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Commentary on ''A roadmap for the prevention of dementia II. Leon Thal Symposium 2008.'' The Multidomain Alzheimer Preventive Trial (MAPT): A new approach to the prevention of Alzheimer's disease

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Abstract

Background: Because no effective curative approaches are available, preventive approaches in the field of Alzheimer's disease (AD) are needed. We present the design of the ongoing Multidomain Alzheimer Preventive Trial (MAPT) Study. Several previous studies suggested that many factors may be involved in the occurrence of AD at late ages. Because of the probable multifactorial nature of AD, it seems logical to initiate multidomain interventions to examine their potential synergistic effects. The MAPT Study aims to evaluate the efficacy of a multidomain intervention (nutritional, physical, and cognitive training) and omega 3 treatment in the prevention of cognitive decline in frail elderly persons aged 70 years or over. The study also collects imaging and biological data that could be used in future AD prevention and treatment trials.

Methods: The MAPT Study is a 3-year, randomized, controlled trial conducted by university hospital practitioners specializing in memory disorders in four French cities (Bordeaux, Limoges, Montpellier, and Toulouse). The study plans to enroll 1200 frail elderly subjects on the basis of at least one of the following criteria: subjective memory complaint spontaneously expressed to a general practitioner, limitation in one instrumental activity of daily living (IADL), and slow walking speed. To demonstrate the protective effect of interventions, subjects are randomized into one of the following four groups: omega 3 alone, multidomain intervention alone, omega 3 plus multidomain intervention, or placebo (n = 300 each). The principal outcome measure is a change in cognitive function at 3 years, as determined by the Grober and Buschke Test.

Conclusions: The MAPT Study is the first preventive trial involving multidomain interventions. Final results should be available in 2013.

Keywords: Multidomain intervention; Nutrition; Physical exercise; Cognitive training; Prevention; Alzheimer's disease

1. Introduction

Its high incidence and prevalence make dementia one of the most common diseases of the elderly. The number of older adults living with Alzheimer's disease (AD) is estimated to increase from the current 26.6 million to 106.2 million by 2050 [1]. Because no effective curative approaches are available, it is of major importance to develop and study

See Appendix for membership of the MAPT Study Group.

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preventive measures. Because of the large numbers of affected patients, interventions that delay disease onset or progression, even on a relatively small scale, could have large public-health effects [1]. The occurrence of dementia at late ages can be attributed to an accumulated risk during the whole lifespan. Persons are born with different genetic predispositions and during life, they are exposed to both risk and protective factors [2]. Some prospective studies underlined the importance of nutrition in the maintenance of good cognitive health [3]. Special attention has been given to the possible protective role of n-3 long-chain polyunsaturated fatty acids in the prevention of cognitive decline and dementia [3]. Other potential modifiable lifestyle factors (e.g., physical exercise, and cognitive and social activities) were linked to decreased cognitive decline or incidence of dementia [4–7], suggesting the importance of maintaining an active and socially integrated life in old age [2]. In addition, Kivipelto et al. [8] highlighted the role of vascular risk factors present at midlife in the development of dementia. At present, it seems difficult to propose any specific recommendations for lifestyle changes, especially because of the lack of randomized controlled trials because of methodological questions (e.g., randomization of large numbers of subjects, or intervention durations extending over a number of years) [9,10]. Only two recent randomized, controlled trials showed promising results for dementia prevention in older adults [11,12]. In the Advanced Cognitive Training for Independent and Vital Elderly Trial, results indicated that reasoning training resulted in less functional decline in self-reported instrumental activities of daily living over a 5 year period in people aged 65 years and older [11]. More recently, data from the Fitness for the Aging Brain Study Trial suggested that exercise modestly improved cognitive function in older adults with subjective and objective memory impairment [12]. Because of the multifactorial nature of AD, it seems logical to initiate multidomain interventions designed to examine their potential synergistic effects [9,10]. We present the methodology of the first Multidomain Alzheimer's Disease Preventive Trial (MAPT), which combines different preventive approaches focused on nutrition, physical exercise, and cognitive training.

2. General objectives

The main objective of the MAPT Study is to test the efficacy of a multidomain intervention (nutritional, physical, and cognitive training) and omega 3 treatment in the prevention of cognitive decline in frail elderly persons aged 70 years or over. The principal outcome measure is the change in cognitive function at 3 years, as determined by the Grober and Buschke Test (a test of memory of 16 words). Secondary objectives include the collection of biological material (blood specimens, RNA, and genomic DNA) to identify new biomarkers of potential use in future AD prevention and treatment trials, assessments of the efficacy of intervention (multidomain or omega 3 treatment) on functional decline and functional capacities, and compliance. In addition, neuroimaging examinations (positron emission tomography [PET] scans and magnetic resonance imaging [MRI]) will be performed in a subgroup of participants to identify the impact of interventions (multidomain or omega 3 treatment) on cerebral atrophy and cerebral metabolism. Body-composition assessments (dual energy X-ray absorptiometry [DEXA]) will also be used to study the potential influence of body-composition changes on frailty and cognitive decline.

3. Methods

3.1. Participants

The recruitment goal for the MAPT Trial is to enroll a sample of frail elderly people, aged 70 years and over, living independently, with good functional and cognitive status. In recent studies, frailty was linked to cognitive decline and dementia in older people [13–15]. The use of a target population with known cognitive decline or dementia risk factors allows us to test the efficacy of our potential preventive strategies in a smaller sample over a shorter follow-up period, and should lead to a quicker rate of cognitive decline during the 3-year trial period [10]. The definition of frailty is not, to date, consensual [16], but for practical purposes, we used three clinical components to identify frail persons based on epidemiological evidence: spontaneous memory complaint expressed to a general practitioner [17], limitation in one instrumental activity of daily living (IADL, i.e., ability to use the telephone, shop, prepare meals, do housekeeping, do one's laundry, use transportation, follow a medication schedule, or manage money) [18,19], and slow walking speed (speed lower than 0.77 m/s, which means that it takes more than 5 seconds to walk 4 m) [16,20,21] (Table 1). We excluded demented subjects (Diagnostic and Statistical Manual of Mental Disorders, 4th edition [DSM IV] criteria) [22], subjects who had a Mini-Mental State Examination (MMSE) score lower than 24 (0–30) [23], subjects who were incapable of basic activities of daily living (ADL score lower than 6 [0–6]) [24], and those who were severely depressed (Geriatric Depression Scale [GDS] score of 15) [25]. In addition, other disorders that could interfere with the interpretation of the study were evaluated, and patients with such disorders were excluded. The inclusion and exclusion criteria are presented in Table 2. Participants were enrolled from various sources, including advertisements in the local media, conferences, general practitioners, and memory clinics in four French cities (Bordeaux, Limoges, Montpellier, and Toulouse). The inclusion period began in June 2008, with an expected duration of 2 years.

3.2. Sample size

The sample size required for this trial is based on a 0.3-SD difference between the four trial arms (three treatment groups plus placebo group) according to a free recall score in the Grober and Buschke Test [26] over the 3 years of the intervention. To detect a 0.3-SD difference between trial arms, with an alpha risk of 1% and a power of 80% power, 201 individuals are required per group. Anticipating a 30% dropout

Table 1
New evidence to recruit frail population in primary prevention trials in AS

Relation between frailty, cognitive decline, or dementia: evidence based on epidemiologic data		
Study	Population	Results
Dufouil et al. [17] (PAQUID Study)	n = 3777 General population 65 years and older	Elderly persons who express a memory complaint to their general practitioner have a higher risk of developing dementia than normal subjects who do not express a complaint, whether their cognitive performances are normal (RR = 3.26, P = .05) or abnormal (RR = 6.09, P = .001)
Nourhashemi et al. [19] (EPIDOS Study)	n = 7500 Healthy elderly women Aged ≥75 years	Dependence evaluated according to IADL scale was found to be independently associated with numerous characteristics of frailty syndrome such as isolated memory deficit, vision and hearing impairments, fear of falling, and perceived poor health
Fitzpatrick et al. [21] (GEM Study)	n = 3035 Healthy elderly Mean age, 78.6 ± 3.3 years	Risk of low cognition (defined as 3MSE score of 80–85) was almost twice as great for participants in the slowest quartile of the rapid-paced walking task than for fastest walkers (odds ratio, 1.96; 95% confidence interval, 1.25–3.08) in models adjusted for demographics and comorbidities
Alfaro-Acha et al. [20] (EPESE Study)	n = 2070 Healthy elderly Aged ≥65 years	Risk of cognitive decline was significantly increased in elderly subjects who took the most time to walk a distance of 2.4 m

Abbreviations: PAQUID, Personnes Age's Quid; RR, relative risk; EPIDOS, Epidemiology of Osteoporosis; GEM, Gingko Evaluation of Memory; 3MSE, Modified Mini-Mental State Examination; EPESE, Established Populations for the Epidemiologic Studies of the Elderly.

over 3 years of intervention, the total sample size required for the study is 1148 (287 per group).

3.3. Primary outcome measure

The primary outcome measure is change in cognitive function at 3 years, as determined by the Grober and Buschke Test (a test of memory of 16 words). In view of the advantages in terms of sample size, duration of follow-up, and stability of the effect, the use of progression in cognitive decline instead of conversion to dementia, with changes in the slope of cognitive tests as a primary outcome in primary prevention trials, was recently recommended by a European Task Force consensus [27]. This consensus also recommended that changes in memory with cued recall (e.g., measured with the Grober Buschke Test) seem particularly related to the changes that occur in AD.

3.4. Study design

The MAPT is multicenter, randomized, and placebo-controlled, and uses a four-group design including three treatment groups (omega 3 alone, multidomain intervention alone, omega 3 plus multidomain intervention, at n = 300 each) and a placebo group (n = 300). Participants are randomized into a group in each city by an interactive voice response system, according to a list of random numbers in blocks of 8 generated by the industrial study sponsor. Visits are scheduled every 6 months to assess physical condition, diseases and corresponding treatments, adherence to and tolerance of omega 3 treatment, and adherence to the multidomain intervention, and to deliver the supplement. Cognitive and functional assessments are conducted at baseline, at 6 months, and annually at 1, 2, and 3 years by independent research staff who do not know the group to which the subject is assigned. The entry and follow-up procedures are illustrated in Fig. 1. All assessments are performed by hospital practitioners specializing in memory disorders and AD. The study protocol was approved by the Institutional Review Board of Toulouse (i.e., the coordinating center). Written, informed consent is obtained from all participants.

3.5. Interventions

3.5.1. Multidomain intervention

The multidomain intervention includes: 1) training sessions in the following three areas: nutrition, physical activity, and cognitive training; and 2) preventive consultations for 3 years (Fig. 2).

Training sessions are conducted in small groups (6–8 participants) in 12 120-minute sessions over the first 2 months (two sessions a week for the first month, and one session a week the second month). After the second month, sessions are planned monthly throughout the 3-year intervention period, to reinforce the key messages of the program and to increase compliance. Participants are asked to use a diary to record their cognitive and physical activities each month. Booster training will be delivered in each multidomain group 1 year and 2 years after their initial training sessions. Each training session includes 60 minutes for cognitive training, 45 minutes for physical training, and 15 minutes for nutritional advice. Training sessions are delivered by qualified trainers. Compliance with the multidomain intervention

Table 2
MAPT inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Subjects of both genders, aged 70 years or over • Subjects with at least one of the following frailty criteria: A spontaneous memory complaint A limitation in one of the instrumental activities of daily living Slow walking speed (speed = 0.77 m/s, i.e., 5 seconds to walk 4 m) • Subjects with an MMSE score of ≥24 • Subjects capable of understanding the protocol, complying with its requirements, and attending study visits • Subjects with sufficient availability to take part in the multidomain intervention • Subjects who, in the opinion of the investigator, are liable to comply with treatment during the study • Subjects capable of giving written informed consent, and agreeing to comply with study requirements • Subjects covered by a health insurance system	• Criteria related to diseases: Known presence of dementia or Alzheimer's disease (DSM IV criteria) Deterioration in global cognitive function (MMSE score <24) Dependency for basic activities of daily living (ADL score <6) Presence of serious diseases that could be life-threatening in the short term History or presence of any disease that could compromise the subject's participation in multidomain intervention sessions • Criteria related to treatments: Taking of supplements containing omega-3 (apart from food) within past 6 months and/or taking omega-3 at inclusion • Criteria related to subjects: Visual or hearing impairments incompatible with performance and/or interpretation of neuropsychological tests History or presence of any previous condition (severe depression or generalized anxiety) that could, in the opinion of the investigator, interfere with results of the study or expose the subject to additional risk Subjects deprived of their freedom by administrative or judicial decision, or under guardianship or admitted to a healthcare or social institution Participation in another clinical study in the previous month, or participation scheduled during the study

will be estimated from the number of sessions followed by each participant. Because of the nature of the intervention, participants are not blinded regarding group membership. Participants are explicitly asked at the beginning of the trial and at each subsequent assessment not to discuss information regarding the intervention with the independent research staff conducting the cognitive assessment, to limit subjective assessment, and with other participants, to limit contamination.

3.5.2. Cognitive training

During the first 2 months, sessions 1–8 are focused on reasoning training, and sessions 9–12 are focused on memory training. Reasoning training involves teaching strategies for finding the pattern in a letter or word series (e.g., acegi…) and identifying the next item in the series. Memory training involves teaching mnemonic strategies (organization, visualization, and association) for remembering verbal material (e.g., word lists, sequences of items, text material, or main ideas and details of stories). One of the main objectives of the cognitive sessions is to teach participants how to use these strategies in solving everyday problems (e.g., mnemonic strategies to remember a grocery list, or reasoning strategies to understand the pattern in a bus schedule). The cognitive component of the multidomain program 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, based on their experience and previous work [11,28,29].

3.5.3. Physical training

The global aim of the physical intervention is to encourage participants to perform at least 150 minutes of moderate-intensity physical activity per week (according to the recommendations of the American College of Sports Medicine) [30]. The most frequently recommended type of activity is walking (30 minutes per day). However, participants can choose other forms of exercise to fulfill their five 30-minute sessions per week (e.g., aerobic exercises or strength training activities). The program includes a general advice component and a personalized, home-based physical-activity program, designed with each participant during individual interviews planned every 6 months (six interviews during the 3 years).

3.5.4. Nutritional advice

Nutritional advice is based on dietary guidelines established by the French National Nutrition and Health Program for the elderly, which are now considered the official reference in France [31]. Eight key guidelines are proposed during the first 2 months. They offer specific recommendations for a healthy diet.

Individualized preventive consultation is scheduled at baseline, 1 year, and 2 years for each participant in the multidomain groups. The main objective of this consultation is to optimize the follow-up and management of medical problems identified in collaboration with the general practitioners in private practice. This consultation was designed by a multidisciplinary task force group [32]. It consists of a multidimensional investigation designed to detect any hearing or visual disorders, mood disorders, anxiety, malnutrition [33], walking and balance problems, fear of falling, poor oral and dental health, and vascular risk factors. A good control of vascular risk factors, including the management of hypertension, diabetes, and hypercholesterolemia (i.e., known dementia risk factors), is recommended among preventive strategies for dementia [2,7,8,32].

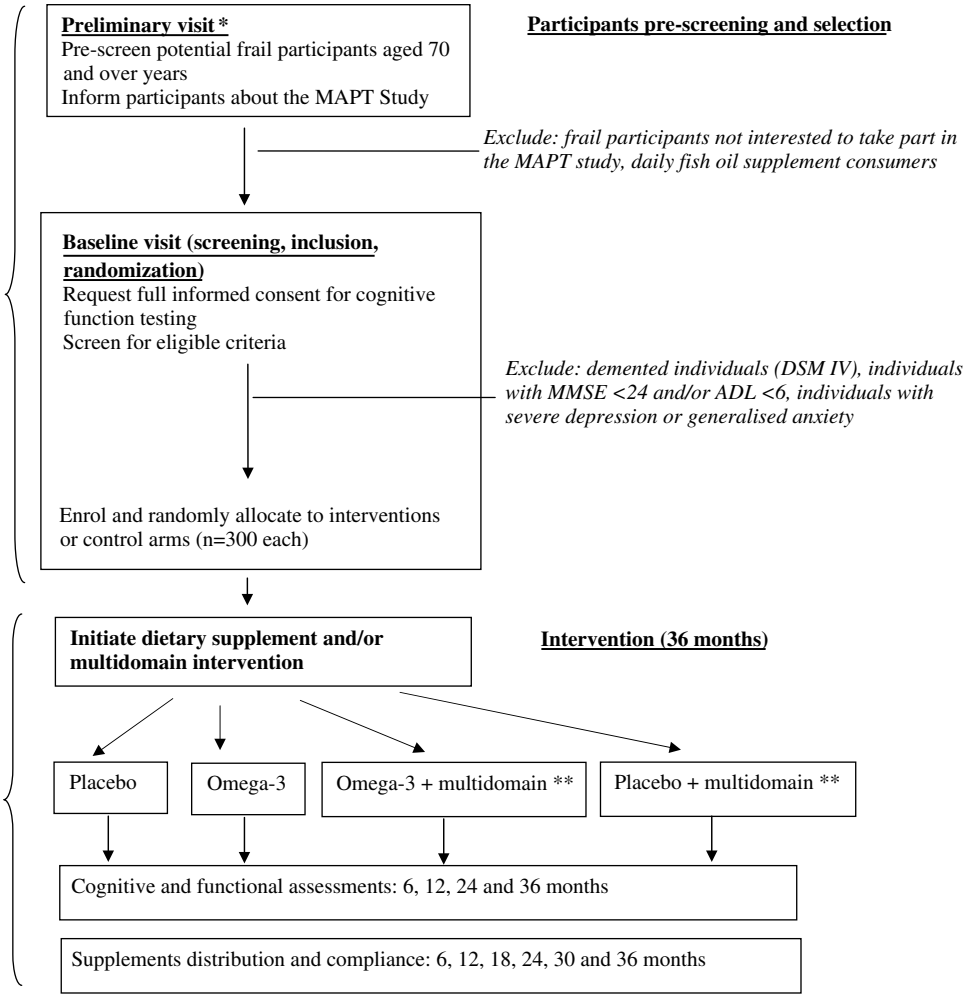

Fig. 1. Flow chart of MAPT Study. *Participants are mainly recruited by hospital practitioners in memory clinics. The preliminary visit can also be conducted by private general practitioners. In this case, the time between preliminary and baseline visits does not exceed 3 weeks. **For participants in multidomain groups, 12 training sessions over the first 2 months (two sessions a week for the first month, and one session a week the second month) are scheduled. After the second month, sessions are planned monthly throughout 3 years. Preventive consultation is conducted at baseline, 1 year, and 2 years.

3.6. Omega 3 treatment duration and dose

The intervention arm will be asked to consume two soft capsules daily as a single dose, containing a total of 400 mg docosahexaenoic acid, i.e., 800 mg docosahexaenoic acid per day, for 3 years. The placebo arm will be asked to consume two identical soft capsules per day for 3 years. Blinding is ensured by the identical appearance (size, color, and shape) of the placebo and active capsules. Unused study supplement is returned at each visit, and compliance with use of the supplement is assessed by tablet count.

3.7. Data collection

3.7.1. Behavioral assessment

At baseline, at 6 months, and then annually, a series of neuropsychological tests is administered for cognitive assessment. These include the Grober and Buschke Test (antero-grade episodic memory/recall) [26], the Controlled Oral Word Association Test and Category Naming Test (verbal fluency) [34], the Digit Symbol Substitution Subtest of the Wechsler Adult Intelligence Scale-Revised (attention and executive function) [35], the Trail-Making Test (motor activity and selective attention) [36], the MMSE [23], and the Clinical Dementia Rating Scale (severity of dementia) [37]. Two visual-analogue scales are also administered, to assess memory functioning and the consequences of memory impairment in everyday life [38]. In addition, functional assessment includes the Alzheimer Disease Cooperative Study-Activities of Daily Living Prevention Instrument (dependency) [39] and the Short Physical Performance Battery (functional capacities) [40]. Frailty is evaluated using the classification system proposed by Fried et al., based on assessments of grip strength, timed walking, body composition, fatigue, and physical activity [41,42]. Comorbid depression is assessed with the GDS [25].

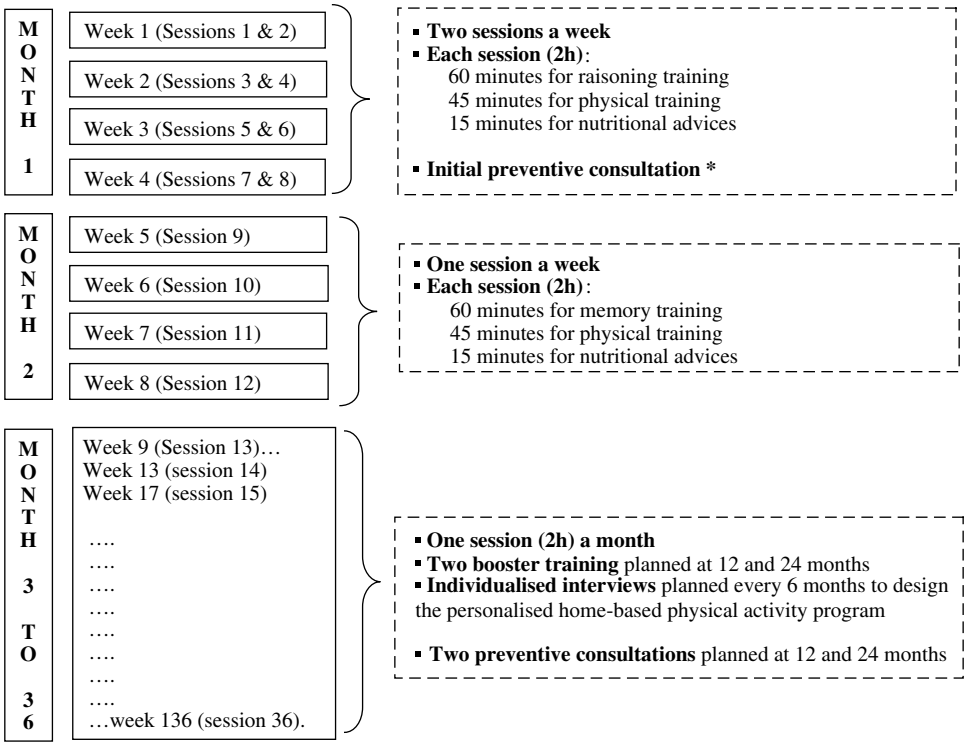

Fig. 2. Flow chart of multidomain intervention (training sessions and preventive consultations, organized over 3-year period of intervention). *Time between baseline visit and initial preventive consultation does not exceed 3 months.

3.7.2. Other assessments

Biological materials (blood specimens, RNA, and genomic DNA) are collected initially and at each annual visit. In a subgroup of participants, neuroimaging examinations will be performed at baseline (PET scans and MRI), and at 6 months (PET scan) and 1 year (PET scan and MRI). In one of the centers (Toulouse), annual body-composition assessments (DEXA) will also be performed.

4. Conclusion

As we have seen during the past 20 years in the prevention of vascular disease, we must also now see in the field of AD (most urgently in the late-onset form of the disease). However, we need to perform large intervention studies in the same manner as for large vascular intervention trials, with long-term follow-up in thousands of participants. We must build a strategy by using all potential protective factors, to promote the greatest potential effect, instead of a simple and unique intervention [43]. In the absence of curative treatment, lifestyle factors (diet, social engagement, cognitive stimulation, and physical exercise) seem the most reasonable basis for prevention trials at present, especially in terms of safety [9,10]. Some specific challenges need to be underlined in designing trials involving multidomain interventions: firstly, concerning the specific selection of subjects [9,10]. We imagine that subjects who agree to modify multiple lifestyle domains are likely to have a higher level of education, and a better state of general health, meaning that it may be difficult to demonstrate the effect of an intervention. Compliance in multidomain trials is also difficult to assess if an intervention combines or acts on different lifestyle factors. These lifestyle interventions are also characterized by the impossibility of maintaining double-blind conditions, and difficulty in defining an adequate control group, especially for physical-exercise interventions [9,10]. The MAPT Study is one of the first trials involving a multidomain intervention in the prevention of cognitive decline. Several intervention trials of this nature, focused only on physical and mental exercise, are underway or in planning stages. For example, the MAX (Mental Activity and eXercise trial for Seniors) Study is a randomized, double-blind trial to determine whether engaging in mental activity or exercise for 12 weeks, either alone or in combination, improves cognitive function in 300 nondemented, inactive older adults (aged 65 years and older) who self-reported a recent decline in memory or thinking clinicaltrials.gov study identifier NCT00522899). Another trial is evaluating the effects of frequent exercise (endurance and resistance training, 90 minutes, three times weekly) and increased mental activity (participation in computer lessons, three times weekly, 90 minutes each) for 6 months on the age-related impairment of cognitive function in 252 elderly women aged over 70 years clinicaltrials.gov study identifier NCT00629174). The MAPT Study was designed to include a sufficiently large series of subjects to evaluate the potential efficacy of two preventive measures (multidomain intervention with cognitive, physical, and nutrition training, or omega 3 supplement) in 1200 frail older people. The multidomain

intervention consists of training sessions focused on physical, cognitive, and nutritional areas, and preventive consultations, for 3 years. It was designed to be cost-effective and easily transferable to the population level, to exert a real public-health impact if the MAPT Study shows positive effects. Final results should be available in 2013.

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Appendix: MAPT Study Group

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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.

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