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Neuropsychological Profile of "Cognitive Frailty" Subjects in MAPT Study

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Abstract

OBJECTIVES—An international group proposed the existence of "cognitive frailty", a condition defined by simultaneous presence of physical frailty and cognitive impairment in the absence of dementia. The objective was to compare the neuropsychological profiles in subgroups of elders differentiated across their physical frailty (Fried phenotype) and cognitive status (Clinical Dementia Rating score) to characterize the "cognitive frailty" entity.

METHOD—We studied baseline characteristics of 1,617 subjects enrolled in Multidomain Alzheimer Disease Preventive Trial (MAPT). Included subjects were aged 70 years or older and presented at least 1 of the 3 following clinical criteria: (1) Memory complaint spontaneously reported to a general practitioner, (2) limitation in one instrumental activity of daily living, (3) slow gait speed. Subjects with dementia were not included in the trial.

RESULTS—"Cognitive frailty individuals" significantly differed from "individuals with cognitive impairment and without physical frailty", scoring worse at executive, and attention tests. They presented subcortico-frontal cognitive pattern different of Alzheimer Disease. Cognitive performance of subjects with 3 criteria or more of the frailty phenotype are cognitively more impaired than subjects with only one.

DISCUSION—The characterization of "cognitive frailty" must be done in frail subjects to set up specific preventive clinical trials for this population.

Keywords

Alzheimer Disease; elderly; MAPT trial; cognitive frailty; physical frailty

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Introduction

The frailty syndrome has recently attracted attention of the scientific community and public health authorities in numerous countries as risk factor for several age-related negative outcomes in older persons (1). In parallel, dementia and cognitive disorders also represent major healthcare and social priorities. The most commonly used definition of frailty was developed by Fried et al. in the Cardiovascular Health Study and in the Women's Health and Aging Studies (2). Frailty was operationally defined as a clinical condition meeting 3 out of 5 criteria closely related to the physical domain: weak muscle strength, slow gait speed, unintentional weight loss, exhaustion, and sedentary behavior (3). Up to date, frailty and cognitive impairment have mostly been studied in parallel with very few attempts of simultaneously considering them. However, some recent work has started considering cognition as part of the definition of frailty, especially from an epidemiological viewpoint. Several biological and clinical conditions may underlie the age-related physical and cognitive declines: 1) depression (4), 2) cardiovascular risk factors (5), 3) genetic mutations (e.g. APO-E4) (6), 4) behavioral factors (e.g. low education, unhealthy dietary patterns, low physical and mental activity, smoking, high alcohol consumption), 5) oxidative damage and functional changes in the hippocampus and prefrontal cortex (7), 6) accumulation of common brain pathological findings (e.g. Alzheimer's disease pathology, microinfarcts, nigral neuronal loss) (8-11), and 7) Low grade chronic inflammation. The absence of consideration of cognitive impairment in frailty syndrome could contribute to important heterogeneity of this entity (12).

An International Consensus Group organized by the International Academy on Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG), proposed the identification of the "cognitive frailty" condition (13). "Cognitive frailty" was hypothetically described as a clinical condition characterized by the simultaneous presence of both physical frailty and cognitive impairment. In particular, the key factors defining such a condition included: 1) presence of physical frailty and cognitive impairment, and 2) exclusion of concurrent Alzheimer's disease (AD) dementia or other dementias. To identify "cognitive frailty", the panel of experts suggested that all frail subjects should perform a comprehensive cognitive assessment exploring memory performance as well as other cognitive functions, in particular executive functions (with Montreal Cognitive assessment test (MoCa) (14), Mini Mental state Examination (MMSE) (15), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) (16), and speed processing tests). However, currently, cognitive pattern of "cognitive frailty" is not clearly characterized and the panel of experts of IANA and IAGG described a hypothetical condition without data available to support it. The cognitive profile identification of "cognitive frailty individuals" could be interesting because a potential for reversibility could also characterize this entity. Our hypothesis is that "cognitive frailty" would be a specific cognitive entity different of that met in AD, and which would be the witness of a more general impairment of the individual.

The main objective of our study was to determine the specific neuropsychological profile of "cognitive frailty individuals", based on a sample of older adults of the Multidomain Alzheimer Preventive Trial (MAPT), aged 70 years and over, living in the community

without any clinical sign of dementia (17,18). In addition, we aimed to assess the association of physical frailty severity with cognitive performance of “cognitive frailty individuals” and “frail older individuals”.

Methods

MAPT study

The MAPT study was a 4-arm randomized controlled trial aimed at assessing the effects of isolated supplementation with omega-3 fatty acid, an isolated multidomain intervention (consisting of nutritional counseling, physical exercise, cognitive stimulation), or a combination of the 2 interventions, versus placebo, on cognitive functions modifications in older persons aged 70 years and older. A total of 1,680 subjects were enrolled in 13 memory clinics and followed up for 3 years. After the baseline assessment, participants also underwent cognitive, functional, and biological assessments after 6, 12, 24 and 36 months. The protocol is registered on a public-access clinical trial database (www.clinicaltrials.gov, Number: NCT01513252). Written, informed consent was obtained from all participants.

Subjects

Included subjects were aged 70 years or older and presented at least 1 of the 3 following clinical criteria: (1) Memory complaint spontaneously reported to a general practitioner, (2) limitation in one instrumental activity of daily living (IADL, i.e., inability in the use the telephone, shopping, preparation of meals, housekeeping, laundry, transportation, medication use, or management of money, (3) slow gait speed (i.e., ≤0.8 m/s). Subjects with dementia, limitation in basic activities of daily living (bathing, dressing, toileting, transferring, continence, eating) and suffering from severe depression were not included in the trial.

Clinical data

Clinical Visits were scheduled every 6 months to assess physical condition, diseases and corresponding treatments, adherence to multi-domain intervention. Cognitive and functional assessments were conducted at baseline, six months, and annually at 1, 2 and 3 years by independent research staff blinded to intervention.

Cognitive assessment—The battery of neuropsychological tests included the free and cued selective reminding test (FCRST, focused on verbal episodic memory/recall) (19), the Controlled Oral Word Association Test and Category Naming Test (COWAT and CNT, for verbal fluency) (20), the Digit Symbol Substitution Subtest of the Wechsler Adult Intelligence Scale-Revised (for attention and executive function) (21), the Trail-Making Test (TMT, measuring switching) (22), the Mini Mental State Examination (MMSE) (15), and the Clinical Dementia Rating Scale (CDR) (23). Two visual-analogue scales were administered, to assess memory function and the consequences of memory impairment in everyday life. Depressive symptoms was assessed with the Geriatric Depression Scale-15 items (GDS) (24).

Physical and frailty assessment—Frailty was evaluated using the classification system proposed by Fried et al., based on assessments of grip strength, timed walking, unintentional weight loss, fatigue, and physical activity (3). In addition, functional assessment included the Alzheimer Disease Cooperative Study-Activities of Daily Living Prevention Instrument (ADCS-ADL) (25) and the Short Physical Performance Battery (SPPB) (26).

Classification of groups

Participants were classified into four groups according to the presence of cognitive impairment and/or frailty syndrome (Box 1). The four groups were mainly defined as follows:

- Group 1: “Robust older persons” with no evidence of physical frailty (i.e., no frailty criteria) and absence of cognitive impairment (i.e., CDR=0),
- Group 2: “Frail older individuals” with at least one Fried criteria and without cognitive impairment (i.e., CDR=0),
- Group 3: “Individuals with cognitive impairment and without physical frailty” with no Fried criteria and with cognitive impairment (i.e., CDR=0.5).
- Group 4: “Cognitive frailty individuals” with at least one Fried criterion and with cognitive impairment (i.e., CDR=0.5),

Analysis

We compared clinical characteristics, in particular neuropsychological profile, of subjects according to their frailty and cognitive status. We compared in a first time 4 groups of subjects: group 1, group 2, group 3, and group 4 (group 4 is the reference group for this analysis). In a second time, to evaluate the impact of physical frailty severity, we compared cognitive performance according to the number of physical frailty criteria (1, 2, and 3 or more) among subjects with CDR score of 0 and 0.5 (group with only 1 Fried criteria is the reference group for this analysis).

We used χ^2 or Fisher’s exact (for expected values <5) tests for categorical variables, one way analyses of variance for quantitative variables with normal distributions (Student tests), and non-parametric tests (Kruskal-Wallis test) for quantitative variables without normal distributions. We compared characteristics of “frailty cognitive individuals” (group 4) with group 1, 2, and 3; using univariate polytomic regressions for categorical variables and univariate linear regressions or Kruskal-Wallis tests for continuous variables. In the absence of a normal distribution, variables were transformed and tested on square root or logarithmic value in order to obtain normal distributions. A multivariate analysis was also conducted to test the effect of potential confounding factors: 1) age, gender, socio-cultural level, BMI, and GDS for the first analysis (cognitive profile of “cognitive frailty” group), and 2) age, gender, socio-cultural level, and GDS for the second analysis (impact of number of physical frailty criteria on cognitive performance).

P values were based on two-sided tests. To account for the multiplicity of tests with an overall risk of 5%, each comparison compared to the reference group is considered significant if the «p» is <0.05/number of comparison, either 0.017 for 3 comparisons (first analysis), and 0.025 for 2 comparisons (second analysis). Analyses were performed using SAS software version 9.4 (SAS institute, Cary, NC, USA).

Results

Population

Figure 1 shows the flow chart of this study. Table 1 shows baseline characteristics for the 1,617 MAPT participants studied in this work. “Cognitive frailty individuals” with at least 1 Fried criterion and with cognitive impairment (i.e., CDR=0.5), represented 356 subjects, 22% of our study population.

“Cognitive frailty individuals” significantly differed from “individuals with cognitive impairment and without physical frailty” for age, GDS and Body Mass Index (Body Mass Index), from “frail older individuals” for gender, GDS and age, and from “robust older persons” for age, gender, education years, GDS and BMI (table 2).

Cognitive profile of “cognitive frailty” group

“Cognitive frailty individuals” significantly differed with lower performance from “frail older individuals” and “robust older persons” for all cognitive tests (MMSE, CDR-SB, FCRST, TMT-A and –B, WAIS-R coding, CNT, and COWAT), visual analogue scales and some physical frailty tests (handgrip strength and slow gait speed) (table 2) in bivariate and multivariate analysis.

“Cognitive frailty individuals” significantly differed with lower performance from “individuals with cognitive impairment without physical frailty” for CDR-SB, free recall and delayed free recall of FCRST, TMT-A and TMT-B, WAIS-R coding, CNT, and visual analogue scales (table 2). Multivariate analysis indicated that “cognitive frailty individuals” and “individuals with cognitive impairment without physical frailty” had similar profiles on FCRST, TMT-B, visual analogue scale 1, and CNT although “cognitive frailty individuals” demonstrated significantly more impairment in visual analogue scale 1, CDR-SB, TMT-A, and WAIS-R coding.

Impact of physical frailty severity on cognitive performance

Subjects without cognitive impairment (i.e., CDR=0)—In multivariate analysis, subjects with only 1 Fried criterion significantly differed with better performance from subjects with 3 Fried criteria and more for delayed free recall of FCRST, CDR-SB, and visual analogue scale 1 (table 3).

Subjects with cognitive impairment (i.e., CDR=0.5)—In multivariate analysis, subjects with only 1 Fried criteria significantly differed with better performances from subjects with 3 Fried criteria and more for WAIS-R coding, and CDR-SB (table 4).

Discussion

In the bivariate analysis, “cognitive frailty individuals” significantly differed with lower performance from “individuals with cognitive impairment and without physical frailty” for CDR-SB, free recall and delayed free recall of FCRST, TMT-A and TMT-B, WAIS-R coding, CNT, and visual analogue scales. Multivariate analysis demonstrated significantly more impairment in visual analogue scale 1, CDR-SB, and WAIS-R coding.

“Cognitive frailty” has been conceived as a clinical condition characterized by the simultaneous presence of both physical frailty and cognitive impairment (after exclusion of dementia). To our knowledge, no previous study has attempted to determinate the cognitive profile of “cognitive frailty individuals” in comparison of subjects with cognitive impairment and without physical frailty. MAPT study provided an opportunity to describe the cognitive functions of a large sample of subjects with cognitive and physical performances well characterized. To achieve this objective, “cognitive frailty individuals” were included from MAPT study on the basis of the following: 1) CDR of 0.5 to objective the cognitive impairment. In MAPT study, all included participants at baseline had basic activities of daily living preserved (inclusion criteria) and no dementia. So, we have considered subjects with CDR score of 0.5 as MCI subjects. 2) At least one Fried Criterion of physical frailty and not 3 or more, because we wanted to cover the entire spectrum of physical frailty and pre-frailty population seen in memory clinic and geriatric centers in this analysis.

Cognitive profile of “cognitive frailty individuals” was an amnesic MCI multidomain. In fact, in bivariate analysis, memory, attention, and executive performances of “cognitive frailty individuals” were lower than in “individuals with cognitive impairment and without physical frailty” (as we may consider as MCI without physical frailty individuals). The multivariate analysis indicated that “cognitive frailty individuals” demonstrated significantly only more impairment for executive functions than in “individuals with cognitive impairment and without physical frailty”. Altered executive functions were mainly processing speed (TMT-A and WAIS-R coding), selective attention (WAIS-R coding) and mental flexibility (semantic fluency). The dissociation in semantic and phonenic fluency could be support the degradation in semantic knowledge in the “cognitive frailty individuals”. WAIS-R coding assessed the scanning and tracking aspect of attention. This test has also been found to measure aspects of visual selective attention and processing speed. Research using previous versions of the WAIS in non-clinical samples has suggested that the age-related decline in WAIS-R coding scores is related to motor ability (27). Performances in our study sample with physical frailty, probably due to lower executive and attention performances but also due to lower motor abilities. The main characteristic of the FCSRT was to assess verbal episodic memory with semantic cueing that permitted one to control for encoding and to facilitate retrieval in order to isolate the storage capacities. The cued recall technique, used in the FCSRT, was aimed at enhancing the recall performance by presentation of semantic cues that help for encoding and for retrieval processes. In this study, free recall and delayed free recall performances were lower in “cognitive frailty individuals” than in “individuals with cognitive impairment and without physical frailty”. Total recall, delayed total recall and index of cuing were not significantly different between

these 2 groups. This memory pattern differed from amnesic syndrome of the medial temporal (or hippocampal) which is characterized by a low free recall performance with a decreased total recall because of insufficient effect of cueing (28). The ability to benefit from cues mainly reflected impairment in strategies to retrieve stored information, as “subcortico-frontal dementia”. The motor features contributing to physical frailty derive from motor control systems which reside in the brain including basal ganglia, brainstem, frontal and subcortico-frontal areas. Thus, it is likely that physical frailty and cognition may show some degree of inter-relationship due to the effect on both from processes occurring in the brain (29). For example, the presence of cerebrovascular disease (8) and nigral neuronal loss (9) in older adults is associated with higher levels of frailty and lower levels of physical and cognitive functions, and could be responsible of “subcortico-frontal dementia”. Depressive symptoms are also related to cognitive outcomes (30,31), in particular to executive functions. Kelaiditi et al maintained that “cognitive frailty” is characterized by reduced cognitive reserve. “Cognitive frailty” could be viewed as simply the inverse of cognitive reserve (32).

We also estimated the association of physical frailty severity (number of frailty criteria) on cognitive performance. Subjects with 2 criteria, and 3 criteria or more, had more impaired cognitive scores (in particular for executive functions) than subjects with only one. Thus, more physical frailty would be severe and more cognitive performances would be impaired. The association between cognition performance and physical frailty severity seemed to be more important in normal cognitive functioning group (“frail older individuals” with at least 1 Fried criteria and CDR=0) than in “cognitive frailty individuals”. This cross-sectional study was not be able to assess the causal direction, whether physical frailty impacts cognitive performance or whether low cognitive performance impacts physical frailty. However, physical frailty probably could impact directly administration of cognitive testing, and cognitive scores more impaired in severe physical frailty could be in relation with both motor and cognitive performance. One other hypothesis is that we are more likely to see effects of physical frailty on cognition in normal cognitive functioning group because “frail older individuals” have not yet cognitive impairment, and in ”cognitive frailty individuals”, probably some subjects have already prodromal AD (or MCI due to AD) which could decrease cognitive effect of physical frailty severity.

The main key points of this study are: 1) it’s the first study which estimated the cognitive profile of subjects with “cognitive frailty”, 2) the large sample study, and 3) the neuropsychological battery realized in MAPT study permitting the well characterization of executive and memory functions. The absence of specific cognitive functions assessment (language, perception, praxia) did not allow to rule on the integrity supposed by these functions in “cognitive frailty individuals”.

“Cognitive frailty individuals” had executive and attention performance worse than “individuals with cognitive impairment and without physical frailty”. They presented a subcortico-frontal cognitive pattern, different of AD which a cortical neurodegenerative dementia. So, after exclusion of dementia and cognitive impairment diagnosis, it seems to be really important to use adequate cognitive screening tools to diagnosis “cognitive frailty individuals” in parallel of usual physical frailty, or cognitive markers because they would be

an interesting target for specific prevention intervention. To identify “cognitive frailty”, we could suggest that frail subjects should perform as screening tests Frontal Assessment Battery (33), the 5 words test (34); and FCRST, TMT-A, TMT-B, WAIS-R coding and verbal fluencies as diagnosis tests. We could also propose Mattis Dementia Rating Scale (35).

This large population (“cognitive frailty” sample represented 22% of the population of MAPT study) could be targeted for non-specific multi-domain trials. The advantages of targeted “cognitive frailty individuals” for multi-domain prevention trials include the importance of intervening and potentially slowing or reversing the frailty syndrome, the large numbers of persons affected, and the ability to target these individuals through primary care physicians. Disadvantages to target this population include the broad heterogeneity and presence of multiple morbidities within this population and the likelihood of poor compliance. The selection of the study sample may not be fully representative of the general population. In addition, the neurobiology of frailty has yet to be defined. Endpoints of a study in this population could include both physical and cognitive functions, in particular attention and executive tests.

“Cognitive frailty” could represent a cognitive entity with specific neuropsychological patterns (executive and selective attention). The results of this cross-sectional study could justify a clinical follow-up to assess the cognitive evolution of “cognitive frailty individuals”. In ”cognitive frailty individuals”, probably some subjects have already prodromal AD. A longitudinal study could permit to determinate cognitive decline of “cognitive frailty individuals” and extract subjects who convert to AD in the longitudinal follow-up to better characterize cognitive pattern and trajectory of this entity. Pathophysiological mechanisms of “cognitive frailty” are currently unknown. Ancillary neuroimaging studies of MAPT could provide an opportunity to better understand the relation between “cognitive frailty” and cerebral atrophy, white matter hyperintensities, and amyloid deposits.

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Appendix

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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 centre:* 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); Kristelle Sudres, Nicolas Lebrun, Nadège Barro-Belaygues (Montauban); Jacques Touchon, Karim Bennys, Audrey Gabelle, Aurélia Romano, Lynda Touati, Cécilia Marelli, Cécile Pays (Montpellier); Philippe Robert, Franck Le Duff, Claire Gervais, Sébastien Gonfrier (Nice); Yves 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:* Christian Vincent, Bertrand Perret, Claire Vinel (Toulouse).

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Box 1

Definitions used to establish the 4 sub-groups of this study

Mild Cognitive Impairment (MCI)

Variable definition but which includes: 1) a subjective disorder affecting memory and/or other cognitive areas and 2) objective impairment of memory and/ or other cognitive area 3) with no significant impact on usual activities. Thus, patients with MCI do not meet the generally accepted diagnostic criteria for dementia or Alzheimer's Disease (AD).

→ In this study, we consider that "individuals with cognitive impairment and without physical frailty" have a clinical dementia rating (CDR) score of 0.5.

Physical frailty

physical frailty is defined as «a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death". Frailty was defined as a clinical syndrome in which three or more of the following criteria were present: 1) unintentional weight, 2) self-reported exhaustion, 3) weakness (grip strength), 4) slow walking speed, and 5) low physical activity.

→ In this study, "frail older individuals" are defined by presence of at least one Fried criteria (and so includes pre-frailty and frailty individuals).

Cognitive frailty

definition includes: 1) presence of physical frailty and cognitive impairment; and 2) exclusion of concurrent AD dementia or other dementias.

→ In this study, we consider subjects with cognitive impairment (i.e., CDR=0.5) and physical frailty or pre-frailty (at least one Fried criteria) are "cognitive frailty individuals". By definition, there is no AD dementia in this study (exclusion criteria of MAPT study).

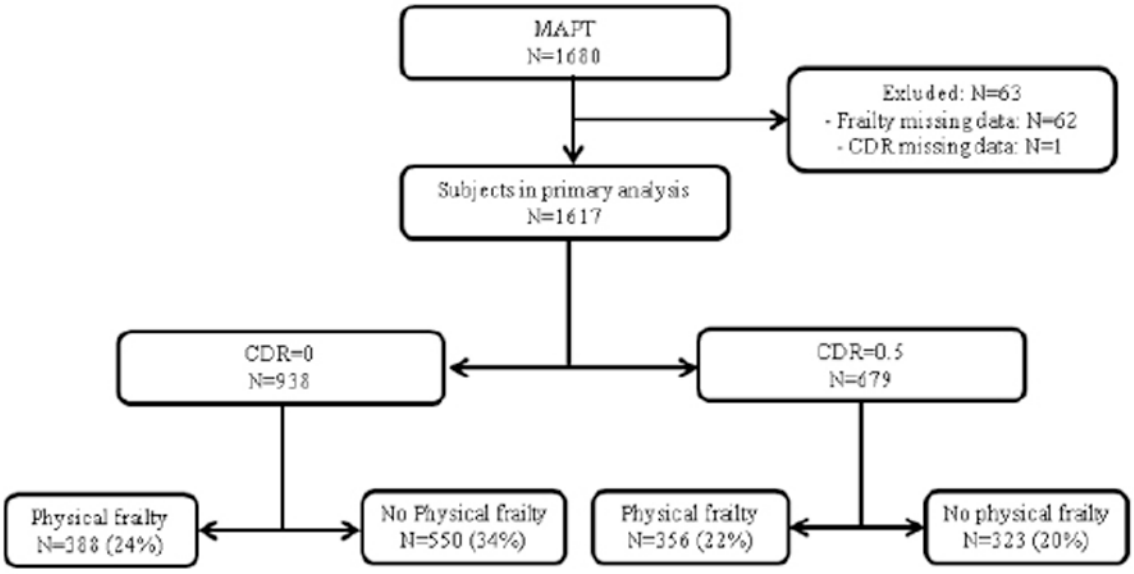

Figure 1.
Flow chart of the study

Table 1

Baseline characteristics of MAPT study subjects (n=1617)

Variables	MAPT population N=1617
Male gender, N (%)	571 (35.31)
Age in years, mean (SD)	75.37 (4.46)
Education years, N (%)	
No diploma	360 (22.74)
Primary school certificate	531 (33.54)
Secondary education, without high-school diploma	232 (14.66)
High-school diploma (Baccalaureat) or higher	460 (29.06)
Body Mass Index, mean (SD)	26.09 (4.07)
Multidomain intervention, N (%)	809 (50.03)
APOE ε4 positive, N (%)	287 (22.84)
Memory complaint, N (%)	1601 (99.01)
MMSE score, /30, mean (SD)	28.07 (1.60)
CDR-SB, mean (SD)	0.31 (0.46)
FCSRT scores, mean (SD)	
Immediate recall/16	15.45 (1.02)
Free recall /48	27.41 (6.80)
Total recall / 48	45.24 (3.89)
Delayed free recall /16	10.61 (2.93)
Delayed total recall/16	15.40 (1.32)
Number of intrusions	
Immediate recall	0.06 (0.32)
Total recall	1.10 (2.15)
Delayed recall	0.31 (0.79)
Index of cueing, % (SD)	88.90 (12.29)
TMT A seconds, mean (SD)	46.64 (17.23)
TMT B seconds, mean (SD)	123.24 (64.21)
WAIS-R coding, mean (SD)	37.65 (10.16)
COWAT 2 minutes score, mean (SD)	19.72 (6.50)
CNT 2 minutes score, mean (SD)	25.79 (7.41)
Visual Analogue Scale 1, /100, mean (SD)	49.88 (17.02)
Visual Analogue Scale 2, /100, mean (SD)	39.93 (23.14)
GDS score/15, mean (SD)	3.27 (2.64)
Fried's criteria, N (%)	
Involuntary weight loss	77 (4.76)
Exhaustion	264 (16.34)
Weakness (handgrip strength)	377 (23.49)
Slow gait speed	65 (4.03)

Variables	MAPT population N=1617
Low physical activity	236 (14.66)
SPPB score, /12, N (%)	
≥10	1251 (77.65)
< 10	360 (22.35)
4-m Gait speed, m/s, mean (SD),	1.09 (0.28)
ADCS-ADL PI, /45, mean (SD)	39.70 (4.82)

MMSE, Mini Mental Scale Examination; CDR, Clinical Dementia Rating Score; SPPB, Short Physical Performance Battery; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; TMT, Trail Making Test; COWAT, Controlled Oral Word Association Test; CNT, Categorial naming testing ; FCRST, Free and Cued Selective Reminding Test; GDS, Geriatric Depression rating; Visual Analogue Scale 1, Visual Analogue Scale, memory functioning; Visual Analogue Scale 2, Visual Analogue Scale, consequences in everyday life. Index of cuing (%) = (free recall-total recall) / (free recall-48).

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Table 2

Cognitive profile of “cognitive frailty individuals” in MAPT study

MAPT study N=1617	Available data	No cognitive impairment (CDR=0)				Cognitive impairment (CDR=0.5)		
		“Robust older persons” N=550	P*	“Frail older individuals” N=388	P*	“Individuals with cognitive impairment and without physical frailty” N=323	P*	“Cognitive frailty individuals” N=356
Male gender, N (%)	1617	174 (31.64)	0.000	105 (27.06)	0.000	135 (41.80)	0.545	157 (44.10)
Age in years, mean (SD)	1617	74.19 (3.97)	<0.0001	75.98 (4.60)	0.0009	74.81 (4.08)	<0.0001	77.02 (4.73)
Education years, N (%)	1583							
No diploma		91 (16.95)	-	90 (23.68)	-	88 (27.67)	-	91 (26.15)
Primary school certificate		178 (33.15)	0.022	131 (34.47)	0.471	107 (33.65)	0.848	115 (33.05)
Secondary education, without high-school diploma		89 (16.57)	0.001	50 (13.16)	0.319	54 (16.98)	0.164	39 (11.21)
High-school diploma or higher		179 (33.33)	0.004	109 (28.68)	0.738	69 (21.70)	0.089	103 (29.60)
Body Mass Index, mean (SD)	1613	25.61 (3.95)	0.0009	26.92 (4.56)	0.1797	25.47 (3.34)	0.0008	26.52 (4.11)
Multidomain intervention, N (%)	1617	290 (52.73)	0.333	184 (47.42)	0.583	159 (49.23)	0.956	176 (49.44)
APOE ε4 positive, N (%)	1251	89 (19.73)	0.096	70 (23.73)	0.708	63 (25.61)	0.895	65 (25.10)
Memory complaint, N (%)	1617	546 (99.27)	0.537	381 (98.20)	0.447	322 (99.69)	0.247	352 (98.88)
MMSE, score /30, mean (SD)	1617	28.48 (1.42)	<0.0001*	28.34 (1.49)	<0.0001*	27.72 (1.69)	0.0353	27.47 (1.63)
CDR-SB score, mean (SD)	1617	0.01 (0.08)	<0.0001	0.02 (0.10)	<0.0001	0.64 (0.34)	0.0002*	0.77 (0.53)
FCSRT scores, mean (SD)								
Immediate recall, /16	1617	15.65 (0.70)	<0.0001*	15.60 (0.75)	<0.0001*	15.25 (1.15)	0.7484	15.18 (1.42)
Free recall /48	1616	29.77 (5.54)	<0.0001*	28.82 (5.94)	<0.0001*	25.51 (6.94)	0.0013	23.94 (7.38)
Total recall, / 48	1616	46.37 (2.18)	<0.0001*	45.99 (2.51)	<0.0001*	43.99 (5.12)	0.2092	43.78 (4.99)
Delayed free recall /16	1616	11.62 (2.40)	<0.0001*	11.20 (2.35)	<0.0001*	9.75 (3.07)	0.0079	9.19 (3.32)
Delayed total recall /16	1616	15.72 (0.62)	<0.0001*	15.69 (0.69)	<0.0001*	15.07 (1.75)	0.0320	14.89 (1.85)
Number of intrusions								
Immediate recall	1615	0.05 (0.23)	0.2500	0.03 (0.18)	0.1259	0.08 (0.39)	0.8805	0.08 (0.44)
Total recall	1612	0.66 (1.07)	<0.0001*	0.81 (1.46)	<0.0001*	1.73 (3.14)	0.6833	1.55 (2.66)

MAPT study N=1617	Available data	No cognitive impairment (CDR=0)				Cognitive impairment (CDR=0.5)		
		"Robust older persons" N=550	P*	"Frail older individuals" N=388	P*	"Individuals with cognitive impairment and without physical frailty" N=323	P*	"Cognitive frailty individuals" N=356
Delayed recall	1613	0.17 (0.45)	<0.0001 *	0.20 (0.55)	<0.0001 *	0.46 (1.08)	0.5510	0.49 (1.04)
Index of cueing, % (SD)	1616	92.18 (9.03) *	<0.0001	90.97 (9.59) *	<0.0001	85.07 (15.05)	0.6498	85.04 (14.37)
TMT A seconds, mean (SD)	1614	43.06 (14.71)	<0.0001 *	46.16 (15.89)	<0.0001 *	46.68 (15.26)	<0.0001 *	52.68 (21.79)
TMT B seconds, mean (SD)	1581	107.48 (48.77)	<0.0001 *	121.01 (53.96)	<0.0001 *	126.19 (60.20)	0.0001	148.18 (87.84)
WAIS-R coding, mean (SD)	1611	40.27 (9.75)	<0.0001 *	38.29 (10.26)	<0.0001 *	37.17 (8.94)	<0.0001 *	33.29 (10.30)
COWAT 2 minutes score, mean (SD)	1615	20.95 (6.40)	<0.0001 *	19.71 (6.55)	0.0045	19.11 (5.92)	0.1323	18.36 (6.79)
CNT 2 minutes score, mean (SD)	1614	27.31 (6.98)	<0.0001 *	26.10 (7.37)	<0.0001 *	25.21 (7.35)	0.0044	23.61 (7.62)
Visual Analogue Scale 1, /100, mean (SD)	1616	47.64 (16.18)	<0.0001 *	47.83 (16.18)	<0.0001*	51.10 (16.93)	0.0097	54.44 (18.30)
Visual Analogue Scale 2, /100, mean (SD)	1617	36.38 (23.08)	<0.0001 *	38.80 (20.93)	<0.0001 *	39.64 (22.90)	<0.0001 *	46.89 (24.33)
GDS score/15, mean (SD)	1608	2.64 (2.21)	<0.0001	3.53 (2.80)	0.0001	2.93 (2.29)	<0.0001	4.27 (3.02)
Fried's criteria, N (%)								
Involuntary weight loss	1617	0 (0)	-	35 (9.02)	0.216	0 (0)	-	42 (11.80)
Exhaustion	1616	0 (0)	-	127 (32.82)	0.107	0 (0)	-	137 (38.48)
Weakness (handgrip strength)	1605	0 (0)	-	214 (56.02)	0.011	0 (0)	-	163 (46.57)
Slow gait speed	1613	0 (0)	-	25 (6.51)	0.025	0 (0)	-	40 (11.24)
Low physical activity	1610	0 (0)	-	110 (28.72)	0.046	0 (0)	-	126 (35.59)
SPPB score/12, N (%)	1611							
< 10		73 (13.30)		126 (32.64)		45 (13.93)		116 (32.86)
≥ 10		476 (86.70)	0.000 *	260 (67.36)	0.950	278 (86.07)	0.000 *	237 (67.14)
4-m Gait speed m/s, mean (SD),	1614	1.18 (0.30)	<0.0001 *	1.04 (0.25)	0.0022	1.12 (0.24)	<0.0001	0.98 (0.25)
ADCS-ADL PI, /45; mean (SD)		1604	40.91 (3.89)	<0.0001 *	40.18 (4.48)	<0.0001 *	39.50 (4.66)	<0.0001 *

MMSE, Mini Mental Scale Examination; CDR, Clinical Dementia Rating Score; SPPB, Short Physical Performance Battery; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; TMT, Trail Making Test; COWAT, Controlled Oral Word Association Test; CNT, Categorial naming testing ; FCRST, Free and Cued Selective Reminding Test; GDS, Geriatric Depression rating; Visual AnaloAnalogue Scale 2, Visuague Scale 1, Visual Analogue Scale, memory functioning; Visual l Analogue Scale, consequences in everyday life; Index of cuing (%) = (free recall-total recall) / (free recall-48);

* indicates that subjects from the "cognitive frailty individuals" significantly differ from either the "normal older individuals" or "frail older individuals" or "individuals with cognitive impairment and without physical frailty" ($p<0.017$) in multivariate analysis (ajustement for age, gender, socio-cultural level, BMI, and GDS).

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Table 3

Impact of physical frailty severity on cognitive performance in “frail older individuals”

Variables		No cognitive impairment (CDR=0)				
	Available data	Fried=1 N=277	Fried=2 N=78	P*	Fried≥3 N=20	P*
Male gender, N (%)	375	78 (28.16)	19 (24.36)	0.506	4 (20.00)	0.434
Age in years, mean (SD)	375	75.81 (4.50)	76.81 (5.04)	0.1129	76.25 (0.6573)	0.6573
Education years, N (%)	367					
No diploma		61 (22.34)	15 (20.00)	-	9 (47.37)	-
Primary school certificate		94 (34.43)	26 (34.67)	0.746	7 (36.84)	0.197
Secondary education, without high-school diploma		38 (13.92)	10 (13.33)	0.882	2 (10.53)	0.202
High-school diploma or higher		80 (29.36)	24 (32.00)	0.591	1 (5.26)	0.021
Body Mass Index, mean (SD)	375	26.80 (4.54)	26.95 (4.43)	0.7984	27.55 (4.86)	0.4739
GDS score/15, mean (SD)	371	3.22 (2.63)	4.29 (3.10)	0.0047	5 (2.92)	0.0077
MMSE score /30, mean (SD)	375	28.35 (1.44)	28.29 (1.65)	0.7610	28.05 (1.82)	0.3855
CDR-SB score, mean (SD)	375	0.01 (0.08)	0.01 (0.06)	0.4261	0.13 (0.22)	<0.0001*
FCSRT scores, mean (SD)	375					
Immediate recall/16		15.62 (0.70)	15.54 (0.86)	0.8180	15.65 (0.81)	0.5011
Free recall /48		29.23 (6.02)	27.58 (6.18)	0.0318	27.95 (4.45)	0.3560
Total recall / 48		46.09 (2.50)	45.69 (2.83)	0.2478	45.80 (1.64)	0.0854
Delayed free recall /16		11.43 (2.30)	10.76 (2.50)	0.0249	9.80 (2.31)	0.0028*
Delayed total recall/16		15.74 (0.66)	15.58 (0.78)	0.0411	15.45 (0.83)	0.0181
Index of cueing, % (SD)		91.36 (9.49)	90.05 (10.63)	0.3912	89.54 (7.51)	0.1262
TMT A seconds, mean (SD)	374	45.74 (15.52)	47.64 (17.04)	0.3729	46.58 (16.10)	0.8300
TMT B seconds, mean (SD)	371	117.53 (47.44)	125.90 (63.27)	0.4130	158.89 (86.48)	0.0047
WAIS-R coding, mean (SD)	374	38.71 (10.29)	38.01 (10.48)	0.5942	33.95 (8.55)	0.0455
COWAT 2 minutes score, mean (SD)	375	19.88 (6.58)	19.68 (6.60)	0.8088	17.75 (6.92)	0.1636
CNT 2 minutes score, mean (SD)	374	26.38 (7.36)	26.46 (7.69)	0.9346	22.50 (5.82)	0.0232
Visual Analogue Scale 1, /100, mean (SD)	374	46.55 (15.65)	49.87 (17.50)	0.1095	56.15 (17.33)	0.0106*
Visual Analogue Scale 2, /100, mean (SD)	375	37.04 (20.39)	42.19 (21.40)	0.0541	47.85 (23.78)	0.0253

MMSE, Mini Mental Scale Examination; CDR-SB, Clinical Dementia Rating Score-Sum of Boxes; TMT, Trail Making Test; COWAT, Controlled Oral Word Association Test; CNT, Categorial naming testing ; FCRST, Free and Cued Selective Reminding Test; Visual Analogue Scale 1, Visual Analogue Scale, memory functioning; Visual Analogue Scale 2, Visual Analogue Scale, consequences in everyday life; Index of cuing (%) = (free recall-total recall) / (free recall-48);

* indicates that subjects from the “Fried=1” group significantly differ from either the ‘Fried=2” or “Fried ≥ 3” groups ($p<0.025$) in multivariate analysis (ajustement for age, gender, socio-cultural level, and GDS).

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Table 4

Impact of physical frailty severity on cognitive performance in “cognitive frailty individuals”

Variables		Cognitive impairment (CDR=0.5)				
	Available data	Fried=1 N=236	Fried=2 N=82	P*	Fried≥3	P* N=30
Male gender, N (%)	348	106 (44.92)	34 (41.26)	0.558	14 (46.67)	0.856
Age in years, mean (SD)	348	76.56 (4.58)	78.12 (5.09)	0.0098	77.67 (4.32)	0.2251
Education years, N (%)	340					
No diploma		57 (24.46)	21 (26.58)		9 (32.14)	
Primary school certificate		73 (31.33)	32 (40.51)	0.600	9 (32.14)	0.623
Secondary education, without high-school diploma		28 (12.02)	4 (5.06)	0.110	5 (17.86)	0.838
High-school diploma or higher		75 (32.19)	22 (27.85)	0.557	5 (17.86)	0.140
Body Mass Index, mean (SD)	347	26.44 (4.12)	26.81 (4.40)	0.4851	26.83 (3.52)	0.6288
GDS score/15, mean (SD)	347	3.83 (2.82)	5.09 (3.16)	0.009	4.93 (2.89)	0.519
MMSE score /30, mean (SD)	348	27.50 (1.55)	27.46 (1.77)	0.8454	27.13 (1.83)	0.2418
CDR-SB score, mean (SD)	348	0.72 (0.43)	0.80 (0.54)	0.0009	1.03 (0.96)	0.0519 *
FCSRT scores, mean (SD)	348					
Immediate recall/16		15.14 (1.47)	15.22 (1.48)	0.5190	15.37 (0.81)	0.9821
Free recall /48		24.08 (7.51)	23.84 (7.60)	0.7990	23.10 (6.46)	0.4957
Total recall / 48		43.91 (5.20)	43.48 (4.78)	0.1579	43.37 (4.37)	0.1769
Delayed free recall /16		9.34 (3.35)	8.91 (3.53)	0.3224	8.60 (2.67)	0.2546
Delayed total recall/16		14.94 (1.85)	14.74 (2.05)	0.5548	14.77 (1.48)	0.2082
Index of cueing, % (SD)		85.78 (14.47)	83.49 (14.60)	0.1216	82.70 14.02)	0.1387
TMT A seconds, mean (SD)	346	50.97 (20.59)	56.01 (22.63)	0.0358	54.97 (29.07)	0.4504
TMT B seconds, mean (SD)	334	139.92(80.31)	164.73 (100.09)	0.0195	148.00 (71.73)	0.5077
WAIS-R coding, mean (SD)	344	34.57 (10.08)	31.32 (10.53)	0.0133	28.76 (9.44)	0.0038 *
COWAT 2 minutes score, mean (SD)	347	18.45 (7.05)	18.37 (5.83)	0.9264	17.83 (7.54)	0.6433
CNT 2 minutes score, mean (SD)	347	23.72 (7.40)	23.51 (8.33)	0.8338	23.60 (8.05)	0.9363
Visual Analogue Scale 1, /100, mean (SD)	348	54.51 (18.39)	55.29 (17.97)	0.7388	49.80 (18.87)	0.1860
Visual Analogue Scale 2, /100, mean (SD)	348	46.01 (24.75)	48.45 (24.11)	0.4377	45.77 (23.89)	0.9595

MMSE, Mini Mental Scale Examination; CDR-SB, Clinical Dementia Rating Score-Sum of Boxes; TMT, Trail Making Test; COWAT, Controlled Oral Word Association Test; CNT, Categorial naming testing ; FCRST, Free and Cued Selective Reminding Test; Visual Analogue Scale 1, Visual Analogue Scale, memory functioning; Visual Analogue Scale 2, Visual Analogue Scale, consequences in everyday life; Index of cuing (%) = (free recall-total recall) / (free recall-48),

* indicates that subjects from the “Fried=1” group significantly differ from either the ‘Fried=2” or “Fried ≥3” groups ($p<0.025$) in multivariate analysis (ajustement for age, gender, socio-cultural level, and GDS).

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