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A comprehensive preventive program for dementia tailored on the neuropsychological profile of persons with Mild Cognitive Impairment: cognitive stimulation, physical intervention and healthy nutrition, a randomized controlled trial

(GR-2013-02356043)

RESEARCH Open Access

Recent global trends in the prevalence and incidence of dementia, and survival with dementia

Prince *et al. Alzheimer's Research & Therapy* (2016) 8:23

Abstract

Background: Current projections of the scale of the coming dementia epidemic assume that the age- and sex-specific prevalence of dementia will not vary over time, and that population ageing alone (increasing the number of older people at risk) drives the projected increases. The basis for this assumption is doubtful, and secular trends (that is, gradual decreases or increases in prevalence over long-term periods) are perfectly plausible.

Methods: We carried out a systematic review of studies of trends in prevalence, incidence and mortality for people with dementia, conducted since 1980.

Results: We identified nine studies that had tracked dementia prevalence, eight that had tracked dementia incidence, and four that had tracked mortality among people with dementia. There was some moderately consistent evidence to suggest that the incidence of dementia may be declining in high-income countries. Evidence on trends in the prevalence of dementia were inconsistent across studies and did not suggest any clear overall effect. Declining incidence may be balanced by longer survival with dementia, although mortality trends have been little studied. There is some evidence to suggest increasing prevalence in East Asia, consistent with worsening cardiovascular risk factor profiles, although secular changes in diagnostic criteria may also have contributed.

Conclusions: We found no evidence to suggest that the current assumption of constant age-specific prevalence of dementia over time is ill-founded. However, there remains some uncertainty as to the future scale of the dementia epidemic. Population ageing seems destined to play the greatest role, and prudent policymakers should plan future service provision based upon current prevalence projections. Additional priorities should include investing in brain health promotion and dementia prevention programs, and monitoring the future course of the epidemic to chart the effectiveness of these measures.

Keywords: Dementia, Trends, Epidemiology, Projection, Global health, Worldwide, Systematic review, Meta-analysis

SANTA LUCIA

Modifiable risk factors

Older age, APOE genotype ε4 allele, and family history of dementia are consistent but non-modifiable risk factors for dementia.

(Sosa-Ortiz AL. Archives of Med. Res. 2012; 43: 600-608).

Up to half of dementia cases worldwide may be attributable to these potentially modifiable risk factors:

*-**Low cognitive reserve** (education and occupational attainment)*

*-**Cardiovascular risk factors** (hypertension, diabetes, and obesity)*

*-**Lifestyle and psychosocial factors** (physical inactivity, alcohol consumption, smoking habits, unhealthy diet, depression)*

	Population prevalence	Relative risk (95% CI)	PAR (confidence range)	Number of cases attributable (thousands; confidence range)
Worldwide				
Diabetes mellitus	6·4%	1·39 (1·17–1·66)	2·4% (1·1–4·1)	826 (365–1374)
Midlife hypertension	8·9%	1·61 (1·16–2·24)	5·1% (1·4–9·9)	1746 (476–3369)
Midlife obesity	3·4%	1·60 (1·34–1·92)	2·0% (1·1–3·0)	678 (387–1028)
Depression	13·2%	1·90 (1·55–2·33)	10·6% (6·8–14·9)	3600 (2295–5063)
Physical inactivity	17·7%	1·82 (1·19–2·78)	12·7% (3·3–24·0)	4297 (1103–8122)
Smoking	27·4%	1·59 (1·15–2·20)	13·9% (3·9–24·7)	4718 (1338–8388)
Low education	40·0%	1·59 (1·35–1·86)	19·1% (12·3–25·6)	6473 (4163–8677)
Combined (maximum)	..	..	50·7%	17 187 028*
USA				
Diabetes mellitus	8·7%	1·39 (1·17–1·66)	3·3% (1·5–5·4)	174 (77–288)
Midlife hypertension	14·3%	1·61 (1·16–2·24)	8·0% (2·2–15·1)	425 (119–798)
Midlife obesity	13·1%	1·60 (1·34–1·92)	7·3% (4·3–10·8)	386 (226–570)
Depression	19·2%	1·90 (1·55–2·33)	14·7% (9·6–20·3)	781 (506–1078)
Physical inactivity	32·5%	1·82 (1·19–2·78)	21·0% (5·8–36·6)	1115 (308–1942)
Smoking	20·6%	1·59 (1·15–2·20)	10·8% (3·0–19·8)	574 (159–1050)
Low education	13·3%	1·59 (1·35–1·86)	7·3% (4·4–10·3)	386 (236–544)
Combined (maximum)	..	..	54·1%	2 866 951*

PAR=population attributable risk. *Absolute number.

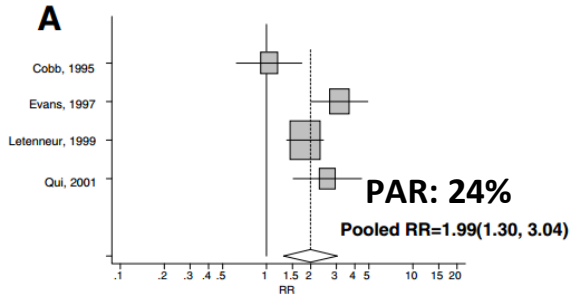
Table: **Alzheimer's disease cases attributable to potentially modifiable risk factors worldwide and in the USA**

(Barnes DE Lancet Neurol. 2011; 10: 819–828).

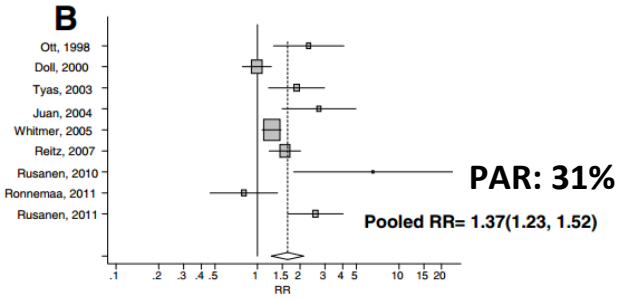
Epidemiologic studies of modifiable factors associated with cognition and dementia:systematic review and meta-analysis

BMC Public Health

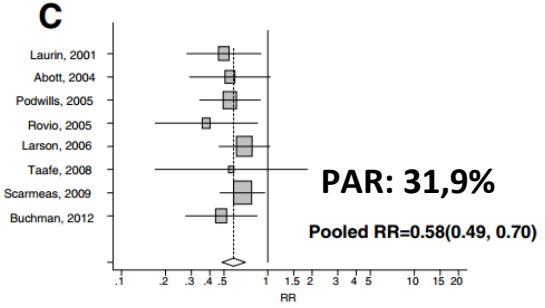
Beydoun *et al. BMC Public Health* 2014, **14**:643
http://www.biomedcentral.com/1471-2458/14/643



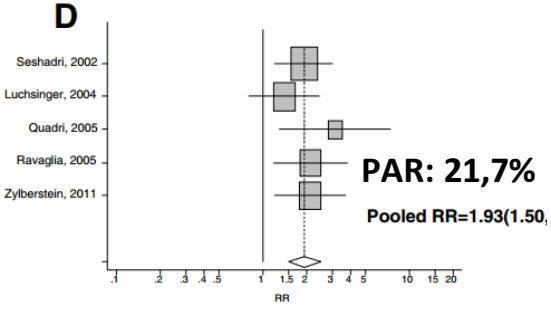
Education (low<8y vs. high>=8y) and risk of incident AD



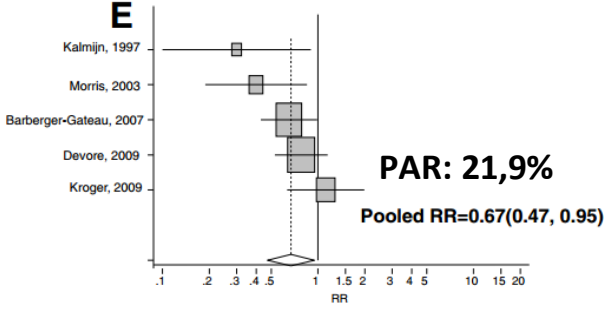
Smoking status (current or ever vs. never) and risk of incident AD



Physical activity (high vs. low) and risk of incident AD



Homocysteine (high vs. low) and risk of incident AD

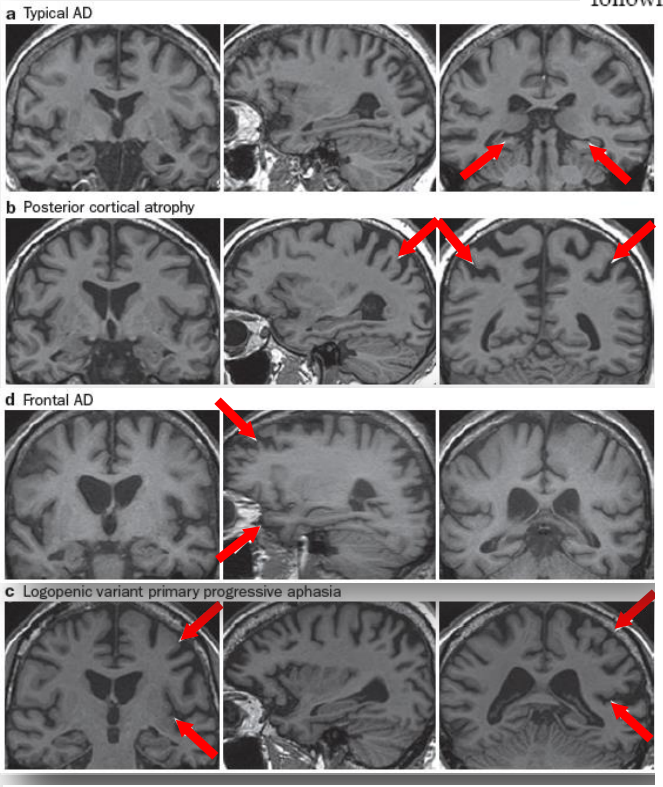


n-3 fatty acids (high vs. low) and risk of incident AD

Figure 3 Meta-analysis of selected risk and protective factors for incident AD (n = 31). (A) Education. **(B)** Smoking status. **(C)** Physical activity. **(D)** Homocysteine. **(E)** n3 fatty acids.

4.1. Probable AD dementia is diagnosed when the patient

Meets criteria for dementia described earlier in the text, and in addition, has the following characteristics:



Insidious onset. S
sudden over hou

Clear-cut history

The initial and m
and examination

a. Am
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b. Nonamnestic presentations:

- Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
- Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
- Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

Longitudinal Assessment

Symptoms predominating at the time of initial presentation continued to dominate the clinical picture over the follow-up period, ranging from 1-10 years, indicating maintenance of clinical distinctions with disease progression. Nevertheless, all patients with language, visual and praxic presentations have developed over time additional cognitive deficits seen in the typical AD cases.

Julie S. Snowden and Others
Cortex, (2007) 43, 835-845

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

McKhann GM et al. Alzheimers Dement. 2011 May ; 7(3): 263–269.

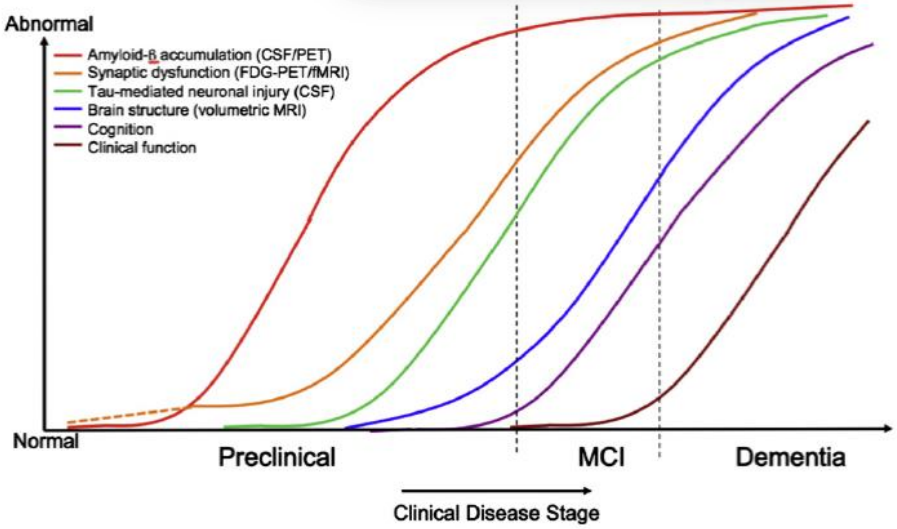


Fig. 3. Hypothetical model of dynamic biomarkers of the AD expanded to explicate the preclinical phase: Aβ as identified by cerebrospinal fluid $A\beta_{42}$ assay or PET amyloid imaging. Synaptic dysfunction evidenced by fluorodeoxyglucose (F18) positron emission tomography (FDG-PET) or functional magnetic resonance imaging (fMRI), with a dashed line to indicate that synaptic dysfunction may be detectable in carriers of the ε4 allele of the apolipoprotein E gene before detectable Aβ deposition. Neuronal injury is evidenced by cerebrospinal fluid tau or phospho-tau, brain structure is evidenced by structural magnetic resonance imaging. Biomarkers change from normal to maximally abnormal (*y*-axis) as a function of disease stage (*x*-axis). The temporal trajectory of two key indicators used to stage the disease clinically, cognitive and behavioral measures, and clinical function are also illustrated. Figure adapted with permission from Jack et al [22].

Available drug treatments in AD are symptomatic, and no new drugs have been introduced since 2002.

Prevention is now increasingly highlighted as the main therapeutic goal, and evidence-based effective interventions are urgently needed.

Amtiaz et al., Biochem Pharmacol. 2014

Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions

Lancet Neurol 2015; 14: 926–44

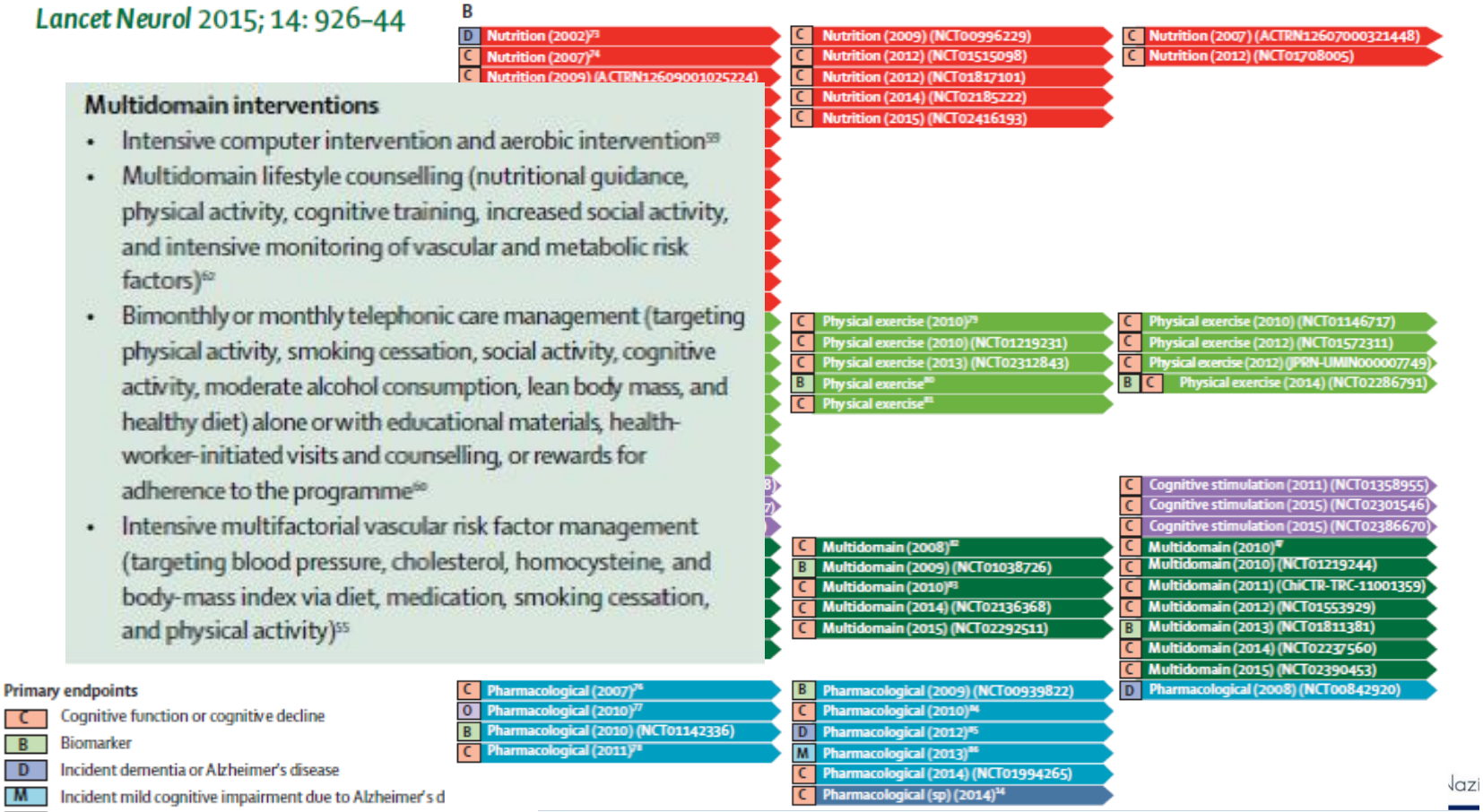


Figure 2: **Types of interventions tested and primary endpoints used to assess efficacy in completed and ongoing dementia prevention trials**

(A) Completed (published) trials. (B) Ongoing trials. Each shape represents an intervention tested in a randomised controlled trial for the prevention of dementia (or a related outcome, such as cognitive decline or a biomarker outcome). The type of primary endpoint used to assess efficacy is shown in the box on the left-hand side of each trial. When two different endpoints are shown for the same intervention, they are coprimary endpoints. The years in brackets represent the start date of each trial when available. Pharmacological (sp) indicates a pharmacological intervention specifically targeted towards Alzheimer's disease or targeting disease pathology (eg, cholinesterase inhibitors, memantine, or anti-amyloid treatments). Other pharmacological treatments—eg, non-steroidal anti-inflammatory drugs or hormone replacement therapy—are regarded as non-specific treatments. *†§Interventions sharing the same symbol were tested separately in the same trial.

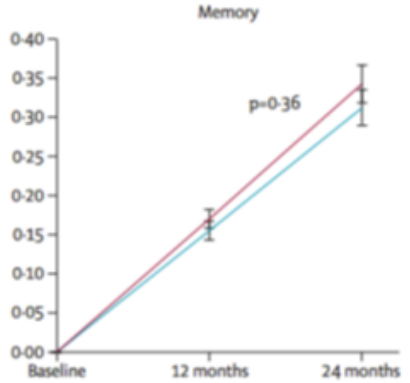
Table 3
Characteristics of RCTs with Multidomain interventions for prevention of cognitive impairment, dementia and Alzheimer's disease.

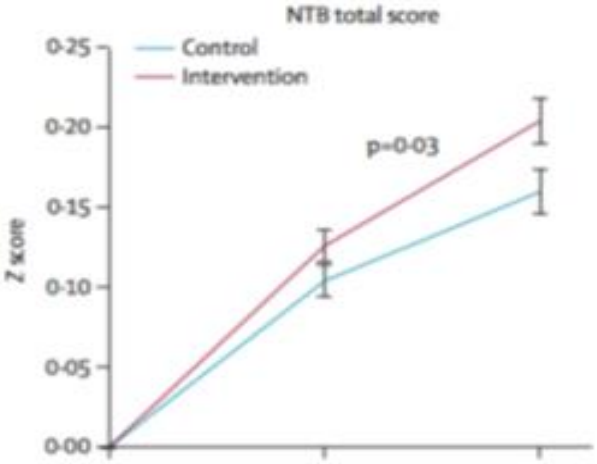
RCT	preDIVA[93]	Finger[91]	MAPT [92,98]
Objective of study	Prevention of dementia by intensive vascular care	To prevent/delay dementia in elderly at increased risk of cognitive decline through multidomain intervention	To prevent AD by multidomain interventions
Country	Netherlands	Finland	France
Number of participants	3700	1200	1680
Age	70–78 years	60–77 years	70 years and above
Study design	Multisite, open, cluster randomized parallel group study	Multicenter, randomized, controlled trial	Multicenter, randomized, placebo controlled study
Inclusion criteria	Non demented elderly from GP practices	Elderly with CAIDE risk score >6 and further screening by CERAD neuropsychological battery depicting mild cognitive impairment	Frail elderly people (defined by having subjective memory complaint, limitation in one IADL, slow walking speed)
Intervention	Control group: intensive management of vascular risk factors by practice nurse SC group: participants would receive regular care according to Dutch general practice	Control Group: Intensive intervention in nutrition, physical exercise, cognitive training and vascular risk factors Other group: Regular health advice	All participants sub grouped into 4 groups, 3 based on treatment options (omega 3 alone, multidomain intervention alone, both combined) and one placebo group
Follow up	6 years on whole IVC group: every 4 month visit with practice nurse for life style and medical interventions, then 2,4 and final 6 years follow up SC group: 2,4 years follow up and final 6 years visit	2 years Both groups meet study nurse 3 times and final visit with physician in 2 years Control group in addition undergoes intensive monitoring in each domain through frequent visits	3 years Cognitive and functional assessments conducted at baseline, 6 months and then annually Supplement distribution, compliance at 6,12,18,24,30 and 36 months
Primary outcome	Incident dementia and disability measured by ALDS	Cognitive performance evaluated by mNTB, Stroop and Trail making test	Change in cognition over 3 years determined by Grober and Buschke test
Secondary outcome	Overall mortality, incidence of vascular events as MI, peripheral vascular disease, mood (GDS), cognitive decline (MMSE, VAT)	Dementia, cognition, vascular risk factors, disability, falls, depression, cardio and cerebrovascular morbidity and mortality, health service utilization, neuroimaging and other AD biomarkers	Biological and neuroimaging markers to assess efficacy of intervention, body composition changes on frailty and cognitive decline
Current status	Ongoing, will be completed in 2015	Ongoing, intervention will be completed in 2014 when a 5 year extended follow up will begin	Ongoing, will be completed in 2014 and then undergo 2 year extended follow up

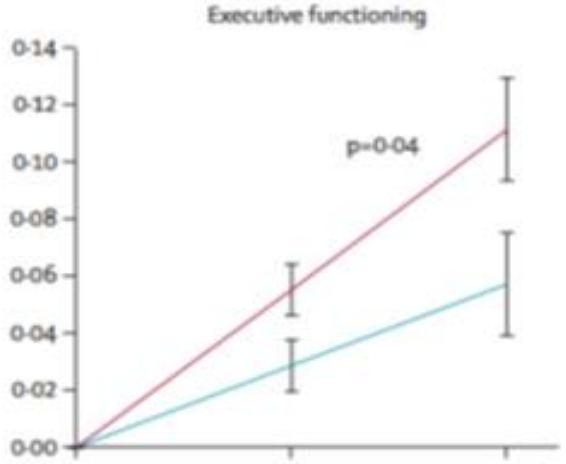
Abbreviations: preDIVA, prevention of dementia by intensive vascular care; GP, general practitioner; SC, standard care; IVC, intensive vascular care; ALDS, AMC linear disability scale; MI, myocardial infarction; GDS, geriatric depression scale; MMSE, mini mental scale examination; VAT, visual association test; FINGER, finnish geriatric intervention study to prevent cognitive impairment and disability, CAIDE, cardiovascular risk factors; aging and incidence of dementia study; mNTB, modified neuropsychological test battery; MAPT, the multidomain alzheimer prevention trial; IADL, instrumental activities of daily living.

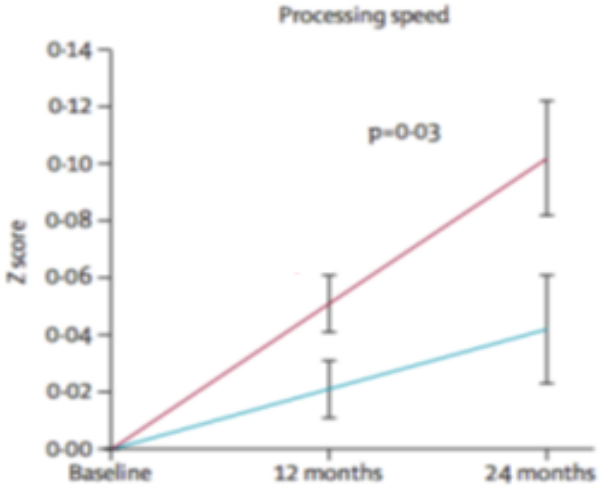
O.R. (treated vs ctrls)

NTB total score	1 (reference)	1·31 (1·01–1·71)	0·04
Cognitive decline per domain			
NTB memory score	1 (reference)	1·23 (0·95–1·60)	0·12
NTB executive functioning score	1 (reference)	1·29 (1·02–1·64)	0·04
NTB processing speed score	1 (reference)	1·35 (1·06–1·71)	0·01









A comprehensive preventive program for dementia tailored on the neuropsychological profile of persons with Mild Cognitive Impairment: cognitive stimulation, physical intervention and healthy nutrition, a randomized controlled trial (GR-2013-02356043)

Objectives

To compare the separate and combined effect of cognitive stimulation (CS) and physical exercise (PE) to reduce the risk of conversion to AD dementia (Add) and the progression of cognitive impairment of persons with MCI (pMCI).

Specific aims:

• To evaluate if pMCI with predominant MEM/VS/LAN or EXE deficits could be identified that will have different probabilities of developing ADd over time.

• To verify if CS may slow the cognitive decline or/and reduce the risk of dementia; if a specific CS, tailored on the worst affected domain(s) is more effective than aspecific CS, focused also on residual cognitive capabilities; if the possible effects are only short-term or persist after 9, 18, 27 months follow up.

• To further verify the effectiveness of PE in reducing the risk for dementia, which of CS and PE is the most effective intervention, if PE and CS exert an independent action or if any effect of interaction may be observed.

Methods

300 pMCI aged 55+ years will be recruited among people who access Alzheimer Evaluation Units and Senior Centers of Rome. Each visit will consist in a full clinical and neuropsychological assessment.

- **Cognitive evaluation:** MMSE, Backward and Forward Digit Span, Short-Story immediate and delayed recall (MEM), Frontal assesment battery (EXE), Rey-Osterrieth complex figure test (VS), verbal fluency and Denomination tests (LAN). The speed and accuracy of visual search will be registered with MFTC and line bisection test.
- **Functional evaluation:** Instrumental Activities of Daily Living (IADL), Functional Assessment Questionnaire (FAQ).

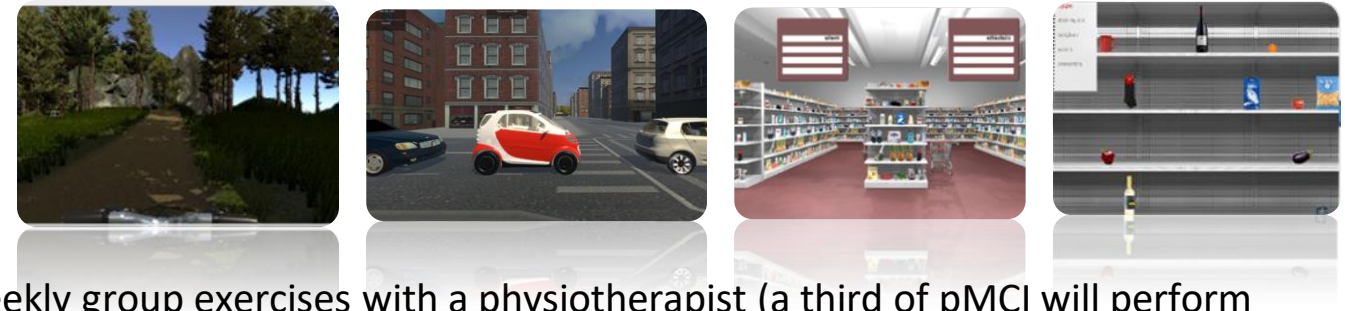
Inclusion criteria: pMCI with cognitive impairment possibly due to AD in 1+domains among MEM/VS/LAN/EXE and without significant functional impairment (FAQ scores < 10 and IADL > 80% max achievable).

Study design: RCT with 2X2 factorial design. Each subject are twice randomly assigned to receive CS (or no CS) and/or PE (or no PE).

Interventions

Cognitive stimulation:

- 12 weeks twice-weekly group paper-and-pencil or computerized exercises with a neuropsychologist (1/3 pMCI will perform individually the training in a virtual environment, simulating common activities of daily living).
- 24 optional weeks of twice-weekly individual exercises at home / at the senior center.
- 1/2 participants: CS tailored on the most affected CD.



Physical Exercise:

- 12 weeks twice-weekly group exercises with a physiotherapist (a third of pMCI will perform individually the training in a virtual environment, simulating common activities of daily living).
- 24 optional weeks of twice-weekly group exercises with a physiotherapist.

Nutrition: All participants will receive indications for a healthy nutrition, based on Mediterranean diet.

Preliminary results

Enrollment started in October 2016 and will be completed in March 2018.

Currently, 230 persons have been included, 78 of them have been underwent t1 evaluation (12 assigned to CS, 34 to PE, 24 to CS and PE).

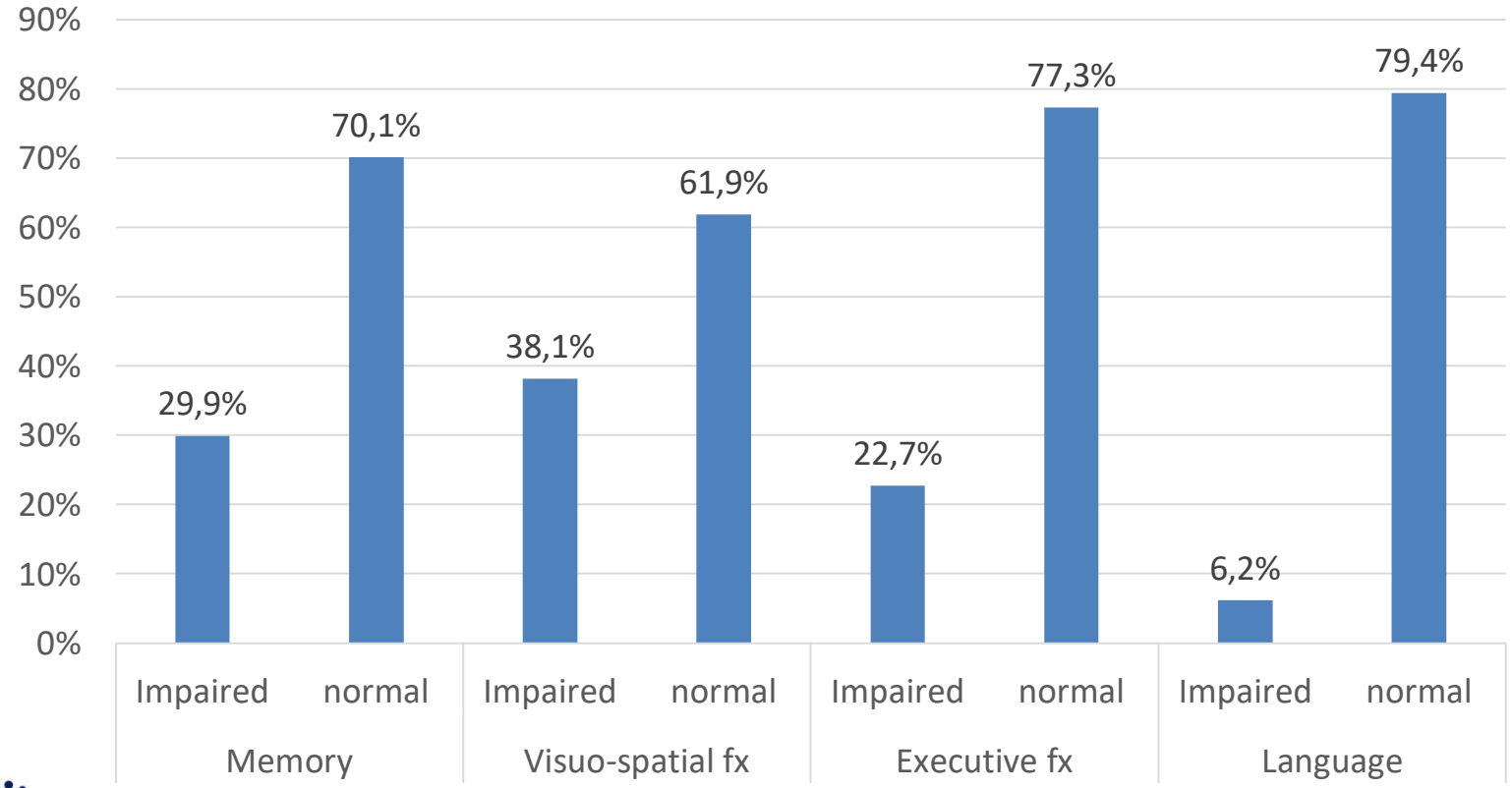
The mean age is 75,1±6,2 years,

mean instruction is 8,27±3,5.

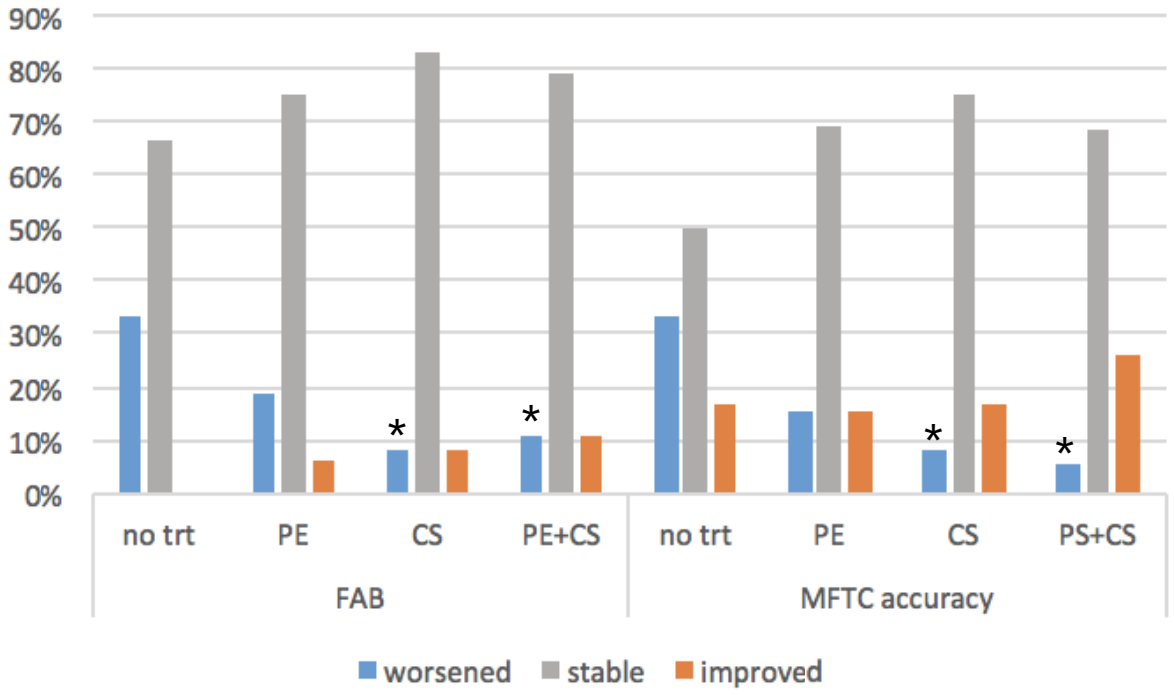
24 (25,3%) pMCI presented initial mnestic impairment.

Patients	Females	Males
N	82	15
Age (yrs)	75,04±6,04 [60-86]	78±6,97 [67-87]
Scolarity (yrs)	8,23±3,5 [2-18]	10,73±4,33 [5-18]
Cognitive evaluation		
MMSE	26,2±2,3 [20-30]	25,5±2,2 [20-30]
Digit span forward	5,5±0,9 [2-7]	5,8±0,9 [4,3-7,5]
Digit span backward	3,6±1,3 [0-6]	3,8±1,1 [0-5]
Short story immediate recall	8,8±3,9 [0-22]	8,1±3,9 [2-14]
Short story delayed recall	10,2±4,3 [0-22]	9,4±3,7 [4-16]
Barrage s	37,2±9,4 [20-60]	38,9±12,9 [20-66]
MFTC accuracy	0,89±0,09 [0,53-1]	0,88±0,07 [0,73-1]
FAB	14,16±2,57 [7-18]	13,67±2,8 [7-17]
Fonemic fluency	11,5±3,7 [2-20]	8,7±2,8 [4-13]
Semantic fluency	16,3±3,8 [6-27]	15,9±3,5 [8-21]
Denomination	35,6±2,08 [29-38]	34,4±2,3 [30-37]
ROCFT	29,7±5,9 [9-36]	25,1±7,9 [9-33]
Functional and behaviroal evaluation		
FAQ	1,48±2,07 [0-9]	1,67±1,76 [0-5]
IADL	7,93±0,3 [6-8]	7,47±0,92 [5-8]

Preliminary results



Preliminary results



Expected outcomes

- In 3 years up 40-60% of pMCI will show cognitive signs consistent with a clinical diagnosis of ADd.
- A consistent % of the subjects who will develop ADd will have prominent impairment in non-mnestic CD.
- Subjects randomized to perform CS and PE will have reduced probability to convert to ADd and reduced rates of cognitive/functional decline compared to controls.
- CS and PE will exert beneficial independent but synergic effects and pMCI assigned to receive both treatments will show decreased risk of ADd or slowed cognitive/functional decline compared to other 3 groups.

Thank you!