chollet (Toulouse).

PET scans group: Pierre Payoux, Thierry Voisin, Julien Delrieu, Sophie Peiffer, Anne Hitzel, (Toulouse); Michèle Allard (Bordeaux); Michel Zanca (Montpellier); Jacques Monteil (Limoges); Jacques Darcourt (Nice).

Medico-economics group: Laurent Molinier, Hélène Derumeaux, Nadège Costa (Toulouse).

Biological sample collection: Bertrand Perret, Claire Vinel, Sylvie Caspar-Bauguil (Toulouse).

Safety management: Pascale Olivier-Abbal

DSA Group: Sandrine Andrieu, Christelle Cantet, Nicola Coley.

Funding

The present work was performed in the context of the Inspire Program, a research platform supported by grants from the Region

Occitanie/Pyrénées-Méditerranée (Reference number: 1,901,175) and the European Regional Development Fund (ERDF) (Project number: MP0022856). The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; in the preparation of the manuscript; or in the review or approval of the manuscript.

This study received funds from Alzheimer Prevention in Occitania and Catalonia (APOC Chair of Excellence - Inspire Program).

The MAPT study was supported by grants from the Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), Pierre Fabre Research Institute (manufacturer of the omega-3 supplement), ExonHit Therapeutics SA, and Avid Radiopharmaceuticals Inc. The promotion of this study was supported by the University Hospital Center of Toulouse. The data sharing activity was supported by the Association Monegasque pour la Recherche sur la maladie d'Alzheimer (AMPA) and the INSERM-University of Toulouse III UMR 1027 Unit.

Ethical approval

The Ethical Committee (CPP SOOM II) based in Toulouse approved the MAPT study. All participants signed a consent form before study assessments.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be

made available on request.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.maturitas.2021.05.011.

References

- [1] World Health Organization, Integrated Care For Older People (ICOPE): Guidance for Person-Centred Assessment and Pathways in Primary Care, WHO, Geneva, 2019. <https://apps.who.int/iris/bitstream/handle/10665/326843/WHO-FWC-ALC-19.1-eng.pdf?sequence=17> (accessed November 14, 2019).
- [2] J.R. Beard, A.T. Jotheeswaran, M. Cesari, I. Araujo de Carvalho, The structure and predictive value of intrinsic capacity in a longitudinal study of ageing, *BMJ Open* 9 (2019), e026119, <https://doi.org/10.1136/bmjopen-2018-026119>.
- [3] M. Cesari, I.A. De Carvalho, J.A. Thiagarajan, C. Cooper, F.C. Martin, J. Y. Reginster, B. Vellas, J.R. Beard, Evidence for the domains supporting the construct of intrinsic capacity, *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.* 73 (2018) 1653–1660, <https://doi.org/10.1093/gerona/gly011>.
- [4] J.A. Thiagarajan, I. Araujo de Carvalho, J.P. Peña-Rosas, S. Chadha, S.P. Mariotti, T. Dua, E. Albanese, O. Bruyère, M. Cesari, A. Dangour, A. Dias, M. Guerra, J. Keefe, N. Kerse, Q. ul A. Khan, C. Liu, G.V.S. Murthy, S.N. Ndegwa, J.-Y. Reginster, L.M.F.G. Robledo, K. Tremblay, J. Woo, M. Prince, J.R. Beard, Redesigning care for older people to preserve physical and mental capacity: WHO guidelines on community-level interventions in integrated care, *PLOS Med.* 16 (2019), e1002948, <https://doi.org/10.1371/journal.pmed.1002948>.
- [5] E. González-Bautista, S. Andrieu, L.M. Gutiérrez-Robledo, R.E. García-Chanes, P. De Souto Barreto, In the Quest of a Standard Index of Intrinsic Capacity. A Critical Literature Review, *J. Nutr. Health Aging.* (2020), <https://doi.org/10.1007/s12603-020-1394-4>.
- [6] R. Rösslein, H. Dressel, [Causes for care dependency in the context of long-term care insurance], *Pflege Z* 67 (2014) 558–561.
- [7] B. Vellas, I. Carrière, S. Gillette-Guyonnet, J. Touchon, T. Dantoine, J.F. Dartigues, M.N. Cuffi, S. Bordes, Y. Gagnier, P. Robert, L. Bories, O. Rouaud, F. Desclaux, K. Sudres, M. Bonnefoy, A. Pesce, C. Dufouil, S. Lehericy, M. Chupin, J.F. Mangin, P. Payoux, D. Adel, P. Legrand, D. Catheline, C. Kanony, M. Zaim, L. Molinier, N. Costa, J. Delrieu, T. Voisin, C. Faisant, F. Lala, F. Nourhashemi, Y. Rolland, G. A. Van Kan, C. Dupuy, C. Cantet, P. Cestac, S. Belleville, S. Willis, M. Cesari, M. W. Weiner, M.E. Soto, P.J. Ousset, S. Andrieu, MAPT study: a multidomain approach for preventing Alzheimer's disease: design and baseline data, *J. Prev. Alzheimer's Dis.* 1 (2014) 13–22. <http://www.ncbi.nlm.nih.gov/pubmed/26594639> (accessed February 5, 2020).
- [8] S. Andrieu, S. Guyonnet, N. Coley, C. Cantet, M. Bonnefoy, S. Bordes, L. Bories, M. N. Cufi, T. Dantoine, J.F. Dartigues, F. Desclaux, A. Gabelle, Y. Gagnier, A. Pesce, K. Sudres, J. Touchon, P. Robert, O. Rouaud, P. Legrand, P. Payoux, J.P. Caubere, M. Weiner, I. Carrière, P.J. Ousset, B. Vellas, S. Guyonnet, I. Carrière, L. Brigitte, C. Faisant, F. Lala, J. Delrieu, H. Villars, E. Combrouze, C. Badufle, A. Zueras, S. Andrieu, C. Cantet, C. Morin, G.A. Van Kan, C. Dupuy, Y. Rolland, C. Caillaud, P.J. Ousset, B. Fougère, S. Willis, S. Belleville, B. Gilbert, F. Fontaine, J. F. Dartigues, I. Marcet, F. Delva, A. Foubert, S. Cerda, M. Noëlle-Cuffi, C. Costes, O. Rouaud, P. Manckoundia, V. Quipourt, S. Marilier, E. Franon, L. Bories, M. L. Pader, M.F. Basset, B. Lapoujade, V. Faure, M. Li, Y. Tong, C. Malick-Loiseau, E. Cazaban-Campistron, F. Desclaux, C. Blatge, T. Dantoine, C. Laubarie-Mouret, I. Saulnier, J.P. Clément, M.A. Picat, L. Bernard-Bourzeix, S. Willebois, I. Désormais, N. Cardinaud, M. Bonnefoy, P. Livet, P. Rebaudet, C. Gédéon, C. Burdet, F. Terracol, A. Pesce, S. Roth, S. Chaillou, S. Louchart, K. Sudres, N. Lebrun, N. Barro-Belaygues, J. Touchon, K. Bennys, A. Gabelle, A. Romano, L. Touati, C. Marelli, C. Pays, P. Robert, F. Le Duff, C. Gervais, S. Gonfrier, Y. Gagnier, S. Bordes, D. Begorre, C. Carpuat, K. Khaled, J.F. Lefebvre, S.M. El Idriissi, P. Skolil, J.P. Salles, C. Dufouil, S. Lehericy, M. Chupin, J.F. Mangin, A. Bouhayia, M. Allard, F. Ricolfi, D. Dubois, M. Paule, B. Martel, F. Cotton, A. Bonafé, S. Chanalet, F. Hugon, F. Bonneville, C. Cognard, F. Chollet, P. Payoux, T. Voisin, S. Peiffer, A. Hitzel, M. Allard, M. Zanca, J. Monteil, J. Darcourt, L. Molinier, H. Derumeaux, N. Costa, C. Vincent, B. Perret, C. Vinel, P. Olivier-Abbal, Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial, *Lancet Neurol* 16 (2017) 377–389, [https://doi.org/10.1016/S1474-4422\(17\)30040-6](https://doi.org/10.1016/S1474-4422(17)30040-6).
- [9] I.M. Ventry, B.E. Weinstein, The hearing handicap inventory for the elderly: a new tool, *Ear Hear* 3 (1982) 128–134, <https://doi.org/10.1097/00003446-198205000-00006>.
- [10] A. Bagai, Does This Patient Have Hearing Impairment? *JAMA* 295 (2008) 416–428.
- [11] J.A. Yesavage, J.I. Sheikh, Geriatric Depression Scale (GDS), *Clin. Gerontol.* 5 (1986) 165–173, https://doi.org/10.1300/J018v05n01_09.
- [12] L. Fried, C. Tangen, Frailty in older adults evidence for a phenotype, *J. Gerontol. A Biol. Sci. Med. Sci.* 56A (2001) M146–M156. <http://biomedgerontology.oxfordjournals.org/content/56/3/M146.short> (accessed June 11, 2014).
- [13] M.P. Lawton, E.M. Brody, Assessment of Older People: self-Maintaining and Instrumental Activities of Daily Living1, *Gerontologist* 9 (1969) 179–186, https://doi.org/10.1093/geront/9.3_Part_1.179.
- [14] S. Katz, T.D. Downs, H.R. Cash, R.C. Grotz, Progress in development of the index of ADL, *Gerontologist* 10 (1970) 20–30, https://doi.org/10.1093/geront/10.1_Part_1.20.
- [15] F.E.J. Harrell, R.M. Califf, D.B. Pryor, K.L. Lee, R.A. Rosati, Evaluating the yield of medical tests, *JAMA* 247 (1982) 2543–2546.
- [16] M.A. Hernán, The hazards of hazard ratios, *Epidemiology* 21 (2010) 13–15, <https://doi.org/10.1097/EDE.0b013e3181c1ea43>.
- [17] W.J. Youden, Index for rating diagnostic tests, *Cancer* 3 (1950) 32–35, [https://doi.org/10.1002/1097-0142\(1950\)3:1<32::AID-CNCR2820030106>3.0.CO;2-3](https://doi.org/10.1002/1097-0142(1950)3:1<32::AID-CNCR2820030106>3.0.CO;2-3).
- [18] S.I. Chaudhry, G. McAvay, Y. Ning, H.G. Allore, A.B. Newman, T.M. Gill, Geriatric impairments and disability: the cardiovascular health study, *J. Am. Geriatr. Soc.* 58 (2010) 1686–1692, <https://doi.org/10.1111/j.1532-5415.2010.03022.x>.
- [19] L.P. Fried, Q.-L. Xue, A.R. Cappola, L. Ferrucci, P. Chaves, R. Varadhan, J. M. Guralnik, S.X. Leng, R.D. Semba, J.D. Walston, C.S. Blaum, K. Bandeen-Roche, Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment, *J. Gerontol. A Biol. Sci. Med. Sci.* 64 (2009) 1049–1057, <https://doi.org/10.1093/gerona/glp076>.
- [20] M. Kuzuya, Process of physical Disability among older adults—contribution of frailty in the super-aged society, *Nagoya J. Med. Sci.* 74 (2012) 31–37. <https://pubmed.ncbi.nlm.nih.gov/22515109/>.
- [21] J. Vermeulen, J.C.L. Neyens, E. van Rossum, M.D. Spreeuwenberg, L.P. de Witte, Predicting ADL disability in community-dwelling elderly people using physical frailty indicators: a systematic review, *BMC Geriatr* 11 (2011) 33, <https://doi.org/10.1186/1471-2318-11-33>.
- [22] S. Perera, K.V. Patel, C. Rosano, S.M. Rubin, S. Satterfield, T. Harris, K. Ensrud, E. Orwoll, C.G. Lee, J.M. Chandler, A.B. Newman, J.A. Cauley, J.M. Guralnik, L. Ferrucci, S.A. Studenski, Gait Speed Predicts Incident Disability: a Pooled Analysis, *J. Gerontol. A Biol. Sci. Med. Sci.* 71 (2016) 63–71, <https://doi.org/10.1093/gerona/glv126>.
- [23] T.M. Gill, Assessment of Function and Disability in Longitudinal Studies, *J. Am. Geriatr. Soc.* 58 (2010) S308–S312, <https://doi.org/10.1111/j.1532-5415.2010.02914.x>.
- [24] G.V. Ostir, J.E. Carlson, S.A. Black, L. Rudkin, J.S. Goodwin, K.S. Markides, Disability in older Adults 1: prevalence, causes, and consequences, *Behav. Med.* 24 (1999) 147–156, <https://doi.org/10.1080/08964289.1999.11879271>.
- [25] Z. Feng, M. Lugtenberg, C. Franse, X. Fang, S. Hu, C. Jin, H. Raat, Risk factors and protective factors associated with incident or increase of frailty among community-dwelling older adults: a systematic review of longitudinal studies, *PLoS ONE* 12 (2017), e0178383, <https://doi.org/10.1371/journal.pone.0178383>.
- [26] J.E. Morley, Frailty screening comes of age, *J. Nutr. Health Aging.* 18 (2014) 453–454, <https://doi.org/10.1007/s12603-014-0457-9>.
- [27] B.K. Swenor, M.J. Lee, J. Tian, V. Varadaraj, K. Bandeen-Roche, Visual Impairment and Frailty: examining an Understudied Relationship, *Journals Gerontol. Ser. A.* 75 (2020) 596–602, <https://doi.org/10.1093/gerona/glz182>.
- [28] J.G. Orme, J. Reis, E.J. Herz, Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale, *J. Clin. Psychol.* 42 (1986) 28–33, [https://doi.org/10.1002/1097-4679\(198601\)42:1<28::aid-jclp2270420104>3.0.co;2-t](https://doi.org/10.1002/1097-4679(198601)42:1<28::aid-jclp2270420104>3.0.co;2-t).
- [29] L. Lorenzo-López, A. Maseda, C. De Labra, L. Regueiro-Folgueira, J.L. Rodríguez-Villamil, J.C. Millán-Calenti, Nutritional determinants of frailty in older adults: a systematic review, *BMC Geriatr* 17 (2017), <https://doi.org/10.1186/s12877-017-0496-2>.
- [30] A. Ticinesi, F. Lauretani, C. Milani, A. Nouvenne, C. Tana, D. Del Rio, M. Maggio, M. Ventura, T. Meschi, Aging gut microbiota at the cross-road between nutrition, physical frailty, and sarcopenia: is there a gut–muscle axis? *Nutrients* 9 (2017) <https://doi.org/10.3390/nu9121303>.
- [31] E. González-Bautista, P.D.S. Barreto, K.V. Giudici, S. Andrieu, Y. Rolland, B. Vellas, Frequency of Conditions Associated with Declines in Intrinsic Capacity According to a Screening Tool in the Context of Integrated Care for Older People, *J. Frailty Aging* 2020 (2020) 1–9, <https://doi.org/10.14283/JFA.2020.42>.
- [32] D.G. Loughrey, M.E. Kelly, G.A. Kelley, S. Brennan, B.A. Lawlor, Association of age-related hearing loss with cognitive function, cognitive impairment, and dementia: a systematic review and meta-analysis, *JAMA Otolaryngol. - Head Neck Surg.* 144 (2018) 115–126, <https://doi.org/10.1001/jamaoto.2017.2513>.
- [33] S. Saydah, R.B. Gerzoff, C.A. Taylor, J.R. Ehrlich, J. Saaddine, Vision Impairment and Subjective Cognitive Decline-Related Functional Limitations — United States, 2015–2017, *MMWR. Morb. Mortal. Wkly. Rep.* 68 (2019) 453–457, <https://doi.org/10.15585/mmwr.mm6820a2>.
- [34] F. Guerville, P. Souto Barreto, K.V. Giudici, Y. Rolland, B. Vellas, Association of 3-Year Multidomain Intervention and Omega-3 Supplementation with Frailty Incidence, *J. Am. Geriatr. Soc.* 67 (2019) 1700–1706, <https://doi.org/10.1111/jgs.15994>.

Research Report

Development and Validation of a Cutoff for the Chair Stand Test as a Screening for Mobility Impairment in the Context of the Integrated Care for Older People Program

Emmanuel Gonzalez-Bautista, MSc,^{1,2,*} Philippe de Souto Barreto, PhD,^{1,2} Aaron Salinas-Rodriguez, MSc,^{3,◉} Betty Manrique-Espinoza, PhD,³ Sandrine Sourdet, MD,^{1,2} Yves Rolland, MD,^{1,2} Leocadio Rodríguez-Mañas, PhD,^{4,◉} Sandrine Andrieu, PhD,^{1,2} and Bruno Vellas, PhD,^{1,2}; for the MAPT/DSA Group[#]

¹Gérontopole of Toulouse, Institute of Aging, Toulouse University Hospital (CHU Toulouse), Toulouse, France. ²CERPOP UMR 1295, University of Toulouse III, INSERM, UPS, Toulouse, France. ³Center for Surveys and Evaluation Research, National Institute of Public Health (INSP), Cuernavaca, Morelos, Mexico. ⁴Geriatrics Service, Getafe University Hospital, Madrid, Spain.

*Address correspondence to: Emmanuel Gonzalez-Bautista, MSc, Gérontopole of Toulouse, Institute of Aging, Toulouse University Hospital (CHU Toulouse), 37 Allée Jules Guesde, 31000 Toulouse, France. E-mail: emmanuel.gonzalez-bautista@univ-tlse3.fr

[#]Members are listed at the end of the manuscript.

Received: November 22, 2021; Editorial Decision Date: February 22, 2022

Decision Editor: Lewis A. Lipsitz, MD, FGSA

Abstract

Background: The 5-repetition chair stand test (CST) is increasingly being used to assess locomotion capacity in older adults. However, there is a lack of age-stratified cutoffs for adults aged ≥ 70 validated against a higher risk of functional loss.

Methods: We used 2 population-based studies (Study on global AGEing and adult health in Mexico [SAGE Mexico] and Toledo Study for Healthy Aging [TSHA]) and receiver operating characteristic (ROC) analyses to develop and cross-validate age-stratified chair stand cutoffs with activities of daily living (ADL) disability as the outcome. Then, we used data from an randomized controlled trial (RCT) (Multidomain Alzheimer Preventive Trial [MAPT]) and a frailty day-hospital for external validation with cross-sectional and longitudinal measures of ADL disability. The merged sample of SAGE Mexico and TSHA was $n = 1\,595$; sample sizes for external validation were: MAPT $n = 1\,573$ and Frailty day-hospital $n = 2\,434$. The Cox models for incident disability in MAPT had a mean follow-up of 58.6 months.

Results: Cutoffs obtained were 14 second (ages 70–79) and 16 second (ages 80+). Those cutoffs identified older adults at higher odds of incident ADL disability odds ratio (OR) = 1.72 (95% confidence interval [CI] 1.06; 2.78) for ages 70–79 and odds ratio (OR) = 2.27 (95% CI 1.07; 4.80) in those aged 80+. Being a slow chair stander according to the cut points was associated with ADL disability in cross-sectional and longitudinal measures.

Conclusions: Fourteen- and 16-second cut points for the CST are suitable to identify people at higher risk of functional decline among older adults in Mexico and Toledo, Spain. Adjusting the cut point from 14 to 16 second generally improved the psychometric properties of the test. The validation of these cutoffs can facilitate the screening for limited mobility and the implementation of the Integrated Care for Older People program.

Keywords: Chair stand test, Cutoffs, Integrated care, Intrinsic capacity, Locomotion assessment, Mobility clinimetrics

The 5-repetition chair stand test (CST) is a proxy of leg power, strength, and anteroposterior balance used in the context of functional assessment in older adults (1–3). Childhood socio-economic

circumstances, chronological age, and knee extension strength have been recognized as factors explaining the CST result in older adults (4,5). Impaired locomotion plays a role in multimorbidity, depres-

sion, probable sarcopenia and disability, and has been assessed using the CST (1,5–8).

The CST is part of the intrinsic capacity assessment in the World Health Organization's Integrated Care for Older People (ICOPE) strategy (9). If an older person performs 5 chair-stands in more than 14 second, the ICOPE handbook recommends that he/she should be further assessed for limited mobility with the complete Short Physical Performance Battery (SPPB) test (1). However, to the best of our knowledge, the 14 second cut point has not been validated to detect older adults at higher risk of functional decline. The CST, as part of SPPB, uses the cutoffs 11.2, 13.7, and 16.7 second for defining chair stand performance categories (1). Other studies have set 5-repetition chair stand cut points ranging from 9.7 to 14 second (listed in [Supplementary Table A](#)), with 1 meta-analysis reporting age-stratified mean values for the 5-repetition CST (11.4 second for 60–69 years; 12.6 second for 70–79 years; 14.8 second for 80–89 years) (10). Nevertheless, we did not find any cutoff validated against a functional decline in ages 80+. So far, the CST validation literature is lacking of: representative samples, longitudinal outcomes, and a focus on very old adults. There are no cutoffs validated for old and very old adults (aged 80+) in different clinical settings to stratify their risk of functional decline.

In the context of the ICOPE program, applying best-performing cut points for the CST would serve to flag those adults who need a closer follow-up along their care pathways (9,11). Therefore, our objective was to obtain cutoff points for the CST using population-based studies, with further cross-validation and external validation in populations from different settings.

Method

Data from 2 population-based studies were used for obtaining and cross-validating the age-stratified chair stand cutoffs (70–79 and ≥80 years) retrospectively. We used 2 different data sets (randomized controlled trial [RCT] and real-world users of the health system) for external validation in a second stage.

Study samples and characteristics are summarized in [Table 1](#).

Chair Stand Cutoff Points: Development and Cross-validation

Population

We used the WHO Study on global AGEing and adult health in Mexico (SAGE Mexico) and the Toledo Study for Healthy Aging (TSHA) cohort. Briefly, SAGE Mexico is a prospective cohort designed to be representative of adults aged 50 and over at the national level. All participants provided their informed consent, and the scientific board of the National Institute of Public Health approved the SAGE Mexico study. Further information on study design can be found elsewhere (12).

The TSHA is a prospective cohort designed to represent adults aged 65 and older living in the Spanish province of Toledo and comprising 24% of the census population of this population group (13). The Clinical Research Ethics Committee approved the TSHA of the Toledo Hospital. Data for both studies was collected by previously trained and standardized staff.

SAGE Mexico and TSHA measured the chair stand and ADL using the same standardized procedures. Adults aged 70 years or over were included in the present study, given that the incidence of ADL disability in younger participants was very low.

We randomly selected 50% of the combined data set (SAGE Mexico plus TSHA) stratified by age group to perform the cross-validation. Half of the population was used for obtaining the cut points, and the other half was used to cross-validate them. Based on previous observations about the difference in chair stand time by age group and the need for validating a cutoff tailored for very old adults, we performed our analysis separately for participants aged 70–79 and those aged 80 and over (1,14). Additionally, we compared the performance of sex-stratified cut points versus only age-stratified and sex-and age-stratified cut points ([Table 2](#)).

Chair stand measurement

Chair stand test: both studies measured the time in seconds taken by the participant to perform 5 chair rises at maximum speed with their arms folded across their chest. Standardized staff previously verified that at least 1 stand could be performed safely. Time was measured by previously standardized interviewers using a stopwatch to the nearest 0.1 second, from the starting sitting position to the last standing position at the end of the fifth stand (1).

Outcome measurement

The endpoint for elaborating the chair stand cutoff points and their cross-validation was the incidence of disability for the basic activities of daily living (ADLs, Katz scale—ambulating, feeding, dressing, personal hygiene, continence, and toileting) (15). Participants with the event at baseline (Katz <6) were excluded from this analysis, and incidence was defined as reporting disability for one or more ADLs during the follow-up.

Covariates

Age, sex, level of education (harmonized in 7 categories going from less than the primary school to postgraduate education), gait speed at usual pace (3- and 4-meter walk in TSHA and SAGE, respectively, harmonized in m/s), and study source (TSHA or SAGE).

Chair Stand Cutoff Points: External Validation

We used data from a randomized controlled trial (RCT—the Multidomain Alzheimer Preventive Trial (MAPT)) and a clinical database of users of the frailty day-hospital of the Toulouse University Hospital.

Populations

MAPT methodology has been described elsewhere (16). In brief, MAPT was a 3-year RCT examining the effects of a multidomain intervention on cognitive function among community-dwelling adults aged 70 years and older. An additional 2-year observational period was carried on after the intervention. The trial protocol (ClinicalTrials.gov identifier: NCT00672685) was approved by the French Ethical Committee located in Toulouse (CPP SOOM II). All participants signed their consent forms before any study assessment. Inclusion criteria were meeting at least one of (a) spontaneous memory complaints, (b) limitation in 1 instrumental activity of daily living, or (c) slow gait speed (≤ 0.8 m/s). Exclusion criteria comprised: Mini-Mental State Examination (MMSE) score <24, diagnosis of dementia, limitation in any basic ADLs, and taking polyunsaturated fatty acid (PUFA) supplements at baseline.

We also used cross-sectional routinely collected data from the frailty ambulatory clinic of the Toulouse University Hospital (2011–2019). This service receives patients referred from their family

Table 1. Qualitative Features and Relevant Variables of the Studies Used

Study features	SAGE Mex + TSHA		MAPT		Toulouse Frailty Clinic	
Used for	Development and cross-validation		External validation		External validation	
Dates of data collection	SAGE: 2014–2017 TSHA: 2011–2013		2008–2013		2011–2019	
Mean follow-up	SAGE: 3 years TSHA: 3 years		4.5 years		Cross-sectional	
Type of population	Community-dwelling older adults*. Sampling stratified by sex, age, and rural/urban location; representative at the national level for Mexico and at the local level for Toledo		Community-dwelling volunteers in an RCT in 13 memory clinics in France		Users of the health system in Toulouse	
Methods	ROC analysis (Youden's index) and logistic regression with incident ADL as an outcome for cross-validation		Incident ADL disability: Cox regression Number of ADLs impaired: Mixed-effects linear regression		Logistic regression for association with ADL disability	
Key variables	SAGE Mex + TSHA		MAPT		Toulouse Frailty Clinic	
<i>n</i> (%)	70–79	80+	70–79	80+	70–79	80+
<i>n</i>	1 229 (77.1)	366 (22.9)	1 295 (82.3)	278 (17.7)	786 (32.3)	1 648 (67.7)
Age (y), mean (<i>SD</i>)	73.9 (2.9)	82.9 (3.1)	73.7 (2.8)	82.6 (2.5)	75.9 (2.9)	85.9 (3.8)
Women	650 (52.9)	188 (51.4)	849 (65.6)	170 (61.2)	497 (63.2)	1 053 (63.9)
Chair stand time (s), mean (<i>SD</i>)	13.6 (3.9)	14.9 (4.5)	11.4 (3.4)	12.8 (3.8)	13.6 (4.7)	15.2 (5.2)
Incident ADL*	198 (16.1)	99 (27.1)	109 (13.5)	29 (25.4)	286† (36.5)†	765† (46.7)†

Notes: ADL = activities of daily living; MAPT = Multidomain Alzheimer Preventive Trial; RCT = randomized controlled trial; ROC = receiver operating characteristic.

*Except for 1.9% of the total population of TSHA who was institutionalized.

†Prevalence (only cross-sectional data are available for the Toulouse frailty clinic).

doctors. After a comprehensive geriatric assessment, an integrative care plan is designed and transmitted to the caregivers by the Gerontopole's team. Patients are informed by a notice that their data might be used for research. In all cases we used data from people aged 70 and older.

Variables of Interest

The CST was also used in MAPT and frailty day-hospital (1). Incident ADL disability was measured using the Katz scale as for SAGE and TSHA (15). ADL data were available at baseline for MAPT and the frailty clinic and at 48 and 60 months for MAPT. Covariates used in our cross-validation models were: sex, age, MAPT randomization group, level of education, MMSE score (17), and 15-item geriatric depression scale (GDS-15) (18).

Statistical Analysis

Chair Stand Cut Point Elaboration and Cross-validation

Data from SAGE and TSHA were merged. We randomly selected 50% of the age-stratified merged populations (70–79 and ≥80 years old in SAGE + TSHA) using the “sample” routine in STATA. In this first half of the randomly selected sample we ran 1 000 bootstrap repetitions of the cutoff point estimation using Youden's index overall and for age-, sex- and, sex-and age stratified cut points.

The psychometric parameters (ie, sensitivity, specificity, accuracy) of those cut points found were tabulated and compared to those of the cut point suggested by the WHO (14 seconds). Comparison for age-, sex- and sex-and age stratified cut points are shown in Table 2.

Additionally, we obtained cut points according to different levels of either sensitivity or specificity, as an alternative to Youden's index (Online resource [Supplementary Table B](#)). We also compared the area under the ROC curve (AUC) for gait speed with that of CST as a reference ([Supplementary Figure S1](#)).

The second half of the randomly selected population was used to cross-validate the cut points' capacity of identifying older adults with a higher probability of incident disability in a bootstrapped logistic regression adjusted for age, sex, education, gait speed, and study source to control for the “intrinsic” characteristics of the study within the merged sample.

External Validation

MAPT: (a) Cox models (time-to-first event) for incident ADL disability were adjusted by age, sex, education level, MAPT group, baseline MMSE (17), and baseline GDS (18). The proportionality assumption was confirmed by the Schoenfeld residuals test. (b) Linear mixed-effect models were used to assess the association between slow chair standers and functional decline for ADLs.

Frailty day-hospital data set: we ran binary logistic regression models for ADL disability. We estimated the odds of ADL disability for slow chair standers (disability for ≥1 ADL vs full functionality). All analyses were performed using Stata (StataCorp, College Station, TX), with $\alpha = 0.05$.

Role of the Funding Source

The funder had no role in study design, data collection, data analysis, data interpretation, or report writing. The corresponding author had

Table 2. Age-, Sex- and Age-and-sex Stratified Cut Points Found Using the Youden's Index and Their Psychometric Properties Compared to the Current Cut Point

		No Age Stratification			70–79		80+		
		param	95% CI	% change	param	95% CI	param	95% CI	% change
	New cut point found				Cut point found is the same as current 14 s				
		14 s			14 s	16 s			
No Sex Stratification	Sensitivity	0.56 (0.50; 0.62)	—		0.53 (0.46; 0.60)		0.44 (0.35; 0.55)	–28	
	Specificity	0.61 (0.58; 0.64)	—		0.63 (0.60; 0.66)		0.74 (0.69; 0.79)	42*	
	ROC area	0.58 (0.55; 0.62)	—		0.58 (0.54; 0.63)		0.61 (0.56; 0.68)	7*	
	Accuracy	0.60 (0.57; 0.63)	—		0.62 (0.58; 0.65)		0.66 (0.61; 0.71)	21	
	PPV	0.25 (0.21; 0.28)	—		0.22 (0.18; 0.26)		0.39 (0.30; 0.49)	20*	
	NPV	0.86 (0.83; 0.88)	—		0.88 (0.85; 0.90)		0.78 (0.73; 0.83)	0	
		14.6 s			14 s	14.6 s			
Women	Sensitivity	0.57 (0.49; 0.65)	–8		0.58 (0.48; 0.67)		0.71 (0.57; 0.83)	0	
	Specificity	0.62 (0.58; 0.66)	11*		0.58 (0.54; 0.63)		0.55 (0.47; 0.64)	22*	
	ROC area	0.59 (0.55; 0.64)	1		0.58 (0.53; 0.63)		0.63 (0.56; 0.71)	9	
	Accuracy	0.61 (0.56; 0.65)	7		0.58 (0.53; 0.63)		0.60 (0.49; 0.70)	14*	
	PPV	0.27 (0.22; 0.32)	6		0.23 (0.18; 0.28)		0.36 (0.27; 0.47)	15*	
	NPV	0.85 (0.82; 0.88)	0		0.86 (0.82; 0.90)		0.85 (0.76; 0.91)	3	
		15.8 s			14 s	17.1 s			
Men	Sensitivity	0.35 (0.27; 0.44)	–28		0.48 (0.36; 0.59)		0.36 (0.23; 0.51)	–31	
	Specificity	0.83 (0.79; 0.85)	24*		0.69 (0.65; 0.73)		0.84 (0.76; 0.90)	41*	
	ROC area	0.59 (0.55; 0.63)	2		0.58 (0.52; 0.64)		0.60 (0.52; 0.67)	7	
	Accuracy	0.74 (0.71; 0.77)	17*		0.66 (0.61; 0.70)		0.70 (0.64; 0.76)	23*	
	PPV	0.30 (0.23; 0.37)	26*		0.20 (0.14; 0.26)		0.46 (0.30; 0.63)	39*	
	NPV	0.86 (0.83; 0.89)	0		0.89 (0.86; 0.92)		0.77 (0.69; 0.84)	1	

Notes: CI = confidence interval; NPV = negative predictive value; param = psychometric parameter; PPV = positive predictive value; ROC area = area under the receiver–operator–characteristics curve vis à vis ADL incidence. The psychometric properties for the current cut point of 14 s are provided in [Supplementary Table C](#).

*Psychometric features of the new cut point were >10% higher compared with the current cut point.

full access to all the data in the study and had the final responsibility for submitting it for publication.

Results

Chair Sand Cutoff Points: Elaboration and Cross-validation

The cutoffs derived were 14 second for the overall study sample. Also 14 second for those aged 70–79 and 16 second for those aged 80 and over. Sex-and-age-stratified cut points are shown in [Table 2](#). We will refer to older adults with a chair stand result at or above the cutoff points as “slow chair standers”; those with chair stand result below the cutoff were “fast chair standers.” Both cutoff points provided AUC values higher than 0.5 ([Table 2](#)). The age-stratified cut point (16 second for the 80+ age group) performed with higher specificity, accuracy, and positive predictive value compared to the 14 second cut point ([Table 2](#)). The highest increases in accuracy were found with age-stratified cut points, even when compared to sex- and age-stratified cut points. Cross-validation found that slow chair standers in both age groups had 2-fold higher odds of incident ADL disability than their counterparts OR = 1.72 (95% confidence interval [CI] 1.06; 2.78) for 70–79 year and OR = 2.27 (95% CI 1.07; 4.80) for 80+ ([Table 3](#)).

Chair Stand Cut Point External Validation

Data from MAPT showed that slow chair standers are at higher risk of incident ADL disability than their faster counterparts in Cox models adjusted for covariates with a mean follow-up of 58.6 months (for 70–79: Hazard ratio (HR) = 1.65 (95% CI 1.07; 2.57) and for 80+: HR = 1.85 (95% CI 0.75; 4.61). ([Table 3](#)).

Slow chair standers had a significantly steeper functional decline for ADLs over time than fast chair standers for both age groups and the difference was clinically relevant for those aged 80+. Between-group differences over 5 years were 0.038 (95% CI –0.07; –0.01), and 0.325 (95% CI –0.50; –0.15) points for 70–79 and 80+ age groups, respectively ([Table 3](#) and [Supplementary Figure S2](#)).

Data from the Frailty day-hospital showed that slow chair standers had 2.3 times and 2.1 higher odds and of being disabled in ADLs than their fast counterparts for 70–79 and 80+ age groups, respectively ([Table 3](#)).

Discussion

The cutoff points found for the CST were 14 second for the 70–79 age group and 16 second for those aged 80+ for incident ADL disability. According to these cut points, slow chair standing was linked

Table 3. Cross-validation and External Validation of the Cut Points

Model	70–79				80+			
	<i>n</i>	param	95% CI	<i>p</i>	<i>n</i>	param	95% CI	<i>p</i>
Cross-validation								
A	612	1.72	(1.06; 2.78)	.027	183	2.27	(1.07; 4.80)	.032
External validation								
B	794	1.65	(1.07; 2.57)	.025	112	1.85	(0.75; 4.61)	.072
C	794	-0.04	(-0.07; -0.01)	.018	112	-0.32	(-0.50; -0.15)	<.001
D	721	2.33	(1.68; 3.21)	<.001	1523	2.08	(1.67; 2.59)	<.001

ADL = activities of daily living; CI = confidence interval; GDS = geriatric depression scale; MAPT = Multidomain Alzheimer Preventive Trial; MMSE = Mini-Mental State Examination; param = estimated parameter. Model A. Odds ratio from a logistic model for incident disability for basic ADLs over 3-year FU, adjusted for age, sex, education, gait speed, and study (SAGE + TSHA). Model B. Hazards ratio from a Cox model for incident disability for basic ADLs over a 5-year FU, adjusted for age, sex, education, MAPT group, and baseline MMSE, GDS (MAPT). Model C. Mean difference in number of functionally-preserved basic ADLs between fast chair standers and slow chair standers after 5-year FU from a mixed-effects model adjusted for age and sex (MAPT; [Supplementary Figure S2](#)). Model D. Odds ratio from a cross-sectional logistic model for basic ADLs disability, adjusted for age, sex, education, and baseline MMSE (Toulouse Frailty clinic).

to ADL disability in a cross-sectional and longitudinal fashion among older adults from different clinical settings. Our findings provide the first development and validation of age-stratified cutoffs for the CST in older adults using population-based studies.

The validated cutoff point of 14 second for the age group 70–79 is consistent with what is currently proposed in the screening (Step 1) of the ICOPE handbook. It is also congruent with cutoffs found by 5 out of 10 previous studies from different countries (see online resource [Supplementary Table A](#)). Lower cutoff points (10 second) have been found in younger/healthier populations with lower incident disability rates ([19,20](#)).

We did not find any reference focusing on the age group 80+, highlighting the importance of the present work. The cutoff point we found for this age group is congruent with Bohannon's meta-analysis reporting a mean time of 14.8 second for those aged 80–89 ([10](#)) and with the population in the validation study of the SPPB ([1](#)).

The 14 second cutoff proposed in the WHO ICOPE handbook ([9](#)) was validated in our study for the adults aged 70–79. Indeed, our results suggest that the cutoff of 16 second for adults aged 80 and over would be more appropriate. Adjusting the cut point from 14 to 16 second in adults aged 80+ would bring important improvements in specificity, accuracy, and positive predictive value. Thus, fewer adults would be falsely catalogued as having impaired mobility and a potential reduction in the health systems' burden. Innovative approaches for measuring the CST in older adults such as sensors or mobile apps are advantageous for research or clinical contexts ([21,22](#)).

Our study has several strengths: the cutoffs were derived from population-based studies from different countries and then tested in data sets representing volunteers for an RCT and users of the health system. Limitations are that we cannot be sure that these cut points will apply in other latitudes. Regarding the relatively low values for the AUC 0.58 (CI 95% 0.54; 0.63) and 0.61 (CI 95% 0.56; 0.68) for the 70–79 and 80+, respectively ([Table 2](#)), it is essential to note that previous studies have published AUC values <0.70 for chair stand discrimination of incident disability ([20](#)). The relatively low AUC values found throughout studies suggests that the CST cutoff should be used along other parameters such as the rest of the domains of intrinsic capacity to better discriminate those older adults at higher risk of ADL disability ([23,24](#)) ([Supplementary Figure S1](#)).

Noteworthy, cutoff points obtained using Youden's index are not the only possible ones, as different thresholds might be chosen in

different settings according to the main objective of the test (online resource [Supplementary Note and Table B](#)). Also, similar studies focused on younger adults should assess functional outcomes different from ADL disability.

In conclusion, 14 second and 16 second cut points for the CST were validated to identify individuals at higher risk of functional decline in adults aged 70–79 and 80+ years from Mexico, Toledo, and Spain. Also, those cut points worked well in volunteers of a RCT and in users of a frailty clinic. Validation of these cut points in other populations is desirable.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

The present work was performed in the context of the Inspire Program, a research platform supported by grants from the Region Occitanie/Pyrénées-Méditerranée (reference number: 1901175) and the European Regional Development Fund (ERDF; Project number: MP0022856). This study has been partially supported through the grant EUR CARE N°ANR-18-EURE-0003 in the framework of the Programme des Investissements d'Avenir. The MAPT study was supported by grants from the Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), Pierre Fabre Research Institute (manufacturer of the omega-3 supplement), ExonHit Therapeutics SA, and Avid Radiopharmaceuticals Inc. The promotion of this study was supported by the University Hospital Center of Toulouse. The data-sharing activity was supported by the Association Monegasque pour la Recherche sur la Maladie d'Alzheimer (AMPA) and the INSERM-University of Toulouse III Maintain Functions and Intrinsic capacities with Aging (MAINTAIN) Research team, Center for Epidemiology and population health research (CERPOP) Inserm, Université Paul Sabatier, Toulouse, France.

Conflict of Interest

None declared.

Ethics approval and consent to participate: All participants provided their informed consent. The trial protocol (ClinicalTrials.gov identifier: NCT00672685) was approved by the French Ethical Committee located in Toulouse (CPP SOOM II) and was authorized by the French Health Authority.

The scientific board of the National Institute of Public Health approved the SAGE Mexico study. The Clinical Research Ethics Committee approved the TSHA of the Toledo Hospital.

Acknowledgments

The authors thank Yuka Sumi and Ritu Sadana for their valuable inputs, Aging and Health unit, Department of Maternal, Newborn, Child & Adolescent Health and Aging World Health Organization (WHO), Geneva.

Author Contribution

E.G.-B., S.A., S.S., A.S.-R., B.M.E., L.R.-M., P.S.B., Y.R., and B.V. substantially contributed to the conception and design, analysis, and interpretation of data. E.G.-B. and P.S.B. performed statistical analyses and wrote the manuscript. E.G.-B., S.A., S.S., A.S.-R., B.M.E., L.R.-M., P.S.B., Y.R., and B.V. provided valuable intellectual inputs and reviewed the manuscript. E.G.-B., S.A., S.S., A.S.-R., B.M.E., L.R.-M., P.S.B., Y.R., and B.V. final approval of the version to be published.

MAPT/DSA Group

MAPT Study Group

Principal investigator: Bruno Vellas (Toulouse); Coordination: Sophie Guyonnet; Project leader: Isabelle Carrié; CRA: Lauréane Brigitte; Investigators: Catherine Faisant, Françoise Lala, Julien Delrieu, Hélène Villars; Psychologists: Emeline Combrouze, Carole Badufle, Audrey Zueras; Methodology, statistical analysis and data management: Sandrine Andrieu, Christelle Cantet, Christophe Morin; Multidomain group: Gabor Abellan Van Kan, Charlotte Dupuy, Yves Rolland (physical and nutritional components), Céline Caillaud, Pierre-Jean Ousset (cognitive component), Françoise Lala (preventive consultation). The cognitive component was designed in collaboration with Sherry Willis from the University of Seattle, and Sylvie Belleville, Brigitte Gilbert and Francine Fontaine from the University of Montreal.

Co-Investigators in associated centers: Jean-François Dartigues, Isabelle Marcet, Fleur Delva, Alexandra Foubert, Sandrine Cerda (Bordeaux); Marie-Noëlle-Cuffi, Corinne Costes (Castres); Olivier Rouaud, Patrick Manckoundia, Valérie Quipourt, Sophie Marilier, Evelyne Franon (Dijon); Lawrence Bories, Marie-Laure Pader, Marie-France Basset, Bruno Lapoujade, Valérie Faure, Michael Li Yung Tong, Christine Malick-Loiseau, Evelyne Cazaban-Campistron (Foix); Françoise Desclaux, Colette Blatge (Lavaur); Thierry Dantoine, Cécile Laubarie-Mouret, Isabelle Saulnier, Jean-Pierre Clément, Marie-Agnès Picat, Laurence Bernard-Bourzeix, Stéphanie Willebois, Iléana Désormais, Noëlle Cardinaud (Limoges); Marc Bonnefoy, Pierre Livet, Pascale Rebaudet, Claire Gédéon, Catherine Burdet, Flavien Terracol (Lyon); Alain Pesce, Stéphanie Roth, Sylvie Chaillou, Sandrine Louchart (Monaco); Kristel Sudres, Nicolas Lebrun, Nadège Barro-Belaygues (Montauban); Jacques Touchon, Karim Bennis, Audrey Gabelle, Aurélia Romano, Lynda Touati, Cécilia Marelli, Cécile Pays (Montpellier); Philippe Robert, Franck Le Duff, Claire Gervais, Sébastien Gonfrier (Nice); Yannick Gasnier and Serge Bordes, Danièle Begorre, Christian Carpuat, Khaled Khaled, Jean-François Lefebvre, Samira Misbah El Idrissi, Pierre Skolil, Jean-Pierre Salles (Tarbes).

MRI group: Carole Dufouil (Bordeaux), Stéphane Lehericy, Marie Chapin, Jean-François Mangin, Ali Bouhayia (Paris); Michèle Allard (Bordeaux); Frédéric Ricolfi (Dijon); Dominique Dubois (Foix); Marie Paule Bonceour Martel (Limoges); François Cotton (Lyon); Alain Bonafé (Montpellier); Stéphane Chanalet (Nice); Françoise Hugon (Tarbes); Fabrice Bonneville, Christophe Cognard, François Chollet (Toulouse).

PET scans group: Pierre Payoux, Thierry Voisin, Julien Delrieu, Sophie Peiffer, Anne Hitzel, (Toulouse); Michèle Allard (Bordeaux); Michel Zanca (Montpellier); Jacques Monteil (Limoges); Jacques Darcourt (Nice).

Medico-economics group: Laurent Molinier, Hélène Derumeaux, Nadège Costa (Toulouse).

Biological sample collection: Bertrand Perret, Claire Vinel, Sylvie Caspar-Bauguil (Toulouse).

Safety management: Pascale Olivier-Abbal.

DSA Group

Sandrine Andrieu, Christelle Cantet, Nicola Coley.

Data Availability


Documentation and metadata of the SAGE, TSHA, and MAPT studies can be accessed by contacting the study management teams of the studies on reasonable request. Data on the Frailty Clinic will not be publicly available. Code is available upon request to the corresponding author.

References

- Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* 1994;49(2):M85–M94. doi:10.1093/geronj/49.2.M85
- Bohannon RW. Sit-to-Stand test for measuring performance of lower extremity muscles. *Percept Mot Skills.* 1995;80(1):163–166. doi:10.2466/pms.1995.80.1.163
- Cai Y, Tian Q, Gross AL, et al. Motor and physical function impairments as contributors to slow gait speed and mobility difficulty in middle-aged and older adults. *J Gerontol A Biol Sci Med Sci.* 2022. doi:10.1093/GERONA/GLAC001
- Bohannon RW, Bubela DJ, Magasi SR, Wang YC, Gershon RC. Sit-to-stand test: performance and determinants across the age-span. *Isokinet Exerc Sci.* 2010;18(4):235–240. doi:10.3233/IES-2010-0389
- Kuh D, Karunanathan S, Bergman H, Cooper RA. Life-course approach to healthy ageing: maintaining physical capability. *Proc Nutr Soc.* 2014;73(2):237–248. doi:10.1017/S0029665113003923
- Dodds RM, Murray JC, Granic A, et al. Prevalence and factors associated with poor performance in the 5-chair stand test: findings from the Cognitive Function and Ageing Study II and proposed Newcastle protocol for use in the assessment of sarcopenia. *J Cachexia Sarcopenia Muscle.* 2021;12(2):308–318. doi:10.1002/jcsm.12660
- Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc.* 2005;53(4):649–654. doi:10.1111/j.1532-5415.2005.53214.x
- Peek MK, Ottenbacher KJ, Markides KS, Ostir GV. Examining the disablement process among older Mexican American adults. *Soc Sci Med.* 2003;57(3):413–425. doi:10.1016/s0277-9536(02)00367-2
- World Health Organization. *Integrated Care for Older People (ICOPE): Guidance for Person-Centred Assessment and Pathways in Primary Care.* Geneva: WHO; Accessed November 14, 2019. <https://apps.who.int/iris/bitstream/handle/10665/326843/WHO-FWC-ALC-19.1-eng.pdf?sequence=17>
- Bohannon RW. Reference values for the five-repetition sit-to-stand test: a descriptive meta-analysis of data from elders. *Percept Mot Skills.* 2006;103(5):215–222. doi:10.2466/pms.103.1.215-222
- World Health Organization. *World Report on Ageing and Health.* Geneva: WHO; 2015. ISBN:978 92 4 069481 1.
- Kowal P, Chatterji S, Naidoo N, et al. Data resource profile: the World Health Organization Study on global AGEing and adult health (SAGE). *Int J Epidemiol.* 2012;41(6):1639–1649. doi:10.1093/ije/dys210
- García-García FJ, Gutierrez Avila G, Alfaro-Acha A, et al. The prevalence of frailty syndrome in an older population from Spain. The Toledo study for healthy aging. *J Nutr Health Aging.* 2011;15(10):852–856. doi:10.1007/s12603-011-0075-8
- González-Bautista E, Barreto PDS, Giudici KV, Andrieu S, Rolland Y, Vellas B. Frequency of conditions associated with declines in intrinsic capacity according to a screening tool in the context of integrated care for older people. *J Frailty Aging.* 2021;10(2):94–102. doi:10.14283/JFA.2020.42
- Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist.* 1970;10(1):20–30. doi:10.1093/geront/10.1_part_1.20

16. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol.* 2017;16(5):377–389. doi:10.1016/S1474-4422(17)30040-6
17. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189–198. doi:10.1016/0022-3956(75)90026-6
18. Yesavage JA, Sheikh JJ. Geriatric Depression Scale (GDS). *Clin Gerontol.* 1986;5(1–2):165–173. doi:10.1300/J018v05n01_09
19. Seino S, Yabushita N, Kim M-J, et al. Physical performance measures as a useful indicator of multiple geriatric syndromes in women aged 75 years and older. *Geriatr Gerontol Int.* 2013;13(4):901–910. doi:10.1111/ggi.12029
20. Makizako H, Shimada H, Doi T, et al. Predictive cutoff values of the five-times Sit-to-Stand Test and the Timed “Up & Go” test for disability incidence in older people dwelling in the community. *Phys Ther.* 2017;97(4):417–424. doi:10.2522/ptj.20150665
21. Park C, Sharafkhan A, Bryant MS, Nguyen C, Torres I, Najafi B. Toward remote assessment of physical frailty using sensor-based sit-to-stand test. *J Surg Res.* 2021;263:130–139. doi:10.1016/j.jss.2021.01.023
22. App Review: PowerFrail for the assessment of relative muscle power and frailty in older people—BJSM blog—social media’s leading SEM voice. Accessed February 1, 2022. <https://blogs.bmj.com/bjsm/2021/02/04/app-review-powerfrail-for-the-assessment-of-relative-muscle-power-and-frailty-in-older-people/>
23. González-Bautista E, de Souto Barreto P, Andrieu S, Rolland Y, Vellas B. Screening for intrinsic capacity impairments as markers of increased risk of frailty and disability in the context of integrated care for older people: Secondary analysis of MAPT. *Maturitas.* 2021;150:1–6. doi:10.1016/j.maturitas.2021.05.011
24. Stolz E, Mayerl H, Freidl W, Roller-Wirnsberger R, Gill TM. Intrinsic capacity predicts negative health outcomes in older adults. *J Gerontol A Biol Sci Med Sci.* 2022;77(1):101–105. doi:10.1093/GERONA/GLAB279

Clinically meaningful change for the chair stand test: monitoring mobility in integrated care for older people

Emmanuel Gonzalez-Bautista^{1,2*} , Philippe de Souto Barreto^{1,2}, Aaron Salinas-Rodriguez³, Betty Manrique-Espinoza³, Yves Rolland^{1,2}, Sandrine Andrieu^{1,2}, Bruno Vellas^{1,2} for the MAPT/DSA group

¹Gerontopole of Toulouse, Institute of Aging, Toulouse University Hospital (CHU Toulouse), Toulouse, France; ²CERPOP UMR 1295, University of Toulouse III, INSERM, UPS, Toulouse, France; ³Center for Surveys and Evaluation Research, National Institute of Public Health (INSP) Mexico, Cuernavaca, Mexico

Abstract

Background Clinically meaningful changes in the five-repetition chair stand test are essential for monitoring mobility in integrated care for older people. Recommendations for the clinically meaningful change of the chair stand test are not well known. Our study aimed to estimate the absolute and relative clinically meaningful changes for older adults' five-repetition chair stand test.

Methods We applied distribution-based and anchor-based methods in addition to receiver operator characteristics analyses to a population-based study of community-dwelling adults (SAGE Mexico study, $n = 897$) to derive the clinically meaningful change in the chair stand test. We used three self-reported clinical anchors: moving around, vigorous activities, and walking 1 km. Our primary outcome was the incidence of disability for basic activities of daily living (ADL). Secondly, we examined our estimates of clinically meaningful change in a clinical trial population of healthy volunteers (MAPT, France, study $n = 1575$) concerning the risk of incident ADL disability.

Results The age of SAGE Mexico participants ranged from 60 to 96 years; mean (SD) = 69.0 (6.2); 54.4% were female. Their baseline chair stand time averaged 12.1 s (SD = 3 s). Forty-eight participants (5.6%) showed incident disability over 3 years. The absolute and relative clinically meaningful change cut points found over 3 years of follow-up were 2.6 s and 27.7%, respectively. Absolute clinically meaningful change ranged from 0.5 to 4.7 s, depending on the estimation method. Relative clinically meaningful change ranged from 9.6 to 46.2%. SAGE Mexico participants with absolute and relative clinically meaningful declines (increasing 2.6 s and 27.7% from baseline time, respectively) showed an increased risk of ADL disability [aRR = 1.93; $P = 0.0381$; 95% CI (1.05, 3.46) and aRR = 2.27; $P = 0.0157$; 95% CI (1.22, 4.10)], respectively, compared with those without a clinically meaningful decline. MAPT participants [age range = 70–94; mean (SD) = 75.3 (4.4); 64.8% female; incident ADL disability over 5 years = 145 (14.8%)] with a relative clinically meaningful decline ($\geq 27.7\%$ from baseline over 3 years) had a 74% higher risk of incident ADL disability than their counterparts [aHR = 1.74; $P = 0.016$; CI95% (1.11, 2.72); mean follow-up of 58 months].

Conclusions Community-dwelling older adults with an increase of 3 s or 28% in chair stand test performance over 3 years (approximately 1 s or 10% per year) could be the target of interventions to enhance mobility and prevent incident disability.

Keywords Physical functional performance; Five-repetition chair stand test; Clinically meaningful change; Older adults

Received: 17 March 2022; Revised: 12 May 2022; Accepted: 13 June 2022

*Correspondence to: Emmanuel Gonzalez-Bautista, Gerontopole of Toulouse, Institute of Aging, Toulouse University Hospital (CHU Toulouse), 37 Allée Jules Guesde, 31000 Toulouse, France. Mobile: +336 22 10 14 96. Email: emmanuel.gonzalez-bautista@univ-tlse3.fr
MAPT/DSA group members are listed at the end of the manuscript.

Introduction

Clinically meaningful changes (also known as clinically relevant changes) are essential in the context of the integrated care for older people (ICOPE) strategy¹ to stratify individuals at risk for care dependency. Indeed, the ICOPE care model is being used to monitor older adults' five intrinsic capacity domains to detect early declines and prevent disability.² Locomotion is a crucial indicator of independence during ageing.^{3,4} It is assessed in the ICOPE model using the five-repetition chair stand test. During their clinical follow-up, older adults are expected to show variations in chair stand test performance⁵; nevertheless, the clinically meaningful change for the five-repetition chair stand test has not been established yet.

Compared with previously reported cut points for cross-sectional locomotion assessment,^{6,7} the clinically meaningful change has an added value during clinical monitoring when repeated measures of the chair stand test are obtained over time. Clinical staff might be empowered to detect substantial declines in older adults' locomotion domain even before crossing the conventional cut point.

Clinical significance can be operationalized using (i) distribution-based interpretations, statistically driven, like the standard error of measurement (SEM), and (ii) anchor-based interpretations, comparing the results in the outcome of interest to other clinical changes or 'anchors'.^{8–10} The relevance of clinically meaningful change for performance measures in the geriatric clinical and research settings has been recently highlighted by the International Conference of Frailty and Sarcopenia Research Task Force.¹¹ In mobility/locomotion, previous reports have integrated distribution-based and anchor-based methods to provide overall recommendations for meaningful change of gait speed, short physical performance battery (SPPB) score, and 6-min distance walk for older adults. Still, they did not include estimates and recommendations for the chair stand test.^{12,13}

Among the studies approaching the clinically meaningful mobility performance changes, we did not find any reporting data for the chair stand test.^{13–15} There is a knowledge gap about the magnitude of the clinically meaningful change that could be applied to the chair stand test to monitor the locomotion in older adults. Given the increasing international implementation of ICOPE, understanding the clinically meaningful amount of decline in chair stand test becomes crucial to inform timely interventions and decrease the risk of disability. Therefore, our study aimed to derive recommendations for absolute and relative (percent) clinically meaningful change for the chair stand test in older adults.

Methods

We used data from a population-based study: the World Health Organization (WHO) Study on global AGEing and adult

health in Mexico, also known as SAGE Mexico. Based on previous reports,¹¹ we derived the clinically meaningful absolute and relative changes in the chair stand test that could warn clinicians of older adults' higher risk of becoming disabled for basic activities of daily living (ADL). Absolute clinically meaningful change was defined as the difference in seconds (s) between the baseline and follow-up measurements of the chair stand time. Relative clinically meaningful change (%) was defined as the percentage change between baseline and follow-up measures. We used distribution methods, which are based on the statistical distribution of the chair stand test. Anchor-based methods were also applied, which are 'anchored' to patient-reported mobility outcomes (e.g. 'how much difficulty did you have in walking a long distance such as a kilometre?').

Finally, we tested if participants with clinically meaningful absolute and relative declines were at significantly higher risk of incident ADL disability using data from the Multidomain Alzheimer Preventive Trial (MAPT).

Data sources

SAGE Mexico

We used the second and third waves (3-year apart from each other) of SAGE Mexico, given that the first wave of this study did not assess the chair stand test. Briefly, the WHO Study on global AGEing and adult health in Mexico, also known as SAGE Mexico, is a prospective cohort study with a multi-stage, stratified, and clustered sample designed to represent non-institutionalized older adults at the national level. Data were collected at the participant's lodgement by standardized trained staff using electronic records (CAPI). All participants provided their informed consent, and the scientific board of the National Institute of Public Health approved the SAGE Mexico study. In this study, we included participants aged 60 and older. Further information on study design can be found elsewhere.¹⁶

MAPT

We used data from the MAPT randomized controlled trial, which methodology has been described elsewhere.^{17,18} In brief, MAPT was a 3-year randomized controlled trial among community-dwelling adults aged 70 years and older examining the effects on cognitive function of a multidomain intervention (nutritional and physical activity counselling, cognitive training, and annual preventive consultations for the management of cardiovascular risk factors) with and without supplementation of omega-three polyunsaturated fatty acids. After the intervention, an additional 2-year observational period was carried out (total period: 2008–2016). The trial protocol (ClinicalTrials.gov identifier: NCT00672685) was approved by the French Ethical Committee located in Toulouse (CPP SOOM II) and

was authorized by the French Health Authority. All participants signed their consent forms before any study assessment. Inclusion criteria were meeting at least one of (i) spontaneous memory complaints, (ii) limitation in one instrumental activity of daily living, or (iii) slow gait speed (≤ 0.8 m/s). Exclusion criteria comprised Mini-Mental State Examination score < 24 , diagnosis of dementia, limitation in ADLs, and taking polyunsaturated fatty acid supplements at baseline. MAPT study provided data for several time points (baseline, 6, 12, 24, 36, 48, and 60 months).

SAGE Mexico and MAPT studies have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Measures

Chair stand test

Both SAGE Mexico and MAPT measured the time in seconds the participant took to perform five chair stands at maximum speed with their arms folded across their chest. The protocol started by the interviewer by asking the question: 'Do you think it would be safe for you to try to stand up from a chair five times without using your arms?' The interviewer then demonstrated and explained the test using the chair usually employed by the participant placed with its back against a wall. Following, the interviewer indicated: 'Please stand up straight as quickly as you can five times, without stopping in between. After standing up each time, sit down and then stand up again. Keep your arms folded across your chest. I'll be timing you with a stopwatch'. Trained assessors measured time from the starting sitting position to the end of the fifth stand.¹⁹

The test was stopped if the participants became tired or short of breath during repeated chair stands; used their arms; after 1 minute, had not yet completed five rises; or at the interviewers' discretion, if concerned for their safety.

Disability for the basic ADL

The incidence of ADL disability (Katz scale)²⁰ was the outcome for elaborating the clinically meaningful change cut point. Scores on this scale vary from 0 (*total disability*) to 6 (*no disability*). Participants with the event at baseline (Katz < 6) were excluded from this analysis, and incidence was defined as reporting disability for one or more ADLs. We applied the exact definition in SAGE Mexico and MAPT.

Anchor measures

We used three items from the self-reported activities questionnaire in SAGE Mexico. These items were chosen because they are closely related to the locomotion domain.

Item 1: Overall, in the last 30 days, how much difficulty did you have with moving around?

Item 2: Overall, in the last 30 days, how much difficulty did you have in vigorous activities? ('vigorous activities' require hard physical effort and cause significant increases in breathing or heart rate)

Item 3: Overall, in the last 30 days, how much difficulty did you have in walking a long distance such as a kilometre?

These items were initially scored by self-reported difficulty levels using a Likert-type scale from 1 to 5. For our study, and following literature,⁸ we re-coded them in four strata: no change, small meaningful worsening (those who worsened within the mild–moderate difficulty), substantial, meaningful worsening (those who declined to severe and extreme difficulty), and no possibility of worsening (extreme difficulty at baseline or observed improving at follow-up).

Data analysis

Overview

The relative clinically meaningful difference was calculated using $(\Delta \text{ chair-stand-time} \times 100 / \text{baseline chair-stand-time})$. The absolute and relative clinically meaningful changes were obtained by (i) applying distribution-based (effect size and standard error of measurement SEM), (ii) anchor-based approaches (comparison of means between those who did and did not self-report decline in mobility items), and (iii) receiver operator characteristics (ROC)-derived Youden's index. We verified that these clinically meaningful changes were lower than the mean decline observed in participants with incident ADL disability (marginal means).

Next, we computed the adjusted risk ratios of incident disability for ADLs based on those participants with clinically meaningful declines in SAGE Mexico and MAPT using a logistic model adjusted for age, sex, and baseline chair stand time. Finally, we estimated the hazard ratio for incident disability for MAPT participants with clinically meaningful declines using Cox models adjusted for age, sex, education level, MAPT allocation group, and baseline chair stand time. The proportional hazards assumption was confirmed by Schoenfeld residuals and by time-varying covariates. All analyses were performed using STATA® 17.

Meaningful change according to effect size

Using the effect size formula ($\delta = (\mu_1 - \mu_2) / \sigma_1$) and conventional definitions of small and moderate effect,^{21–23} we calculated the small and moderate meaningful changes as $0.2 \times \sigma_1$ and $0.5 \times \delta_1$, respectively. μ_1 and μ_2 accounted for the mean chair stand test times at baseline and follow-up, respectively, and σ_1 was the standard deviation of the chair stand test performance (seconds) at baseline. Thus, the meaningful changes were estimated by solving for $(\mu_1 - \mu_2)$ in the effect size formula.

Meaningful change according to the SEM

The SEM provides a sort of ‘bottom line’ of the minimum change we would need to observe to discard it is not due to measurement error. The meaningful intra-individual change was calculated using the SEM, defined as $\sigma_1\sqrt{1-r}$.^{21,23,24} Reliability estimates for the chair stand test time were taken from a published source.²⁵

Meaningful change according to the comparison of means

We estimated the mean changes for the chair stand test time for those SAGE Mexico participants with self-reported small and substantial deterioration of the mobility items adjusted by age, sex, and baseline chair stand time. The definitions of small and substantial worsening were given under the ‘Anchor measures’ section. In line with previous literature,¹¹ those who could not worsen because of extreme difficulty at baseline or observed improving at follow-up were omitted from these estimations to reduce bias. These comparisons were estimated for the absolute and relative changes.

Meaningful change derived from ROC analyses

The Youden’s index was applied in ROC curves to derive the cut point of the absolute and relative change in the chair stand test times to better classify the participants according to their probability of incident ADL disability.²⁶

study than those lost during the follow-up (-0.30 s, $P = 0.0016$).

Summary of clinically meaningful changes for the five-repetition chair stand test

Please find a graphic summary of the absolute and relative clinically meaningful changes in *Figure 1*.

As shown in *Figure 1*, there is consistency across methodologies. The smallest is the SEM, followed by the clinically meaningful change according to the effect size and the clinically meaningful change derived from the ROC analyses. Subsequently, there is the anchor-based clinically meaningful change based on the changes in the mobility items, and the largest is the marginal means of the time changes observed in those older adults with incident ADL disability.

SAGE Mexico participants with an absolute clinically meaningful decline showed a 93% increase in the risk of ADL disability [aRR = 1.93; $P = 0.0381$; 95% CI (1.05, 3.46)], and the risk for those with a relative decline was 2.27 times higher [aRR = 2.27; $p = 0.0157$; 95% CI (1.22, 4.10)] compared with those without a clinically meaningful decline. See *Table S1*.

Results

Participants of SAGE Mexico and MAPT included in these analyses are described in *Table 1*. Further characterizations have been published elsewhere.^{16,17} Briefly, the majority of SAGE Mexico participants included in this study were younger than 75 [age range = 60–96; mean (SD) = 69.0 (6.2)] and female (54.4%); 23% of them had achieved secondary school or higher. Their baseline time averaged 12.1 s (SD = 3 s) and 14.7 s (SD = 4.9 s) after 3 years of follow-up. The chair stand test time increased (thus locomotion capacities diminished) for 68.8% of the study sample, and the opposite was true for 31.1%. The mean chair stand performance was slightly better for those who remained in the

Meaningful change according to effect size

The small and moderate effects for the absolute decline were 0.7 and 1.7 s, respectively. The small and moderate effects for the relative decline were 12.1 and 30.4%, respectively.

Meaningful change according to the SEM

The standard error of measurement was 0.5 s and 9.6% for the absolute and relative declines, respectively.

Table 1 Description of the study populations of SAGE Mexico and MAPT

Mean (SD) unless shown otherwise	SAGE Mexico		MAPT	
	n = 897		n = 1575	
Age (years)	69.0	(6.2)	75.3	(4.4)
Participants aged 80+, n (%)	57	(6.4)	278	(17.7)
Female, n (%)	488	(54.4)	1,021	(64.8)
Five-repetition chair stand time at baseline	12.1	(3.4)	11.6	(3.5)
Five-repetition chair stand time at baseline at 3-year follow-up	14.7	(4.9)	11.7	(3.5)
Mean absolute change in the chair stand time	2.6	(4.9)	0.2	(3.5)
Mean relative change in the chair stand time	29.0	(60.7)	6.2	(30.7)
Incidence of ADL disability, n (%) ^a	48	(5.6)	145	(14.8)

^a3-year follow-up for SAGE Mexico, 5-year follow-up for MAPT.

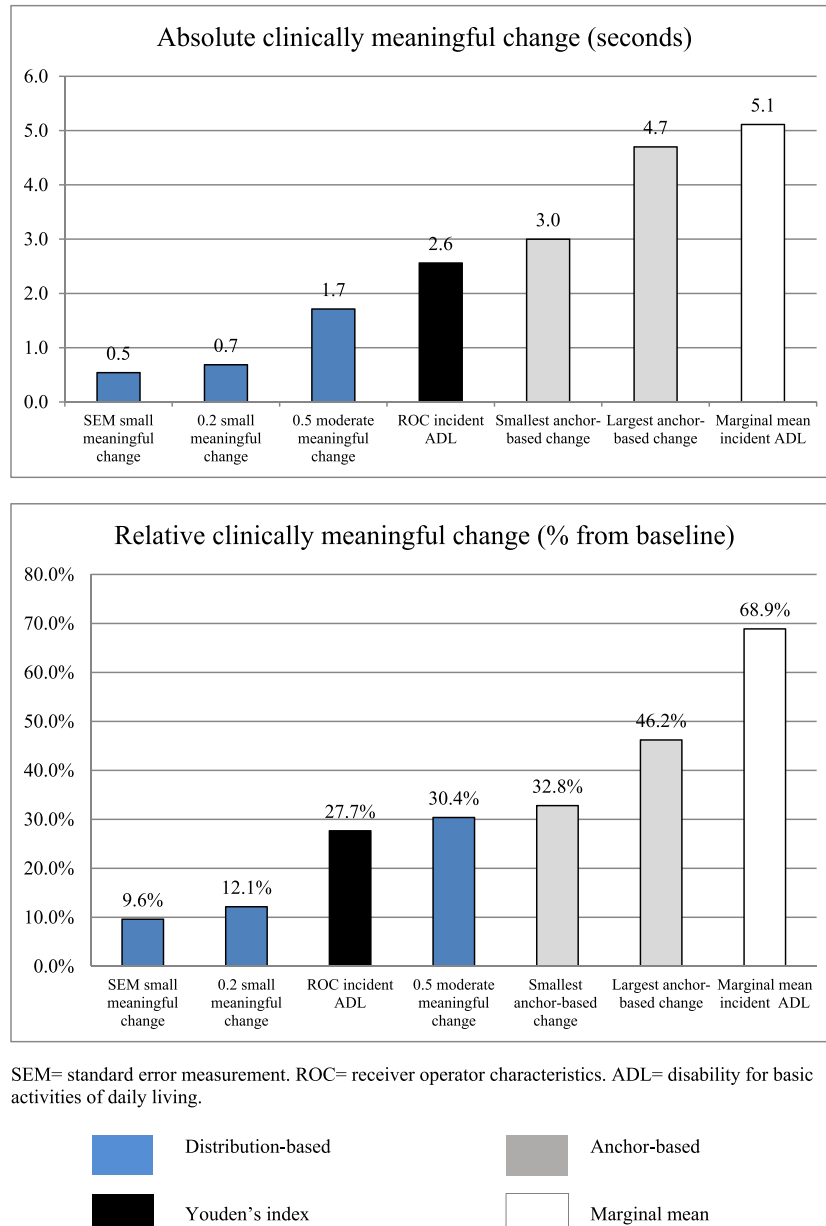


Figure 1 Sorted estimations of clinically meaningful changes in the time for performing the five-repetition chair stand test according to the estimation method. IADL, incident disability for basic activities of daily living; ROC, receiver operator characteristics; SEM, standard error measurement.

Meaningful change according to the comparison of means

Small meaningful changes according to anchor-based measurements averaged 3.1 s and 39%, respectively, for absolute and relative changes (range for absolute change = 3.0–3.2 s; range for relative change = 32.8–45.0%).

Moderate meaningful changes according to anchor-based measurements averaged 3.8 s and 39%, respectively, for ab-

solute and relative changes (range for absolute change = 3.1–4.7 s; range for relative change = 32.9–46.2%).

Meaningful change derived from ROC analyses

The absolute and relative changes found using Youden's index were 2.6 s and 27.7%.

In SAGE Mexico, older adults with incident ADL disability had a mean decline of 5.1 s and 68.9% from baseline over 3 years.

External validation

As shown in *Table 2*, MAPT participants with a clinically meaningful absolute worsening of their chair stand time (≥ 2.6 s) during the first 3 years of follow-up had a 46% higher risk of incident ADL disability (aHR = 1.46; 95% CI 0.95, 2.25). Those with a clinically meaningful relative worsening of their chair stand time ($\geq 27.7\%$ from baseline) had a 74% higher risk of incident ADL disability (aHR = 1.74; 95% CI 1.11, 2.72) with a mean follow-up of 58 months.

Discussion

Using a population-based study (SAGE Mexico), we found that absolute meaningful changes for the five-repetition chair stand time ranged from 0.5 to 1.7 s and from 3.0 to 4.7 s applying distribution-based and anchor-based methods, respectively. Relative meaningful changes ranged from 9.6 to 30.4% using distribution-based and anchor-based methods, respectively. The results from the ROC analyses showed that ≥ 2.6 s and $\geq 27.7\%$ were coherent with distribution-based and anchor-based methods. Furthermore, we corroborated that older adults with a clinically meaningful decline in the chair stand time were at higher risk of incident ADL disability in an external population (the MAPT study).

A change ≥ 2.6 s (or 27.7%) from baseline over 3 years was clinically meaningful in our research. This amount could seem substantial for some clinicians, but bear in mind that we measured changes over 3 years. Yet, we found that changes as small as 0.5 s or 9.6% over 3 years are already meaningful from the statistical point of view. The SEM served as a 'bottom line' for the change attributed to other than measurement error. A change ≥ 2.6 s (or 27.7%) from baseline over 3 years is higher than the minimal detectable change estimated by $1.96 \times \text{SEM} \times \sqrt{2}$ in our data (1.5 s or 26.6%) and consistent with a previous study in older women.²⁷

To the best of our knowledge, no other study has estimated the clinically meaningful change for the five-repetition chair stand test using distribution-based and

anchor-based methods with a population-based sample. In this vein, our study builds on previously published works about the meaningful change for physical performance measures for older adults, with recommendations for clinically meaningful differences in gait speed and the SPPB through the distribution-based and anchor-based methods.^{12,13} Going beyond previous publications, in addition to distribution-based and anchor-based methods, we also used ROC analyses; this approach allowed us to make an objective choice for establishing recommendations on the most appropriate clinically meaningful decline across the range of results (*Figure 1*). Therefore, we defined the clinically meaningful change in the chair stand test using Youden's index (2.6 s and 27.7% for the absolute and relative, respectively) because it was coherent and located in an intermediate position between the distribution-based and anchor-based methods' results.

Our findings suggest that a difference of 1 s or 10% change *per year* in the five-repetition chair stand test would be clinically meaningful, assuming a linear trend. We did not find publications for the clinically meaningful decline in the chair stand test. Still, Onder *et al.* have reported average decreases of 2.2 s or 11.2% and 4.0 s or 21.1% from baseline to 1 and 3 years, respectively, for absolute and relative changes in the Women's Health and Aging study.²⁸ Our results are coherent with such rate of decline considering that we are using population-based data with no function-based selection criteria as the ones applied for the WHAS, which is also an older population [mean (SD) age = 78.9 (8.1)].²⁸ A slight decline of 0.5 s was reported over 7 years on high-functioning community-dwelling American adults aged 70–79 as part of the MacArthur study.²⁹ Also, Rosano *et al.* have reported an average decline of 0.5 s/y in people with severe white matter hyperintensities ($n = 2450$, mean age = 75 years).³⁰

Defining clinically meaningful changes for the chair stand test can empower the healthcare professionals during the follow-up of older adults. Our results on the clinically meaningful changes add value to the cross-sectional cut points for the chair stand test in the context of ICOPE. For example, a clinician might find a patient has declined from 10 to 13 s in the five-repetition chair stand test over 3 years. This patient is below the 14 s cut point recommended by the ICOPE handbook.¹ However, the patient has already expressed a clinically meaningful change. Thus, clinicians might decide to implement interventions in a higher risk population even earlier. Furthermore, distribution-based meaningful changes

Table 2 Adjusted hazard ratio for incident ADL disability in MAPT participants with clinically meaningful decline in the five-repetition chair stand test

<i>n</i> = 872			
Events of incident ADL disability = 125			
Mean FU time = 58.6 months			
	aHR ^a	<i>P</i>	95% CI
\geq absolute clinically meaningful change	1.46	0.087	(0.95, 2.25)
\geq relative clinically meaningful change	1.74	0.016	(1.11, 2.72)

^aHazards ratio adjusted for age, sex, education level, MAPT allocation group, and baseline chair stand time.

might be applicable for monitoring meaningful changes in lower limb strength and power during/after clinical interventions. For example, improvements of 2.9 and 2.5 s have been reported after 6 weeks of pre-operative exercise training³¹ and after 3 months of total hip arthroplasty,³² respectively.

To further explore the trajectory of the chair rise time, we were not able to test if the test time changes in a linear or non-linear fashion because data were only available for two time points in SAGE Mexico. However, we used the chair stand test times available in MAPT for several time points, the trade-off being that it is not a population-based study. We modelled the time trajectory for those with and without incident ADL disability which best fitted a quadratic function (see *Figures S1 and S2*). Then, we retrospectively modelled the time trajectories for those participants who performed better or worse than our recommended clinically meaningful change for three 3-year follow-up. Participants with a clinically meaningful change went from 11 s at baseline to 12, 13, and 14.4 s after 6, 12, and 24 months of follow-up, respectively. MAPT participants with time differences lower than the clinically meaningful roughly maintained their performance throughout the 5-year follow-up.

Our study has several strengths; for instance, it is the first to provide recommendations for clinically meaningful change in community-dwelling older adults derived from population-based data. In addition to using the conventional methods reported by previous literature,^{11,12} we applied ROC analyses to obtain a data-driven cut point of the clinically meaningful change. Also, besides reporting the absolute changes like in previous papers,¹² we have also attained the relative meaningful changes expressed as a percentage of change. It is possible that relative meaningful changes (%) outperform absolute meaningful changes (seconds) in populations distinct to SAGE Mexico, depending on their distribution of the chair rise time and other markers of physical performance.

One limitation of our study is that the external validation was performed in MAPT, which is not a population-based study. MAPT was a randomized controlled trial not designed to test the clinically meaningful changes in the chair stand time. MAPT's population included relatively fit and well-educated older adults (see 'Data sources' section and *Andrieu et al.*¹⁸). Our results on the external validation may not be generalizable to other populations. This limitation concerns only the external validation process and is not related to the main results of our study. Despite this limitation, we were able to demonstrate the usefulness of the clinically meaningful change as a risk-stratifying feature in MAPT participants. Future external validation studies using a variety of populations are needed.

Our work fills the gap regarding the clinically meaningful change for older adults' chair stand test time. The mobility domain can be monitored using other means with established clinically meaningful change, the SPPB, for instance.¹⁹ Never-

theless, using the chair stand test brings advantages like shorter application time and feasibility even with spatial room constraints. Furthermore, it is reactive to acute conditions like self-reported dizziness or flu-like symptoms within weeks.³³ Offering recommendations for the clinically meaningful change in the chair stand test in older adults might lead to early detection of mobility declines and prevention of disability in older age.

Acknowledgements

The present work was performed in the context of the Inspire Program, a research platform supported by grants from the Region Occitanie/Pyrénées-Méditerranée (Reference number: 1901175) and the European Regional Development Fund (ERDF) (Project number: MP0022856).

This study has been partially supported through the grant EUR CARE N°ANR-18-EURE-0003 in the framework of the Programme des Investissements d'Avenir.

The MAPT study was supported by grants from the Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), Pierre Fabre Research Institute (manufacturer of the omega-3 supplement), ExonHit Therapeutics SA, and Avid Radiopharmaceuticals Inc. The promotion of this study was supported by the University Hospital Center of Toulouse. The data sharing activity was supported by the Association Monegasque pour la Recherche sur la Maladie d'Alzheimer (AMPA) and the INSERM-University of Toulouse III CERPOP (UMR 1295) Research Unit. The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.³⁴

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest

Emmanuel Gonzalez-Bautista, Philippe de Souto Barreto, Aaron Salinas-Rodriguez, Betty Manrique Espinoza, Yves Roland, Sandrine Andrieu, and Bruno Vellas declare that they have no conflict of interest.

MAPT study group

Principal investigator: Bruno Vellas (Toulouse). *Coordination:* Sophie Guyonnet. *Project leader:* Isabelle Carrié. *CRA:*

Lauréane Brigitte. *Investigators*: Catherine Faisant, Françoise Lala, Julien Delrieu, Hélène Villars. *Psychologists*: Emeline Combrouze, Carole Badufle, Audrey Zueras. *Methodology, statistical analysis, and data management*: Sandrine Andrieu, Christelle Cantet, Christophe Morin. *Multidomain group*: Gabor Abellan Van Kan, Charlotte Dupuy, Yves Rolland (physical and nutritional components), Céline Caillaud, Pierre-Jean Ousset (cognitive component), Françoise Lala (preventive consultation). The cognitive component was designed in collaboration with Sherry Willis from the University of Seattle and Sylvie Belleville, Brigitte Gilbert, and Francine Fontaine from the University of Montreal.

Co-investigators in associated centres: Jean-François Dartigues, Isabelle Marcet, Fleur Delva, Alexandra Foubert, Sandrine Cerda (Bordeaux); Marie-Noëlle-Cuffi, Corinne Costes (Castres); Olivier Rouaud, Patrick Manckoundia, Valérie Quipourt, Sophie Marilier, Evelyne Franon (Dijon); Lawrence Bories, Marie-Laure Pader, Marie-France Basset, Bruno Lapoujade, Valérie Faure, Michael Li Yung Tong, Christine Malick-Loiseau, Evelyne Cazaban-Campistron (Foix); Françoise Desclaux, Colette Blatge (Lavaur); Thierry Dantoine, Cécile Laubarie-Mouret, Isabelle Saulnier, Jean-Pierre Clément, Marie-Agnès Picat, Laurence Bernard-Bourzeix, Stéphanie Willebois, Iléana Désormais, Noëlle Cardinaud (Limoges); Marc Bonnefoy, Pierre Livet, Pascale Rebaudet, Claire Gédéon, Catherine Burdet, Flavien Terracol (Lyon), Alain Pesce, Stéphanie Roth, Sylvie Chaillou, Sandrine Louchart (Monaco); Kristel Sudres, Nicolas Lebrun, Nadège

Barro-Belaygues (Montauban); Jacques Touchon, Karim Bennys, Audrey Gabelle, Aurélie Romano, Lynda Touati, Cécilia Marelli, Cécile Pays (Montpellier); Philippe Robert, Franck Le Duff, Claire Gervais, Sébastien Gonfrier (Nice); Yannick Gasnier and Serge Bordes, Danièle Begorre, Christian Carpuat, Khaled Khales, Jean-François Lefebvre, Samira Misbah El Idrissi, Pierre Skolil, Jean-Pierre Salles (Tarbes).

MRI group: Carole Dufouil (Bordeaux), Stéphane Lehéricy, Marie Chupin, Jean-François Mangin, Ali Bouhayia (Paris); Michèle Allard (Bordeaux); Frédéric Ricolfi (Dijon); Dominique Dubois (Foix); Marie Paule Bonceour Martel (Limoges); François Cotton (Lyon); Alain Bonafé (Montpellier); Stéphane Chanalet (Nice); Françoise Hugon (Tarbes); Fabrice Bonneville, Christophe Cognard, François Chollet (Toulouse). *PET scans group*: Pierre Payoux, Thierry Voisin, Julien Delrieu, Sophie Peiffer, Anne Hitzel, (Toulouse); Michèle Allard (Bordeaux); Michel Zanca (Montpellier); Jacques Monteil (Limoges); Jacques Darcourt (Nice).

Medico-economics group: Laurent Molinier, Hélène Derumeaux, Nadège Costa (Toulouse). *Biological sample collection*: Bertrand Perret, Claire Vinel, Sylvie Caspar-Bauguil (Toulouse). *Safety management*: Pascale Olivier-Abbal.

DSA Group

Sandrine Andrieu, Christelle Cantet, Nicola Coley.

References

- World Health Organization. *Integrated care for older people (ICOPE): Guidance for person-centred assessment and pathways in primary care*. Geneva: WHO; 2019. Accessed 14 November 2019 from <https://apps.who.int/iris/bitstream/handle/10665/326843/WHO-FWC-ALC-19.1-eng.pdf?sequence=17>
- Tavassoli N, Piau A, Berbon C, de Kerimel J, Lafont C, de Souto Barreto P, et al. Framework implementation of the INSPIRE ICOPE-CARE program in collaboration with the World Health Organization (WHO) in the Occitania region. *J Frailty Aging* 2021; **10**:103–109.
- Verbrugge LM, Jette AM. The disablement process. *Soc Sci Med* 1994; **38**:1–14.
- Wang DXM, Yao J, Zirek Y, Reijnierse EM, Maier AB. Muscle mass, strength, and physical performance predicting activities of daily living: A meta-analysis. *J Cachexia Sarcopenia Muscle* 2020; **11**:3–25.
- Dodds RM, Murray JC, Granic A, Hurst C, Uwimpuhwe G, Richardson S, et al. Prevalence and factors associated with poor performance in the 5-chair stand test: Findings from the cognitive function and ageing study II and proposed Newcastle protocol for use in the assessment of sarcopenia. *J Cachexia Sarcopenia Muscle* 2021; **12**:308–318.
- Gonzalez-Bautista E, Barreto PS, Salinas-Rodriguez A, Manrique Espinoza B, Sourdet S, Rolland Y, et al. Development and validation of a cut-off for the chair stand test as a screening for mobility impairment in the context of the integrated care for older people (ICOPE) program. *J Gerontol A Biol Sci Med Sci* 2022. <https://doi.org/10.1093/gerona/glac055>
- Kim M, Won CW. Cut points of chair stand test for poor physical function and its association with adverse health outcomes in community-dwelling older adults: A cross-sectional and longitudinal study. *J Am Med Dir Assoc* 2021. <https://doi.org/10.1016/j.jamda.2021.11.007>
- Guyatt G, Walter S, Norman G. Measuring change over time: Assessing the usefulness of evaluative instruments. *J Chronic Dis* 1987; **40**:171–178.
- Beaton DE, Bombardier C, Katz JN, Wright JG. A taxonomy for responsiveness. *J Clin Epidemiol* 2001; **54**:1204–1217.
- Lydick E, Epstein RS. Interpretation of quality of life changes. *Qual Life Res* 1993; **2**:221–226.
- Guralnik J, Bandeen-Roche K, Bhasin SAR, Eremenco S, Landi F, Muscedere J, et al. Clinically meaningful change for physical performance: Perspectives of the ICFSR task force. *J Frailty Aging* 2020; **9**:9–13.
- Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc* 2006; **54**:743–749.
- Kwon S, Perera S, Pahor M, Katula JA, King AC, Groessl EJ, et al. What is a meaningful change in physical performance? Findings from a clinical trial in older adults (the LIFE-P study). *J Nutr Health Aging* 2009; **13**:538–544.
- Perera S, Studenski S, Chandler JM, Guralnik JM. Magnitude and patterns of decline in health and function in 1 year affect subsequent 5-year survival. *J Gerontol A Biol Sci Med Sci* 2005; **60**:894–900.
- Perera S, Studenski S, Newman A, Simonsick E, Harris T, Schwartz A, et al. Are estimates

- of meaningful decline in mobility performance consistent among clinically important subgroups? (Health ABC study). *J Gerontol Ser A* 2014;**69**:1260–1268.
16. Kowal P, Chatterji S, Naidoo N, Biritwum R, Fan W, Lopez Ridaura R, et al. Data resource profile: The World Health Organization study on global AGEing and adult health (SAGE). *Int J Epidemiol* 2012;**41**:1639–1649.
 17. Vellas B, Carrie I, Gillette-Guyonnet S, Touchon J, Dantoine T, Dartigues JF, et al. MAPT study: A multidomain approach for preventing Alzheimer's disease: Design and baseline data. *J Prev Alzheimers Dis* 2014;**1**:13–22.
 18. Andrieu S, Guyonnet S, Coley N, Cantet C, Bonnefoy M, Bordes S, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. *Lancet Neurol* 2017;**16**:377–389.
 19. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 1994;**49**:M85–M94.
 20. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970;**10**:20–30.
 21. Wywrich KW, Bullinger M, Aaronson N, Hays RD, Patrick DL. Estimating clinically significant differences in quality of life outcomes. *Qual Life Res* 2005;**14**:285–295.
 22. Wywrich KW, Nienaber NA, Tierney WM, Wolinsky FD. Linking clinical relevance and statistical significance in evaluating intra-individual changes in health-related quality of life. *Med Care* 1999;**37**:469–478.
 23. Norman GR, Gwadry Sridhar F, Guyatt GH, Walter SD. Relation of distribution- and anchor-based approaches in interpretation of changes in health-related quality of life. *Med Care* 2001;**39**:1047.
 24. Lemieux J, Beaton DE, Hogg-Johnson S, Bordeleau LJ, Goodwin PJ. Three methods for minimally important difference: No relationship was found with the net proportion of patients improving. *J Clin Epidemiol* 2007;**60**:448–455.
 25. Bohannon RW, Bubela DJ, Magasi SR, Gershon RC. Relative reliability of three objective tests of limb muscle strength. *Isokinet Exerc Sci* 2011;**19**:77–81.
 26. Youden WJ. Index for rating diagnostic tests. *Cancer* 1950;**3**:32–35.
 27. Goldberg A, Chavis M, Watkins J, Wilson T. The five-times-sit-to-stand test: Validity, reliability and detectable change in older females. *Aging Clin Exp Res* 2012;**24**:339–344.
 28. Onder G, Penninx BW, Lapuerta P, Fried LP, Ostir GV, Guralnik JM, et al. Change in physical performance over time in older women: The women's health and aging study. *J Gerontol A Biol Sci Med Sci* 2002;**57**:M289–M293.
 29. Tabbarah M, Crimmins EM, Seeman TE. The relationship between cognitive and physical performance: MacArthur studies of successful aging. *J Gerontol A Biol Sci Med Sci* 2002;**57**:M228–M235.
 30. Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc* 2005;**53**:649–654.
 31. Hoozeboom TJ, Dronkers JJ, van den Ende CHM, Oosting E, van Meeteren NLU. Pre-operative therapeutic exercise in frail elderly scheduled for total hip replacement: A randomized pilot trial. *Clin Rehabil* 2010;**24**:901–910.
 32. de Groot IB, Bussmann HJ, Stam HJ, Verhaar JA. Small increase of actual physical activity 6 months after total hip or knee arthroplasty. *Clin Orthop Relat Res* 2008;**466**:2201–2208.
 33. Guralnik JM, Ferrucci L, Penninx BWJH, Kasper JD, Leveille SG, Bandeen-Roche K, et al. New and worsening conditions and change in physical and cognitive performance during weekly evaluations over 6 months: The women's health and aging study. *J Gerontol Ser A* 1999;**54**:M410–M422.
 34. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: Update 2021. *J Cachexia Sarcopenia Muscle* 2021;**12**:2259–2261.

$p=0.001$ for walking speed), beyond the effect of each exposure individually. A higher adherence to Mediterranean diet, especially in combination with recommended levels of physical activity and high social support, contribute to delay the decline in physical function observed with aging.

REGIONAL MICROSTRUCTURAL INTEGRITY IN RELATION TO GAIT SPEED: THE ATHEROSCLEROSIS RISK IN COMMUNITIES STUDY

Kevin Sullivan,¹ Chad Blackshear,² Timothy Hughes,³ Rebecca Gottesman,⁴ Prashanthi Vemuri,⁵ Thomas Mosley,¹ Michael Griswold,¹ and B. Gwen Windham,² 1. *The University of Mississippi Medical Center, Jackson, Mississippi, United States*, 2. *University of Mississippi Medical Center, Jackson, Mississippi, United States*, 3. *Wake Forest School of Medicine, Winston-Salem, North Carolina, United States*, 4. *Johns Hopkins University, Baltimore, Maryland, United States*, 5. *The Mayo Clinic, Mayo Clinic, Minnesota, United States*

Brain imaging-based biomarkers of neuropathology are associated with mobility in older adults, but the relation of regional microstructural integrity to gait speed in the context of a broader neuropathological profile is less understood. We examined cross-sectional associations of microstructural integrity with 4-meter usual-pace gait speed (cm/s) in a subsample of ARIC study participants who completed 3T MRI brain scans with diffusion tensor imaging (2011-13; $n=1785$; mean age= 76.2 ± 5.3 , 60% Female, 28% Black). We considered total brain and six regional averages of fractional anisotropy (FA; lower=worse microstructural integrity) and mean diffusivity (MD; higher=worse microstructural integrity): frontal, temporal, parietal, occipital, anterior and posterior corpus callosum. Associations were tested in multivariable linear regression models adjusted for demographics, cardiovascular risk factors, and with and without additional neuropathological indices: total brain volume, white matter hyperintensities, infarcts, and microhemorrhages. When modeled separately, all neuropathology indices were associated with slower gait speed. Every standard deviation (SD) higher total brain FA was associated with $+2.56$ cm/s gait speed (95%CI: 1.64,3.48) and every SD higher MD was associated with -4.27 cm/s gait speed ($-5.34,-3.20$). All regional estimates were comparable. When adjusted for all other neuropathology indices, only posterior corpus callosum FA ($\beta=1.72$; 0.67,2.77), total MD ($\beta=-1.63$; -3.02,-0.25), frontal lobe MD ($\beta=-1.76$; -3.03,-0.48), and temporal lobe MD ($\beta=-1.40$; -2.78,-0.02) remained significantly associated with gait speed. Microstructural integrity is an informative measure of brain pathology in relation to mobility, with regional measures tied to executive, memory, and somatosensory function being more informative when a broader neuropathological profile is considered.

THE CORTICAL DYNAMICS OF DUAL-TASK STANDING IN OLDER ADULTS

Melike Kahya,¹ On-Yee Lo,² Junhong Zhou,³ Alvaro Pascual-Leone,⁴ Lewis Lipsitz,⁵ Jeffrey Hausdorff,⁶ Christoph Michel,⁷ and Brad Manor,⁸ 1. *Marcus Institute for Aging Research, Harvard Medical School, Boston, Massachusetts, United States*, 2. *Hebrew SeniorLife, Harvard Medical School, Boston, Massachusetts, United*

States, 3. *Harvard Medical School/Hebrew SeniorLife, Roslindale, Massachusetts, United States*, 4. *Harvard Medical School, Boston, Massachusetts, United States*, 5. *Hebrew SeniorLife, Boston, Massachusetts, United States*, 6. *Tel Aviv University, Tel Aviv University, Tel Aviv, Israel*, 7. *University of Geneva, University of Geneva, Geneva, Switzerland*, 8. *Hinda and Arthur Marcus Institute for Aging Research, Harvard Medical School, Boston, Massachusetts, United States*

In older adults, the extent to which performing a cognitive task when standing diminishes postural control is predictive of future falls and cognitive decline. The cortical control of such “dual-tasking,” however, remains poorly understood. Electroencephalogram (EEG) studies have demonstrated that the level of attention and cognitive inhibitory activity during cognitive task performance can be quantified by changes in brain activity in specific frequency bands; namely, an increase in theta/beta ratio and a decrease in alpha-band power, respectively. We hypothesized that in older adults, dual-tasking would increase theta/beta ratio and decrease alpha-band power, and that greater alpha-band power during quiet standing would predict worse dual-task performance. To test this hypothesis, we recorded postural sway and EEG (32-channels) in 30 older adults without overt disease as they completed trials of standing, with and without verbalized serial subtractions, on four separate visits. Postural sway speed, as well as absolute theta/beta power ratio and alpha-band power, were calculated. The theta/beta power ratio and alpha-band power demonstrated high test-retest reliability during quiet and dual-task standing across visits (intra-class correlation coefficients >0.70). Compared with quiet standing, dual-tasking increased theta/beta power ratio ($p<0.0001$) and decreased alpha-band power ($p=0.002$). Participants who exhibited greater alpha-band power during quiet standing demonstrated a greater dual-task cost (i.e., percent increase, indicative of worse performance) to postural sway speed ($r=0.3$, $p=0.01$). These results suggest that in older adults, dual-tasking while standing increases EEG-derived metrics related to attention, and that greater cognitive inhibitory activity during quiet standing is associated with worse dual-task standing performance.

VALIDATION OF THE INTEGRATED CARE FOR OLDER PEOPLE SCREENING TOOL: FOCUS ON THE CHAIR RISE TEST TO ASSESS LOCOMOTION

Emmanuel Gonzalez-Bautista,¹ Philippe de Souto Barreto,² Aaron Salinas-Rodriguez,³ Sandrine Sourdet,¹ Yves Rolland,¹ Leocadio Rodriguez-Mañas,⁴ Sandrine Andrieu,⁵ and Bruno Vellas,² 1. *Toulouse University Hospital (CHU Toulouse), Toulouse, Midi-Pyrenees, France*, 2. *CHU Toulouse: Centre Hospitalier Universitaire de Toulouse, Gérontopôle de Toulouse, Institut du Vieillissement, Midi-Pyrenees, France*, 3. *National Institute of Public Health of Mexico, Cuernavaca, Morelos, Mexico*, 4. *Getafe University Hospital, Getafe, Madrid, Spain*, 5. *University of Toulouse III, INSERM, UPS, Toulouse, Midi-Pyrenees, France*

The Integrated Care for Older People (ICOPE) is a function- and person-centered healthcare pathway developed by the World Health Organization (WHO). ICOPE's first step (Step 1) consists of screening for impairments in the

intrinsic capacity (IC) domains (namely sensorial, cognition, nutrition, psychological, and locomotion). For instance, the ICOPE Step1 tool suggests a cut-point of 14 seconds for five-repetition chair rise time as a marker of impaired locomotion. Given the lack of validation of this tool in the literature, we aimed to validate the ICOPE screening tool concerning incident health outcomes, focusing on the locomotion assessment. First, we analyzed the five-domain screening tool's ability to identify older adults (OA) at higher risk of incident outcomes (frailty, disability, dementia) using longitudinal data from the Multidomain Alzheimer Preventive Trial (MAPT). For the locomotion assessment (chair rise test), we derived and cross-validated age-specific cut points from two population-based cohorts using ROC (receiver operating characteristic) analysis. We further verified those cut points among OA real-life users of the health system and clinical trial participants. In conclusion, the ICOPE Step 1 screening tool was able to identify OA at higher risk of incident frailty, disability, and dementia. New chair-rise-time cut points for age groups 70-79 years old and 80 years and older were valid in populations from different settings. The ICOPE Step 1 tool provides a practical and integrative way of screening older adults for impairments in IC and detecting those at higher risk of functional decline.

Session 1285 (Symposium)

RECOGNIZING AND INTERVENING ON ELDER ABUSE, NEGLECT, AND EXPLOITATION IN THE AGE OF COVID-19

Chair: Pi-Ju Liu

Discussant: Pamela Teaster

The rapid outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global pandemic. Public health measures to prevent the spread of COVID-19, such as social distancing and self-quarantine, have drastically altered people's lives and led to social isolation, financial instability, and disrupted access to healthcare and social services. Older adults have not only borne the brunt of the highest COVID-19 mortality rates, but recent studies also describe growing reports of elder mistreatment. It is necessary to attend to these age-related disparities during the remainder of the COVID-19 pandemic and future health crises. This symposium includes four presentations on researchers' findings in elder mistreatment during the COVID-19 pandemic. Dr. E-Shien Chang will compare prevalence of elder mistreatment before and since the pandemic, and highlight associated risk and protective factors during the pandemic. Dr. Lena Makaroun will examine changes in elder mistreatment risk factors among caregivers during the pandemic. Dr. Pamela Teaster will present Adult Protective Services' (APS) policy and practice changes in response to the pandemic to demonstrate the pandemic's impact on service providers. Lastly, Dr. Pi-Ju (Marian) Liu will appraise elder mistreatment victims' awareness of COVID-19 and their unmet needs during the pandemic. Following the four presentations, Dr. Pamela Teaster will moderate a discussion on how elder mistreatment is a growing concern,

especially during the pandemic, and what service providers are doing to protect older adults.

ELDER ABUSE DURING THE COVID-19 PANDEMIC: PREVALENCE, RISK, AND PROTECTIVE FACTORS

E-Shien Chang,¹ and Becca Levy,² 1. *Weill Cornell Medicine, New York City, New York, United States*, 2. *Yale University, Woodbridge, Connecticut, United States*

It has been assumed that the pandemic has brought with it a surge in elder abuse due to heightened health and interpersonal stressors. However, empirical evidence is lacking. This study aimed to estimate the prevalence of, and risk and resilience factors of elder abuse during the pandemic. In a web-based survey of a socio-demographically diverse sample of 897 older persons, one in five older persons (n = 191; 21%) reported elder abuse, an increase of 84% from prevalence estimates before the pandemic. In the multivariate logistic regression models, sense of community was a persistent protective factor for elder abuse (OR= 0.89, 95% CI 0.85–0.93). At the relational level, physical distancing was associated with reduced risk of elder abuse (OR= 0.94, 95% CI 0.90–0.98). At the individual level, financial strain was associated with increased risk of abuse (OR= 1.08, 95% CI: 1.02–1.14). Implications for prevention strategies will be discussed.

CHANGES IN ELDER MISTREATMENT RISK FACTORS REPORTED BY CAREGIVERS OF OLDER ADULTS DURING THE COVID-19 PANDEMIC

Lena Makaroun,¹ Scott Beach,² Tony Rosen,³ and Ann-Marie Rosland,¹ 1. *University of Pittsburgh, Pittsburgh, Pennsylvania, United States*, 2. *University of Pittsburgh, University of Pittsburgh, Pennsylvania, United States*, 3. *Weill Cornell Medical College / NewYork-Presbyterian Hospital, PELHAM, New York, United States*

This study aimed to assess how the COVID-19 pandemic has impacted caregiver (CG)-related risk factors for elder mistreatment (EM) in a community sample of CGs. A non-probability sample of 433 CGs caring for care recipients (CRs) age ≥60 years completed a survey on COVID-19 impacts in April-May 2020. Compared to before COVID-19, over 40% of caregivers reported doing worse financially, 16% were experiencing new financial hardship, 19.4% were a lot more worried about their financial situation, 15% reported drinking more alcohol, and 64% had somewhat or greatly increased feelings of social isolation and loneliness. CGs reported that COVID-19 had made caregiving more physically (18.7%), emotionally (48.5%) and financially (14.5%) difficult and interfered with their own healthcare (19%). Differences found between younger and older caregivers will be presented and implications of these increased CG-related EM risk factors for healthcare and social service providers discussed.

A NATIONWIDE STUDY ON HOW COVID-19 CHANGED APS POLICIES AND PRACTICES

Pamela Teaster, *Virginia Tech, BLACKSBURG, West Virginia, United States*

The purpose of this inquiry by the Virginia Tech Center for Gerontology and WRMA, Inc., was to explore changes being implemented by APS programs across the country in response to the COVID-19 pandemic. With input from the

related to frailty when adjusting for leisure activities and covariates ($\beta = -0.061$; 95% CI = -0.119, 0.032). Active leisure activities accounted for 44.4% of the indirect effect of lower-extremity function on frailty. **Conclusion:** Leisure activities impact the association of lower-extremity function and frailty, and its protective role depends on the type of leisure activity. Interventions on frailty should be designed by focusing on active leisure activities among older adults especially for those with impaired lower-extremity function.

OC36- DIFFERENCES IN INTRINSIC CAPACITY AND BIOLOGICAL PROFILE ACCORDING TO LONGITUDINAL FRAILTY TRAJECTORIES IN COMMUNITY-DWELLING OLDER ADULTS. Emmanuel Gonzalez Bautista^{1,2}, Wan-Hsuan Lu^{1,2}, Bruno Vellas^{1,2}, Philippe de Souto Barreto^{1,2} (1. Gerontopole of Toulouse, Institute of Ageing, Toulouse University Hospital (CHU Toulouse), Toulouse, France; 2. Inserm CERPOP - UMR1295, University of Toulouse III, Toulouse, France)

Backgrounds: Frailty is a dynamic process with heterogeneous progression patterns in older adults (OA) that have not been fully characterized. Little is known about older individuals' functional and biological profiles according to their frailty trajectories over time. **Objectives:** To identify frailty trajectories among community-dwelling OA and compare them according to their baseline intrinsic capacity (IC) and inflammatory profiles. **Methods:** This secondary analysis from the Multidomain Alzheimer Preventive Trial (MAPT) included 614 participants (mean age \pm SD: 76.0 \pm 4.3 years) with yearly frailty assessments. Trajectories of frailty over four years were obtained using group-based trajectory modeling. All participants had their IC and plasma inflammatory markers measured at 12 months. Six domains of IC were measured using standardized scores (cognition, locomotion, psychological, vision, audition, and nutrition). Plasma biomarkers included tumor necrosis factor receptor type 1 (TNFR-1), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), C-reactive protein (CRP), and growth differentiation factor 15 (GDF-15). **Results:** We identified four distinct trajectories of frailty: reversed (19.4%), worsening (21.7%), stably pre-frail (55.7%), and stably frail (3.2%). OA with a stably frail trajectory had lower IC capacities in cognition, locomotion, psychological, and nutrition than the other three groups (all $p < 0.01$). Participants with stably pre-frailty trajectory showed worse IC in the four domains aforementioned than those with reversed and worsening trajectories (post hoc $p < 0.01$). In contrast, the group of reversed frailty showed higher psychological capacity than those in the worsening trajectory. On the other hand, we observed higher concentrations of GDF-15, TNFR-1, IL-6, and CRP in the stably frail group than in the other three groups (all $p < 0.01$). Lower levels of GDF15 were found in older adults with worsening frailty trajectory compared to those in stably pre-frailty (post hoc $p < 0.01$). **Conclusion:** OA in the four frailty trajectories identified had distinct IC levels and inflammatory markers at baseline. Further studies should explore the predictive ability of IC and inflammatory

biomarkers against frailty trajectories. An algorithm based on IC and biomarkers could, for instance, identify robust OA with a high risk of a worsening trajectory in the mid-term.

OC38- LOWER URINARY TRACT SYMPTOMS AND INCIDENT FUNCTIONAL LIMITATIONS IN OLDER COMMUNITY-DWELLING MEN. Scott R. Bauer^{1,2,3}, Peggy M. Cawthon^{4,5}, Kristine E. Ensrud^{6,7}, Anne M. Suskind², John C. Newman^{8,9}, Howard A. Fink^{6,7}, Kaiwei Lu³, Rebecca Scherzer^{1,3}, Kenneth Covinsky^{3,9}, Lynn M. Marshall^{10,11} for the Osteoporotic Fractures in Men (MrOS) Research Group (1. Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, CA, USA; 2. Department of Urology, University of California, San Francisco, CA, USA; 3. San Francisco VA Medical Center, San Francisco, CA, USA; 4. Research Institute, California Pacific Medical Center, San Francisco, CA, USA; 5. Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA; 6. Department of Medicine and Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN, USA; 7. Veterans Affairs Health Care System, Minneapolis, MN, USA; 8. Buck Institute for Research on Aging, Novato, CA, USA; 9. Division of Geriatrics, Department of Medicine, University of California, San Francisco, CA, USA; 10. Oregon Health and Science University-Portland State University School of Public Health, Portland OR, USA; 11. Department of Orthopaedics and Rehabilitation, Oregon Health and Science University, Portland, OR, USA)

Background: Lower urinary tract symptoms (LUTS) can occur during both urine storage and voiding and are increasingly appreciated as an important geriatric syndrome associated with phenotypic frailty. However, the association between LUTS and new functional impairment remains unknown. **Objectives:** To determine the association between LUTS severity and risk of incident functional impairment among older men. **Methods:** This analysis includes 2716 community-dwelling men age ≥ 72 years from the multicenter Osteoporotic Fractures in Men (MrOS) study. American Urologic Association Symptom Index was used to classify baseline LUTS severity as none/mild (score 0-7), moderate (8-19), and severe (20-35). At baseline and 2-year follow-up interviews, men reported their ability to complete tasks used to define 3 primary outcomes: 1) mobility limitation (difficulty walking 2-3 blocks or climbing 10 steps), 2) activities of daily living (ADL) limitation (difficulty bathing, showering, or transferring), and 3) cognition-dependent task limitation (difficulty managing money or medications). We restricted the analysis to men reporting no limitations at baseline. We used Poisson relative risk (RR) regression with a robust variance estimator to model the association of LUTS with incident limitations in mobility, ADL, and cognition-dependent tasks. Models were adjusted for age, site, and comorbidities; further adjustment for other demographic/lifestyle factors did not materially change estimated coefficients. **Results:** Among men with none/mild LUTS, incidence of limitations was 11% for mobility, 8% for ADLs, and 4% for cognition-