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JOURNAL OF GERONTOLOGY AND GERIATRICS

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Special Issue

Nutrition and Neurodegenerative Disease

Guest Editor
Vincenzo Solfrizzi

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Efficacy and safety of direct-acting antivirals in elderly with chronic hepatitis C: results from a retrospective cohort study

R. Villani¹, I. Donatiello², F. Barone², F. Cavallone¹, G. Fioravanti¹, F. Di Cosimo¹,
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Background. Seroprevalence of hepatitis C virus infection has increased over the last decade and because of hepatitis C virus acquisition time and age of most infected persons, the proportion of elderly with CHC is expected to increase over time. With the approval of direct-acting antivirals (DAAs), treatment access has expanded to interferon intolerant patient populations, including older age. However, elderly patients, especially those aged 75 years and older, have been excluded from most clinical trials and few data are available on safety and efficacy of DAAs in this special population.

Methods. We conducted a retrospective cohort study on three age subgroups of patients (< 65 years; 65-74 years and ≥ 75 years) treated with DAAs between March 2015 and March 2017. Two hundred and sixty-two patients were followed up with clinical and laboratory evaluations during antiviral therapy.

Results. HCV genotype distribution significantly differed among the three subgroups. Antiviral treatments were not different between younger and elderly groups. Sofosbuvir-based regimens were used in about 60% of patients without significant differences among the three age-subgroups. All patients except three achieved SVR12 (99.3% in elderly vs 98.3% in younger patients). A total of 62 patients (23.7%) showed at least one adverse event (AE). AEs were not higher in elderly patients.

Conclusions. Our data showed that DAAs in elderly CHC patients were as effective as younger patients without any significant increase of adverse events.

Key words: HCV, Elderly, Direct-acting antivirals

INTRODUCTION

Chronic hepatitis C virus infection (CHC) is a major cause of end-stage liver disease, hepatocellular carcinoma (HCC) and liver related death in the Western world¹. Global epidemiology of HCV infection shows that the seroprevalence of AntiHCV antibody has increased over the last decade from 2.3% to 2.8%, corresponding to > 185 million infections worldwide². Although publication bias resulting in a geographic variability in HCV seroprevalence need to be considered,

Italian population showed the highest prevalence of HCV infection and contributed highest number of data-points for the epidemiology of HCV in Europe^{2,3}.

High prevalence of global HCV infection necessitates renewed efforts in primary prevention, including vaccine development, as well as new approaches to secondary and tertiary prevention to reduce the burden of chronic liver disease and to improve survival for those who already have evidence of liver disease.

Because of hepatitis C virus (HCV) acquisition time (i.e. 1960-1980s) and age of acquisition (i.e. 20-40 years)

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of most infected persons, the proportion of elderly with CHC is expected to increase over time⁴.

With the recent approval of interferon-free regimens (direct-acting antivirals or DAAs), treatment access has expanded to interferon ineligible/intolerant patient populations, including persons of older age⁵.

Moreover, since novel HCV treatment regimens are well tolerated and the advancing age is an important risk factor for progression to cirrhosis and HCC, the number of elderly patients who will receive anti-HCV treatments is likely to increase⁴.

Elderly patients, especially those aged 75 years and older, have been excluded from most clinical trials and the safety and efficacy of DAAs have not been specifically examined in this special population except for very small clinical trial⁶ or in Japanese population by using asunaprevir and daclatasvir⁷⁻¹⁰.

Generally, very few real-world data are available on DAAs treatment in old and very old patients.

Rodriguez-Osorio et al. reported 120 patients > 65 years with a SVR12 rate of 88,3% and a rate of AE of about 65%¹¹; Conti et al. observed a 94,7% of SVR in HCV older patients recruited in North Italy centers¹²; Ippolito et al. showed no differences in terms of SVR in octogenarians but they enrolled highly selected patients with preserved glomerular renal filtration and mainly patients assuming only one concomitant medication¹³. Moreover, data from other observations were limited to a single treatment¹⁴, included co-infected patients¹⁵ and a single genotype^{7,16}.

Therefore, data on efficacy and safety of DAAs in these groups are requested.

In the present study, we retrospectively analyzed the efficacy and safety of six different DAAs treatments in a cohort of old (> 65 years) and very old (> 75 years) population from South Italy with CHC. Frequencies and distribution of concomitant medications were also analyzed in our study.

MATERIALS AND METHODS

STUDY POPULATION

We conducted a retrospective cohort study on 262 consecutively and prospectively treated patients with CHC with advanced fibrosis or cirrhosis referred to one single hepatological centre between March 2015 and March 2017, who started therapy with DAA as standard-of-care treatment for HCV-related chronic hepatitis. Eligible patients were aged 18 years and older with chronic HCV infection assessed by the presence of Anti-HCV antibody and detectable serum HCV RNA. Patients with HIV co-infection or severe chronic kidney disease defined by estimated glomerular filtration rate

(eGFR) < 30 ml/min/1.73m² or who received pegylated interferon as part of their treatment regimen were excluded.

Antiviral therapy and treatment duration (12 or 24 weeks) were indicated for each patient according to the viral genotype/subtype and the severity of liver disease according to the guidelines from Italian Association for the Study of Liver Diseases' available at the time of enrolment and according to the National Drug Agency reimbursement restriction.

All patients received one of the following six regimens:

1. sofosbuvir and simeprevir ± ribavirin;
2. sofosbuvir and ledipasvir ± ribavirin;
3. sofosbuvir and daclatasvir ± ribavirin;
4. sofosbuvir + ribavirin;
5. ombitasvir/paritaprevir/ritonavir + dasabuvir (3D) ± ribavirin;
6. ombitasvir/paritaprevir/ritonavir (2D) ± ribavirin.

For all genotypes weight-based ribavirin was administered according to discretion of physician.

DEFINITION OF OLD AGE

Patients of old age were defined as being 65 years and older. This population included the young-old patients (65-74 years) and old-old patients (≥ 75 years).

ASSESSMENT OF EFFICACY DATA

Patients were followed up with clinical and laboratory evaluations during antiviral therapy. Virological response was assessed at week 4, at the end of treatment, and at 4 and 12 weeks after the end of treatment to determine the SVR. SVR4 and SVR12 were defined as undetectable HCV RNA 4 or 12 weeks after the treatment completion, respectively. Data were retrospectively and anonymously analysed.

ASSESSMENT OF SAFETY DATA

Safety assessments included laboratory data (hemoglobin, platelets, white blood cell count, alanine transaminases, aspartate transaminases, gamma-glutamyltransferase, alkaline phosphatase, albumin, total bilirubin, serum creatinine, international normalized ratio, plasma sodium and potassium concentration, creatinine clearance), physical examinations, evaluation of vital signs (respiratory rate, heart rate and blood pressure) and the reporting of adverse events (AE).

Safety data were assessed at baseline, at week 4, at the end of treatment, and at 12 weeks after the end of treatment. Adverse events were reported according to the Common Terminology Criteria for Adverse Events¹⁷. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used for estimating the glomerular filtration rate (GFR).

The occurrence of ribavirin (RBV) induced haemolytic anaemia was also assessed at each time point.

Significant anaemia was defined as an absolute decline in haemoglobin levels < 10 g/dL and/or a decline of greater than 3 g/dL.

At baseline and at the end of treatment, all patients were evaluated using abdominal ultrasound.

All patients with persistent ALT or AST $>$ upper limit of normal (ULN) after 4 weeks of treatment underwent additional US analysis.

STATISTICAL ANALYSIS

All statistical analyses and graphs were performed using SPSS (Statistical Package for the Social Sciences, version 20, Armonk, New York, NY, USA) and GraphPad Prism version 7 (La Jolla, CA, USA). Quantitative variables are shown as mean \pm s.d. or median and range. Comparisons between groups were made using parametric one way ANOVA, nonparametric Kruskal-Wallis test, chi-square test or Fisher's exact test where appropriate.

$P < 0.05$ was considered statistically significant. Univariate and multivariate logistic regression analysis was used to identify the associations between clinical parameters and virological response.

RESULTS

PATIENTS POPULATION

Two hundred and sixty-two patients with HCV-related significant fibrosis (Metavir F3) or liver cirrhosis were treated with DAAs regimens during the study period.

120 patients (46%) were < 65 years old, 80 patients (30%) were 65-74 years and 62 patients (24%) were ≥ 75 years old.

Baseline clinical characteristics of included patients are provided in Table I.

No gender difference was found between patients aged < 65 and ≥ 65 years and between young – old and old-old patients.

Liver cirrhosis was found in 52.1% of elderly (42.5% of young-old patients and 64.5% of old-old patients) and in 38.3% of younger patients ($p = 0.559$), and pre-treatment Child-Pugh-Turcotte (CPT) score classification was comparable between patients aged < 65 and ≥ 65 years.

Diabetes mellitus was more prevalent in elderly. The highest incidence was observed in the young-old patients (47.5%) and it was significantly different from youngers ($p = 0.02$) and old-old patients ($p = 0.02$).

No significant differences were found in baseline serum liver function tests (i.e. ALT, AST, total bilirubin and PLT). No patients had eGFR lower than 30 ml/min or required pre-treatment or in-treatment hemodialysis.

Pre-treatment serum HCV-RNA levels did not differ

between the young patients and elderly and between the young-old and old-old patients.

HCV genotype distribution significantly differed among the three subgroups ($p < 0.001$). In all age subgroups Genotype 1 (G1) was the most common (youngers: 56.6%; young-old patients: 77.5%; old-old patients 64.5%). Genotype 2 prevalence was 18.3% in patients aged < 65 years and 26.1% in older people (20% in young-old patients and 32.2% in old-old patients). Genotype 3 and 4 were responsible for a total 24.9% of all cases in younger group and less than 4% in patients aged ≥ 65 years (Tab. I).

The rate of IFN-experienced patients was lower in elderly than in youngers with a statistically significant difference (aged < 65 years: 41.6%; aged 65-75 years: 42.5%; aged ≥ 75 years: 16.1%). Finally, 10% of younger, 12.5% of young-old, and 3.2% of old-old patients had experienced protease inhibitor (PI) therapy. The rate of interferon-experienced patients was higher in olders groups.

Ribavirin was administered in 52 patients aged > 65 , 14 patients aged 65-74 and 24 patients aged ≥ 75 years. G1b and G4, irrespective of age and fibrosis, were treated without ribavirin except for those treated with 2D where ribavirin was weight-based dosed.

DISTRIBUTION OF DIRECT-ACTING ANTIVIRALS TREATMENT AND EFFICACY

The distribution of antiviral treatments was not statistically different between the youngers and elderly (Tab. I); sofosbuvir-based regimens were used in about 60% of patients without significant differences among the three age subgroups.

Sixteen percent of patients treated with 2D or 3D-based and 26% of sof-based treatment showed undetectable HCV-RNA by 4 weeks of therapy without differences among age subgroups.

All patients except 3 achieved SVR12 (99.3% in elderly vs 98.3% in younger patients) (Fig. 1).

Two were from sofosbuvir/ledipasvir G1b group and one was a sofosbuvir + daclatasvir treated patient with G3 infection. All were cirrhotic and showed mutations in NS5A region. Figures 2-4 show SVR rates according to baseline features (genotype, DAA regimen and liver fibrosis).

SAFETY OF DIRECT-ACTING ANTIVIRALS

Sixty-two adverse events (AE) were reported in our study population (Tab. II). The number of AE was not higher in elderly patients than in younger. The analysis of age subgroup showed a difference of AE that did not reach a statistically significant level (30% in aged 65-75 years versus 27% in aged ≥ 75 years).

Five patients treated with sofosbuvir had grade 2

Table 1. Baseline characteristic of study population and DAAs regimens according to age groups.

Variable	< 65 (n = 120)	p [§]	≥ 65 (n = 142)	p [#]	≥ 75 (n = 62)
Age, years	55 (35-64)		73 (65-88)		79 (75-85)
Male gender (n/%)	80 (66.7%)	< 0.001	66 (46.5%)	0.496	32 (51.6%)
Cirrhosis (n/%)	46 (38.3%)	0.559	74 (52.1%)	0.100	40 (64.5%)
CPT Class					
A	44	> 0.999	68	0.738	36
B	2		6		4
Type 2 diabetes	28 (23.3%)	< 0.001	50 (35.2%)	0.023	12 (19.3%)
IFN-experienced	50 (41.6%)	> 0.999	44 (31%)	0.026	10 (16.1%)
PI-experienced	12 (10%)	0.647	12 (8.5%)	0.235	2 (3.2%)
HCV genotype					
1a	22 (18.3)	< 0.001	0	0.634	0
1b	46 (38.3%)		102 (71.8%)		40 (64.5%)
2	22 (18.3%)		36 (25.4%)		20 (32.2%)
3	16 (13.3%)		2 (1.4%)		0
4	14 (11.6%)		2 (1.4%)		2 (3.22%)
DAA treatment schedule					
SOF+RBV	24 (20%)	0.296	34 (24%)	0.387	20 (32.3%)
SOF+SIM ± RBV	18 (15%)		20 (14%)		8 (12.9%)
SOF+LDV ± RBV	4 (3.3%)		18 (12.7%)		10 (16.1%)
SOF+DCV ± RBV	26 (21.7%)		14 (9.9%)		2 (3.2%)
OBV+PTV+R ± DASABUVIR ± RBV	48 (40%)		56 (39.4%)		22 (35.5%)
Use of ribavirin (n/%)	52 (43.3%)	0.001	38 (26.8%)	0.087	24 (38.7%)
Treatment duration (n/%)					
12 weeks	80 (66.7%)	0.382	92 (64.8%)	0.224	34 (54.8%)
24 weeks	40 (33.3%)		48 (33.8%)		26 (45.2%)
Log ₁₀ HCV RNA, U/ml	5.69 (3.04-6.83)	0.481	4.51 (2.38-7.73)	0.348	5.36 (3.03-6.68)
AST, U/L	58.5 (15-305)	0.696	54 (17-302)	0.934	52 (23-302)
ALT, U/L	73 (12-272)	0.144	55 (12-327)	0.110	45 (17-327)

[§] comparison between patients aged < 65 years and ≥ 65 years.

[#] comparison between patients aged ≥ 65 years and ≥ 75 years.

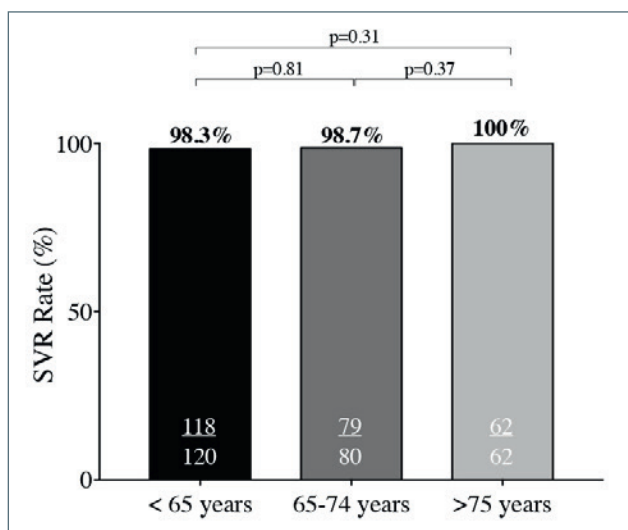


Figure 1. SVR rates according to age groups. SVR rates were not statistically different between the younger and elderly.

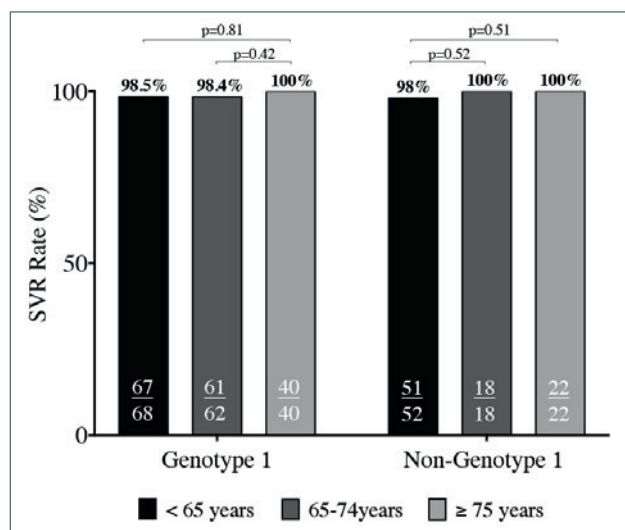


Figure 2. SVR12 for treated patients according to age and genotype. Virological response was not statistically different among the three age subgroups.

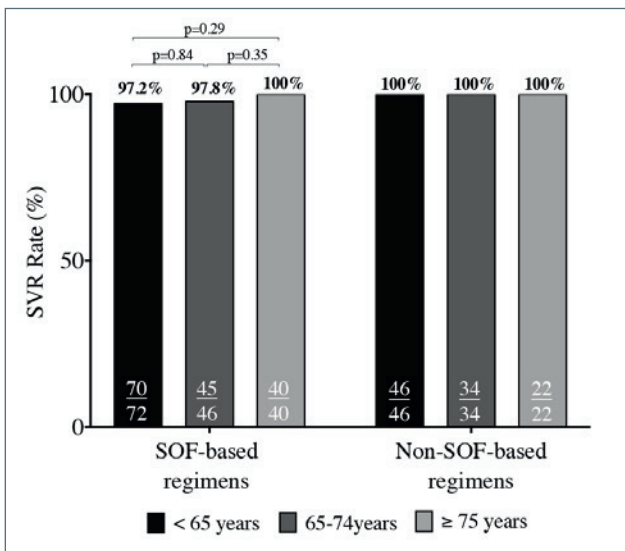


Figure 3. SVR12 for treated patients according to age and DAA regimen. Virological response was not statistically different among the three age subgroups.

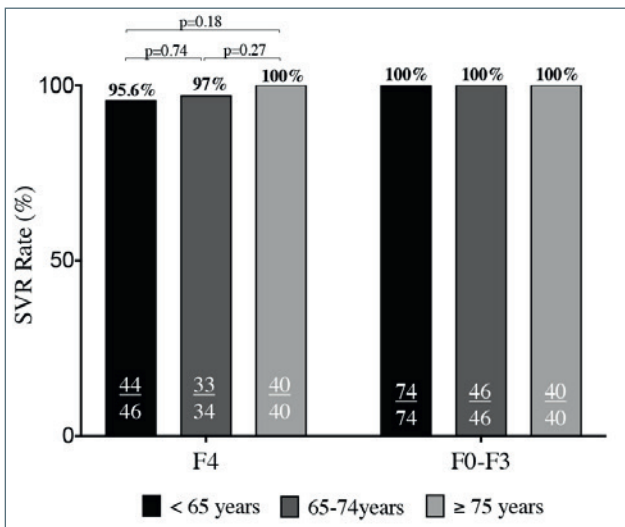


Figure 4. SVR12 for treated patients according to age and liver fibrosis. All patients except 3 achieved SVR12. All were cirrhotic and showed mutations in NS5A region. However virological response was not statistically different among the three age subgroups.

hyperbilirubinemia and one treated with 3D had grade 3 hyperbilirubinemia, respectively. All were cirrhotic and one of them assumed ribavirin.

Significant anemia was observed in 4 patients included in the old-old age group. All were G2-infected patients and were treated with sofosbuvir plus ribavirin.

A ribavirin dose reduction was required in 16 patients,

6 in the younger and 10 in the in ≥ 75 year-old groups. No dose reduction was needed in patients aged 65-75 years and erythropoietin was never used.

No hepatic decompensation was observed. One patient aged ≥ 75 years treated with 3D-based treatment reported pleural effusion resolved spontaneously at the end of the treatment.

Antiviral therapy was discontinued just in one patient aged < 65 years after only 8 weeks for acute ischemic stroke. The patient was in treatment with 3D regimen and reached SVR12 anyway.

HCC recurrence occurred in three patients; two of them completed treatment but died before achieving SVR12 and were excluded from final analysis.

INDEPENDENT PREDICTOR OF SVR12 RATE IN ELDERLY PATIENTS

A multivariate analysis was performed to verify the independent factors significantly associated with SVR12 in overall study population. No statistically significant association was found for age, gender, genotype, stage of liver fibrosis, antiviral regimens, diabetes and ribavirin use (Tab. III).

FREQUENCIES OF CONCOMITANT MEDICATIONS

Frequencies and distribution of concomitant medications were reported in our study (Fig. 5).

Overall, the number of patients who took ACE inhibitors/ATII receptor blockers, diuretics, beta-blockers, calcium channel blockers, insulin, platelet aggregation inhibitors and PPI was significantly higher in patients aged ≥ 65 compared to < 65 years whereas no significant differences were found for statins and oral antidiabetic drugs (Tab. IV).

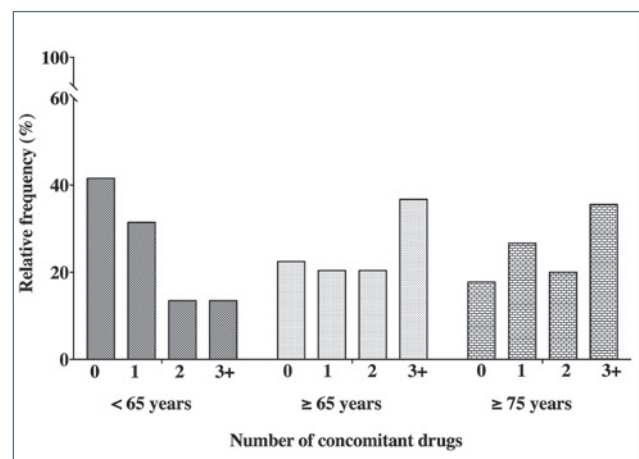


Figure 5. Frequencies and distribution of concomitant medications reported in our study. Elderly assumed more frequently 3 or more concomitant medications as compared to < 65 years patients (36.7% vs 13.4%; $p = 0.0003$).

Table II. AEs and laboratory abnormalities by age.

Variable	< 65 (n = 120)	p [§]	≥ 65 (n = 142)	p [#]	≥ 75 (n = 62)
Serious AEs	0		0		0
Death	0		0		0
Discontinuation due to serious AE	0		0		0
Fatigue	8	0.036	21	0.607	9
Skin complaints (rash/pruritus)	2	> 0.999	2	0.548	0
Insomnia	2	> 0.999	2	0.548	0
Gastrointestinal complaints (nausea/dyspepsia)	4	0.707	6	0.717	2
Headache	0	0.501	2	0.548	0
Irritability	1	> 0.999	1	0.516	1
Laboratory abnormality					
Grade 3 or 4 hyperbilirubinemia	4	0.917	2	0.180	0
Hemoglobin 8-10 g/dl	0		0		4
Hemoglobin < 8 g/dl	0		0		0
RBV dose reduction or discontinuation (N event/N patients with ribavirin use)	6/52	< 0.001	10/14	0.100	10/24
Pleural effusion	0	> 0.999	1	0.516	1

comparison between patients aged ≥ 65 years and ≥ 75 years.

§ comparison between patients aged < 65 years and ≥ 65 years.

Table III. Variables associated with SVR in patients treated with Direct-Acting Antivirals (n = 242). The significance of association was assessed by performing an univariate and multivariate logistic regression analysis. No association was found for gender, genotype, liver fibrosis, age, antiviral regimen, IFN treatment or Diabetes.

Variable	Univariate analysis	Multivariate analysis	
	p	OR [95% CI]	p
Gender	0.291	2.782 [0.281-27.592]	0.382
Genotype (G1)	0.991	0.527 [0.049-4.963]	0.550
Cirrhosis	0.354	0.462 [0.071-3.021]	0.420
Age (≥ 65 years)	0.326	2.386 [0.363-15.695]	0.366
Sofosbuvir-based regimens	0.721	1.329 [0.196-9.024]	0.771
IFN-experience	0.292	4.151 [0.433-39.835]	0.217
Diabetes	0.582	2.007 [0.195-20.669]	0.558
Ribavirin	0.785	0.898 [0.104-7.783]	0.922

The most common drugs taken by elderly were diuretics (50% in ≥ 65 years and 71% in ≥ 75 years vs 14.1% in < 65 years) and ACE inhibitors/ATII receptor blockers (41.5% in ≥ 65 years and 45.1% in ≥ 75 years vs 20.8% in < 65 years).

Elderly assumed more frequently 3 or more concomitant medications as compared to < 65 years patients (36.7% vs 13.4%; p < 0.001).

A subgroup analysis for antiviral regimen was also performed: in the group of < 65 years, patients on 2D/3D regimen took more frequently ACE inhibitors/ATII receptor blockers (p < 0.05) and calcium channel blockers (p < 0.05) than those on sofosbuvir-based therapy; on the other hand, PPIs were more frequently found in ≥ 65 years treated with sofosbuvir-based regimen (Tab. V).

DISCUSSION

The age of patients chronically infected by HCV has increased over the last decades and, due to the life expectancy in industrialized countries¹⁸, older CHC patients will become an increasingly larger group over time.

They are expected to develop cirrhosis and liver cancer with a relevant increase in health-related disease costs¹².

To date reports on antiviral treatment of elderly patients have been limited to side effects and intolerance to IFN-based regimens with final SVR rates lower than youngsters.

Although the epidemiology data of HCV infection are

Table IV. Distribution of most common concomitant medication used in patients treated with DAAs.

Drugs	< 65 (n = 120)	p [§]	≥ 65 (n = 142)	p [#]	≥ 75 years (n = 62)
ACE-Inhibitors/ATII receptor blockers	25 (20.8%)		59 (41.5%)		28 (45.1%)
Ramipril	12	< .001	10	0.631	6
Enalapril	0		6		1
Lisinopril	0		3		3
Delapril	1		0		0
Zofenopril	0		1		1
Candesartan	1		3		0
Irbesartan	3		6		3
Losartan	1		6		3
Olmesartan	3		22		8
Telmisartan	3		4		0
Valsartan	1		4		3
Diuretics	17 (14.1%)		71 (50%)		44 (71%)
Furosemide	6	< .001	27	0.005	15
Hydrochlorothiazide	7		32		20
Potassium canrenoate	3		11		8
Ca2+ Channel Blockers	1		1		1
Beta-Blockers	13 (10.8%)		47 (33%)		23 (37%)
Bisoprolol	4	< .001	10	0.580	7
Carvedilol	3		7		4
Nebivolol	3		16		5
Propranolol	3		6		3
Atenolol	0		7		3
Sotalol	0		1		1
Statins	2 (1.6%)		9 (6.3%)		6 (8%)
Atorvastatin	1	0.060	4	0.400	4
Rosuvastatin	0		3		1
Simvastatin	0		1		0
Pravastatin	0		1		1
Lovastatin	1		0		0
Calcium channel blockers	6 (5%)		24 (16.9%)		12 (19.3%)
Amlodipine	4	0.002	9	0.672	4
Lacidipine	1		3		2
Barnidipine	1		1		1
Lercanidipine	0		8		3
Nifedipine	0		2		1
Diltiazem	0		1		1
Oral antidiabetic drugs	16 (13.3%)	0.736	21 (14.8%)	0.321	6 (9.7%)
Insulin	6 (5%)	0.002	24 (16.9%)	0.304	7 (11.3%)
Platelet Aggregation inhibitors	13 (10.8%)		29 (20.4%)		15 (24.2%)
Acetyl salicylic acid	11	0.035	23	0.547	9
Clopidogrel	2		3		3
Ticlopidin	0		3		3
PPI	22 (15.5%)		51 (35.9%)		23 (37%)
Pantoprazole	9	0.001	18	0.871	6
Esomeprazole	6		4		3
Lansoprazole	5		16		11
Omeprazole	2		9		3

comparison between patients aged ≥ 65 years and ≥ 75 years.

§ comparison between patients aged < 65 years and ≥ 65 years.

limited because of publication bias and selective nature of the survey population, Italy showed high rate of chronic hepatitis C with a geographic and age-dependent gradient^{19,20}. In Northern Italy the prevalence of CHC was found to be 3.2% ranging from < 1% of younger than 40 years up to 10% in older than 60 years¹⁹. Several authors reported in Southern Italy prevalence of HCV infection^{3,20,21}.

Moreover, Southern Italy has the largest number of elderly patients with chronic hepatitis C and therefore data about efficacy and safety of DAA-based therapy are required.

In our retrospective analysis 132 patients aged > 65 years coming from South Italy were analyzed and showed that DAAs is as effective as in patients aged < 65 years.

Small studies have recently showed SVR rates comparable to younger but high risk of adverse events when DAAs were used in CHC patients; one was conducted in Spain and reported 65% of side effects mainly related to ribavirin and protease inhibitors¹¹; the second used data from sofosbuvir/ledipasvir registration trials but included only 24 patients older than 75 years²².

Conti et al. recently reported data from a Northern Italian elderly population and showed an overall SVR rate comparable to that obtained in patients aged < 65 years. In their cohort, genotype distribution was significantly different between elderly and younger, many

elderly subjects had cirrhosis and sofosbuvir-based regimen was mostly administered (75%)¹².

In our retrospective analysis we included a large number of Southern Italian elderly patients (n = 132) and first of all our analysis demonstrated that IFN-free treatment is as effective in elderly as in patients aged < 65 years. A larger number of our patients received 3D or 2D antiviral regimen with comparable efficacy and safety profiles to sofosbuvir-based therapy.

Almost all our cirrhotic patients were in CPT-A class. Patients with CPT-B class cirrhosis showed an SVR rate, viral kinetics and biochemical response comparable with class A patients. However, the number of CPT-B class patients was too small.

Most patients in our study were treated using ribavirin-free regimens without affecting SVR rate. Ribavirin is still considered important in clinical trial for interferon-free DAA combinations because it can increase SVR rates in some subgroups of patients, particularly those that historically have been considered the most difficult to cure²³. Data from first-generation DAA studies showed that ribavirin dosage reduction did not negatively impact SVR rates unless it was reduced by more than 50% of the recommended dosage²⁴. On the other hand, highly potent DAA combinations achieve SVR12 in more than 90% of patients with or without ribavirin. Therefore more data are required to evaluate its role in viral response and relapse.

Table V. Distribution of most common concomitant medication by age and DAA regimen.

Drugs	< 65 years (n = 120)			≥ 65 years (n = 142)			≥ 75 years (n = 62)		
	Sof-based treatment (n = 7)	2D/3D (n = 48)	p	Sof-based treatment (n = 86)	2D/3D (n = 56)	p	Sof-based treatment (n = 40)	2D/3D (n = 22)	p
ACE-Inhibitors/ATII receptor blockers	10 (13.9%)	15 (31.2%)	0.04	37 (43%)	22 (39.3%)	0.79	19 (47.5%)	9 (41%)	0.82
Diuretics	11 (15.3%)	6 (12.5%)	0.87	49 (57%)	22 (39.3%)	0.06	29 (72.5%)	15 (68.1%)	0.95
Beta-Blockers	8 (11.1%)	5 (10.4%)	0.86	31 (36%)	16 (28.6%)	0.46	15 (37.5%)	8 (36.4%)	0.95
Statins	2 (2.8%)	0 (0%)	0.52	6 (7%)	3 (5.3%)	0.97	5 (12.5%)	1 (4.5%)	0.41
Calcium channel Blockers	1 (1.4%)	5 (10.4%)	0.04	13 (15.1%)	11 (19.6%)	0.63	7 (17.5%)	5 (22.7%)	0.87
Oral Antidiabetic Drugs	7 (9.7%)	9 (18.8%)	0.25	11 (12.8%)	10 (17.8%)	0.55	5 (12.5%)	1 (4.5%)	0.41
Insulin	3 (4.2%)	3 (6.3%)	0.68	15 (17.4%)	9 (16%)	0.98	4 (10%)	3 (13.6%)	0.69
Platelet Aggregation inhibitors	6 (8.3%)	7 (14.6%)	0.43	16 (18.6%)	13 (23.3%)	0.65	11 (27.5%)	4 (18.2%)	0.54
PPI	10 (13.9%)	12 (25%)	0.19	37 (43%)	14 (25%)	0.04	16 (40%)	7 (31.8%)	0.72

Regardless of virus genotype, in our cohort SVR rate was 99.3% in elderly and the only one patient who relapsed in this age-group did not take ribavirin. Moreover in our cohort, low dose ribavirin was used in comparison with dosage reported during “old” interferon-based treatment without affecting SVR rates.

Four cases of severe anemia was recorded in old-old patients and about 40% of them required a dose reduction suggesting that adverse effects occurred more commonly in patient aged ≥ 75 years treated with ribavirin-containing antiviral combinations.

Therefore our data provided a rationale against the use of ribavirin in patients aged ≥ 75 years whereas all DAAs combination can be effectively and safely used.

Potential pharmacokinetic interactions of common drugs administered with DAAs were analyzed in the present study and revealed that elderly patients took significantly more drugs than patients < 65 years. More than one third of our elderly patients (36.7%) took 3 or more concomitant drugs potentially interacting with DAAs; however, DAAs efficacy was not different.

PPI therapy has recently reported to be associated with a 26% increased risk of SVR failure when compared to non-users²⁵. Our data showed high response rates regardless PPI use and age.

We observed a low percentage of AEs (24%) that were significantly lower than those reported in approval studies (60-95%)²⁶⁻³¹; the discrepancy is probably related to the nature of the study design. In fact, in other real-world analyses the AE frequency ranged between 24 and 76%^{12 16 32}. We should take into account that our analysis was carried out in a tertiary referral center for chronic viral hepatitis.

In any case, our physicians carefully evaluated the opportunity of any other drug before starting DAAs therapy and any potential interactive drug was suspended if not strictly needed.

Our observations confirmed the data from other reports that showed a similar frequency of AEs between old and very old patients⁵.

In conclusion, the results of our study demonstrate that age does not influence the success of DAA treatment and that all DAA regimens are well tolerated and safe, even in those aged 75 years or older. Although our patients commonly assumed many concomitant medications, compliance, efficacy and safety were not affected by DAAs.

We believe that a careful evaluation of baseline therapy of the old patients before starting DAAs is mandatory and may avoid treatment failure.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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HIV/AIDS epidemic among older adults in Brazil

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Older adults in Brazil (individuals aged 60 years or older) accounted for 9.8% of the general population in 2005 and 14.0% in 2015. The invisibility of sexuality among older adults implies late diagnoses of HIV/AIDS in this population. The results of the present study lead to reflections regarding the representativeness of HIV/AIDS to the health of older adults and contribute data that can assist administrators, health professionals and others who work with the older population to rethink their attitudes during contact with such individuals and establish dialog addressing issues related to sexual activity, which could have an impact on the early diagnosis of HIV in this population.

Key words: HIV, AIDS, STD, Elderly, Brazil

INTRODUCTION

The scientific community faces the challenge of public health issues related to the growing population of older adults in the 21st century. In Brazil, older adults (individuals aged 60 years or old) accounted for 9.8% of the general population in 2005 and this figure increased to 14.0% in 2015, demonstrating that men and women are living longer due to advances in the fields of medicine and technology as well as improvements in cultural, social and economic aspects, all of which have provided better living conditions ¹.

Active ageing is a worldwide public policy that establishes healthy habits and lifestyles and promotes the participation of older adults in group activities ². While this sociability is seen as positive, one of the issues raised regards sexuality, as sex is often practiced without protection in this population, which increased the odds of sexually transmitted diseases (STDs) and HIV/AIDS ^{3,4}.

In recent decades, the epidemiological profile of the HIV/AIDS pandemic has undergone changes, with the increased vulnerability of diverse groups, including older adults. This occurrence is largely due to the lack

of recognition of an active sexual life in this portion of the population ⁵. The invisibility of the sexuality of older adults implies problems regarding the late diagnosis of HIV/AIDS, which is linked to three aspects: 1) health professionals do not recognize the vulnerability of older adults to HIV/AIDS; 2) older adults do not see themselves as vulnerable to STDs; and 3) health professionals attribute symptoms suggestive of the opportunistic infections that occur with AIDS to other diseases considered to be more frequent in the older population ⁶. Considering the concepts of individual, social and programmatic vulnerability proposed by Ayres (2006) ⁷, this paper offers a preliminary reflection on the implications of the representativeness of HIV/AIDS to the health of older adults, focusing on the portion of the population aged 60 years or older in Brazil.

OBJECTIVE

Analyze the HIV/AIDS epidemic among older adults in Brazil based on information from the 2017 HIV/AIDS Epidemiological Bulletin published by the Ministry of Health ⁸.

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METHODS

A prospective, descriptive study was conducted involving cases of HIV and AIDS among individuals aged 60 years or older registered in the National Notification System between 1980 and 2017 and published in the HIV/AIDS Epidemiological Bulletin of the Brazilian Ministry of Health ⁸.

RESULTS

A total of 882,810 cases of AIDS were registered in Brazil between 1980 and June 2017, affecting 576,245 males and 306,444 females. The incidence of AIDS among older adults went from 15.2 per 100,000 inhabitants in 2007 to 19.3 in 2016 (Fig. 1) and the ratio between sexes (M:F) went from 1.5 in 2005 to 2.2 in 2016, affecting more men than women ⁸.

As of 2007, with the free supply of antiretroviral drugs and the increase in the survival rate of individuals affected by HIV, the records of these cases began in the country. The incidence of HIV without AIDS among the elderly increased from 4.8 per 100,000 inhabitants in 2007 to 7.5 in 2016 (Fig. 1).

The mortality rate due to AIDS among older males went from 5.2/100,000 inhabitants in 2007 to 8.5/100,000 inhabitants in 2016. In the same period, the mortality rate due to AIDS among older women went from 2.2/100,000 inhabitants to 3.6/100,000 inhabitants ⁸.

DISCUSSION

The present results reveal a change in the epidemiological profile of the HIV/AIDS pandemic in recent decades among the older population in Brazil, demonstrating the vulnerability of this portion of the population to STD/HIV/AIDS ^{5,6}. This phenomenon is associated with biopsychosocial transformations, advances in

communication technology and the establishment of social and emotional ties that have a positive impact on day-to-day relationships, including love and sexual relationships ^{3,9}. In this context, the prevention of STD/HIV/AIDS and information on contracting diseases and the importance of caring for one's health are relevant issues to discuss with this age group. The interaction between medications taken for the health conditions common to this population is another important aspect to address, as antiretroviral drugs can complicate the health of older adults, leading to the non-adherence to these medications for HIV/AIDS ^{9,10}.

Social prejudice, low levels of income and schooling, the use of alcohol and drugs ¹² and unprotected sexual relations characterize social vulnerability ¹³. This scenario indicates that a large portion of the population aged 60 years or older in Brazil is beyond the reach of online campaigns and poorly integrated strategies that discuss risk and prevention ¹⁰. Thus, DST/HIV/AIDS prevention campaigns have not fully met their goals, whether for mainly targeting young people or for failing to recognize sexuality in the older population. Nonetheless, this is a macro issue that involves, above all, the pillars of prevention and health care. Moreover, health professionals and others who work with prevention methods must face the challenge of understanding individual, social and programmatic vulnerabilities related to HIV/AIDS ^{7,11}, which also involve sexual behavior between genders and generationally distinct groups, as well as changes in attitudes regarding sexuality among older adults ⁴. This point underscores the importance of the training of interdisciplinary teams through permanent education policies in order to broaden the understanding and efficacy of health professionals when dealing with DST/HIV/AIDS.

There is also a need to involve both the public and private care networks, encompassing hosting services, screening, consultations and the offer of goods and services directed at the early diagnosis of HIV/AIDS, which is of fundamental importance to treatment and the prognosis ^{4,10,13,14}. It is first necessary to consider three plausible groups: 1) older adults with a clinical diagnosis of HIV/AIDS; 2) those who contracted HIV/AIDS prior to reaching 60 years of age and remain asymptomatic or undiagnosed; and 3) those who recently acquired HIV after reaching 60 years of age and are in the development stage of AIDS ^{15,16}.

This study offers information and serves as alert to administrators, health professionals and others who work toward the prevention of HIV/AIDS in the older population to rethink their attitudes during contact with such individuals and establish dialog addressing issues related to sexual activity, which could have an impact on the early diagnosis of HIV in this population.

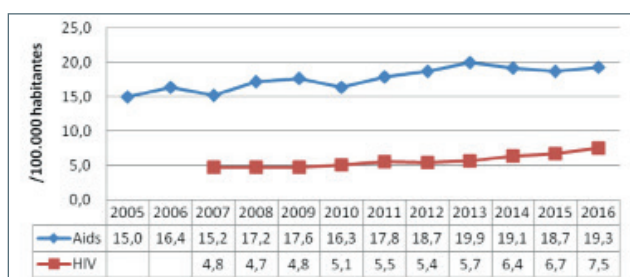


Figure 1. Detection rate (/100,000 inhabitants) of cases of HIV and AIDS among older adults; Brazil, 2005-2016 (from Brazilian STD AIDS Epidemiological Bulletin, 2017, mod.) ⁸.

CONCLUSIONS

The findings of the present study demonstrate that the number of cases of HIV and AIDS among individuals aged 60 years or older has increased in recent decades. This fact underscores the need for public policies and effective strategies directed at this group focused on prevention, management and adherence to treatment for DST/HIV/AIDS as well as the longitudinal monitoring of older adults seen at public and private services, with the notification of cases of STD/HIV/AIDS.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Heterotaxy syndrome presenting as severe pulmonary artery hypertension in a young old female: case report

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Heterotaxy syndrome is a rare congenital disorder characterized by situs ambiguus, congenital heart defects and splenic malformations. We describe a case of 65 year young- old female who presented with sudden onset dyspnoea in emergency department. Her chest x-ray, 2 D echo and computerised tomography of chest was suggestive of severe pulmonary hypertension as a rare manifestation of Heterotaxy syndrome. To the best of our knowledge, pulmonary hypertension has not been previously reported as the main clinical feature in young – old patients with Heterotaxy syndrome.

Key words: Heterotaxy syndrome, Pulmonary hypertension, Young old, Congenital

INTRODUCTION

Heterotaxy syndrome (from the Greek heteros – different and taxis – arrangement) is a rare congenital disorder characterized by predominant malformations in the cardiovascular system, the lungs (symmetric lobulation), the spleen (polysplenia, asplenia, or hypoplastic spleen), and the gastrointestinal tract (situs ambiguus, other malrotations, liver and pancreatic malformation¹). This case depicts two novel features: primary diagnosis of heterotaxy syndrome may be delayed until old age, and this syndrome may be associated with pulmonary hypertension, possibly on the basis of longstanding Porto systemic shunts. Few authors had reported this rare syndrome in adulthood as an incidental finding^{2,3}. Here we describe a case of 65 year young – old female who presented with first time dyspnoea due to pulmonary hypertension as a manifestation of Heterotaxy syndrome.

CASE REPORT

A 65 year young – old previously healthy female was

admitted to the emergency department of this hospital with breathlessness on exertion and palpitations since 1 month and aggravated since 3 days. Breathlessness was NYHA Grade 4. Personal and family histories were otherwise insignificant. She had no history of hypertension, diabetes or any heart disease in the past.

Her physical examination results were normal, and there was no abdominal bruit on auscultation. The patient's blood pressure was normal at 130/70 mmHg, and her heart rate was 110 beats/minute. Her hemoglobin was 8.8 mg% and the total leukocyte count was 8400/mm. Her blood sugar, kidney function, and liver function were within normal limits. Her cardiovascular examination revealed signs of pulmonary hypertension in the form of diastolic shock and left parasternal heave. The electrocardiogram (ECG) showed signs of right ventricular hypertrophy with atrial fibrillation. Chest radiograph showed dilated central pulmonary arteries and cardiomegaly (Fig. 1).

High resolution computed tomography thorax revealed massively dilated pulmonary trunk measuring 63.5 mm in diameter with markedly dilated right and left pulmonary arteries up to the hilum showing abrupt narrowing

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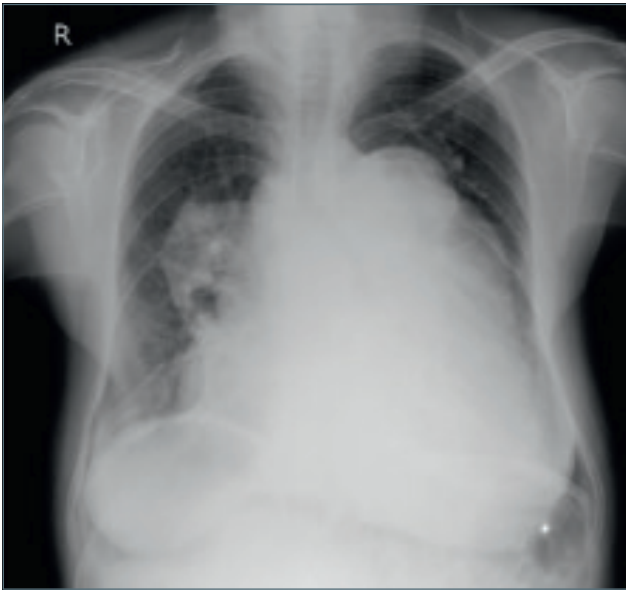


Figure 1. Showing massive cardiomegaly on chest x-ray PA view.

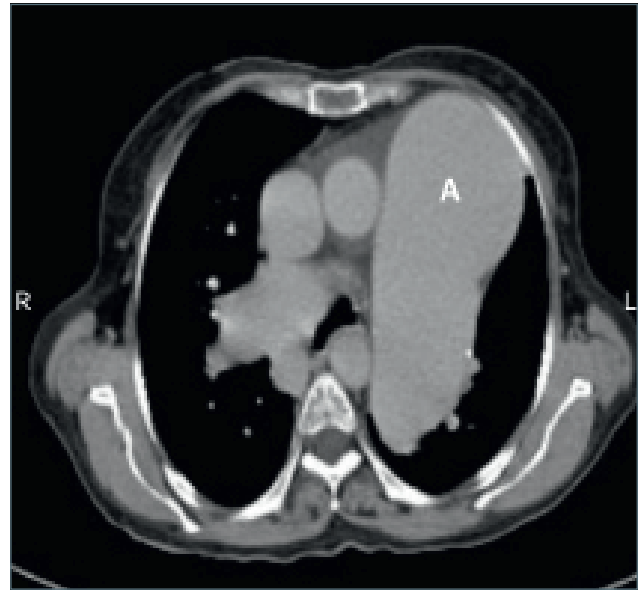


Figure 2. Showing huge pulmonary trunk (denoted by A) and markedly dilated left and right pulmonary arteries (denoted by B and C) on high resolution CT thorax.

of right and left pulmonary artery. Her liver was seen in midline, stomach on right side and spleen on right side with multiple splenenculas (Figs. 2-3). Her portal vein diameter was normal. 2d Echo was suggestive of severe pulmonary arterial hypertension with pulmonary arterial systolic pressure of 67 mm hg (Fig. 4). The diagnosis of heterotaxy syndrome with severe pulmonary hypertension was, therefore, established. Symptomatic treatment with phosphodiesterase-5 inhibitor Sildenafil led to gradual improvement of dyspnoea.

DISCUSSION

Heterotaxy syndrome also known as Ivemark syndrome or isomerism, includes a wide variety of clinical manifestations. Most cases are sporadic, but familial cases have been reported. The habitual and orderly arrangement of the organs in the human body is determined early in the embryonic development. The loss of such orderly arrangement may characterize situs inversus or a disordered and variable arrangement seen in heterotaxy syndrome)^{1 2}. Heterotaxy syndrome presents an approximate incidence of 1:10,000 births and is slightly more prevalent in men, at a ratio of 2:1. As it is mostly manifested in childhood or infancy, their overall prognosis is reduced. Mortality and morbidity are usually related to the degree of Congenital Heart Disease³. Congenital Heart Disease may include abnormal localization of the cardiac apex, a common atrioventricular canal,

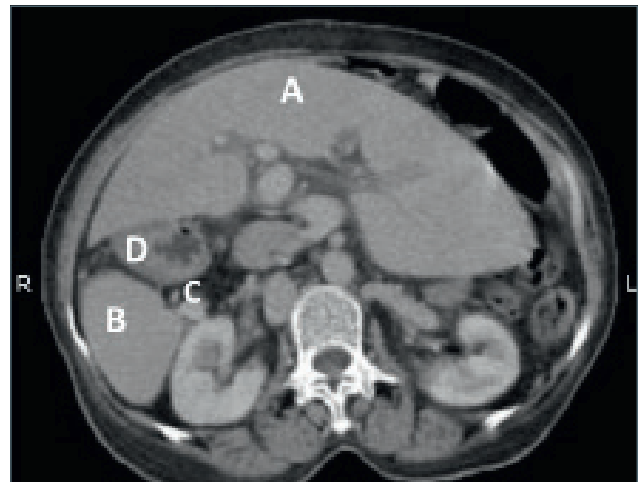


Figure 3. HRCT thorax with abdomen showing:

- A) liver placed in midline
- B) spleen on right side
- C) splenenculi
- D) right sided stomach

anomalous systemic venous return (e.g., bilateral superior vena cava, interruption of the inferior vena cava with azygos continuation), atrial and ventricular malformations and septal defects, absent coronary sinus, malposition or transposition of the great arteries, pulmonic stenosis, pulmonary atresia, patent ductus arteriosus, and anomalous pulmonary venous connection³.



Figure 4. 2D Echo showing dilated right atrium and left atrium.

Our patient presented with symptoms of severe pulmonary hypertension. The most likely reason that our patient with heterotaxy syndrome was asymptomatic and felt well until 65 years of age was that she had no relevant structural or functional cardiac defect. The development of pulmonary hypertension may be due to left-right blood shunting; but in our patient significant cardiac shunt volume was ruled out by 2 D Echo. Pathophysiologically it may be explained by the presence of severe visceral malformations which happens in this syndrome.

Pulmonary hypertension may develop as a consequence of underlying splenic, hepatic, or vascular malformations. Chances are increased in patient with liver cirrhosis complicated with portal hypertension known as portopulmonary hypertension^{4,5}. The exact mechanism of portopulmonary hypertension

is unknown. Altered hemodynamics or incomplete metabolism of vasoactive substances in the liver is possible mechanisms for the development of pulmonary hypertension in these patients. These vasoactive substances include endothelin, vasoactive intestinal peptide, serotonin, and thromboxane A₂. Endothelin is a well-known pulmonary vascular constrictor, and elevated levels of endothelin have been reported in patients with liver cirrhosis⁵. However parenchymal liver disease was excluded in our patient by Ultra Sonography of the abdomen and liver.

The number of asymptomatic patients with heterotaxy syndrome diagnosed in adulthood may rise with the increased utilization of CT and magnetic resonance imaging.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Contributions of Italian science in advancing lifespan extension through autophagy stimulation

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In their recent paper Tancini et al. reviewed advancements of non-italian science in lifespan extension through autophagy stimulation and future perspectives ¹. Here, it may be worthwhile to recall discoveries in Italian laboratories supported by MIUR (40% program), disclosing the way to successful intervention on aging in humans. Seminal work was the discovery that autophagy can be induced by giving fasted animals an antilipolytic drug (either 3,5-dimethylpyrazole or Acipimox) ². Treatment lowers blood FFA and glucose levels in less than 15 minutes, and lowers insulin and increases glucagon and glucocorticoids levels inducing liver autophagy in 30 min ³. A highly reproducible method for the investigation of endocrine-regulated autophagy and protein degradation was set and used to explore the endocrine and amino acid regulation of macroautophagy ⁴. A preliminary report that the autophagic response to stimulation by antilipolytic drugs decreases with increasing age was given at the 1987 binational Italy-US symposium on protein metabolism in Aging. Research advancements in following years were reviewed on the official journal of the Italian Gerontological and Geriatric Society as well as on international journals (e.g. ⁵). Briefly, results confirmed that the *in vivo* and *in vitro* function of autophagy declines with increasing age in ad libitum fed animals and that antiaging calorie restricted (CR) diets (both 40% restriction and every other feeding) may counteract these age-related changes; that protection by CR diets declines with increasing the age at the start of dietary interventions, co-varies with extension of life-span and parallels age-related changes in dolichol concentration, a novel lipid biomarker of membrane aging ⁶ and in the transduction of amino acid and hormone signaling; that treatment with Acipimox may increase autophagic response to fasting and intensify the beneficial antiaging effects of

a milder CR; that a long-lasting inhibition of autophagy (e.g. by chloroquine) may speed up the process of aging and that a long-lasting intensification of autophagy by antilipolytic drugs may delay the appearance of age-associated changes in rats (George Martin gave the name to treatment: PISA – Pharmacological Intensification of Suppression of Aging – see ⁷). Discovery that PISA may cause a selective degradation of older 8-OHdG rich mitochondria ⁸ and older peroxisomes ⁹ clarified the mechanisms of protection and gave a way to monitor efficacy non-invasively, both in animals and humans, by the assay of 8-OHdG output in urine ¹⁰. Finally, it was clarified that the stimulation of autophagy and apoptosis to clear cells and tissues from altered components is only a part in the antiaging mechanism of CR: to get full benefit, time of fasting should be followed by good nutrition, rich in omega-3 polyunsaturated fatty acids and red-wine antioxidants, to rise insulin and IGF-1 levels and foster replacement of the degraded altered organelles and cytomembranes with new ⁷. The full procedure was named D.A.N.I. (Dynamic Antiaging Nutritional Intervention). Thanks to the support of Rotary and Associazione Alberto Sordi (Roma), with the approval of the Italian Institute of Health (Istituto superiore di Sanità), full information is now available to Italian high-school students (and their families) for primary prevention of aging and associated diseases as a part in the regular biology program.

Discovery that antiaging caloric restrictions may act by a cyclically repeated activation of autophagic degradation and replacement of the degraded material with new prompted us to investigate which cell component is so difficult to be fixed that Nature decided that degradation is better than repair ⁷. The obtained results may shed light on the mechanisms of age-related cholesterolemia, of the beneficial effect of fish oil and of the

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dangerous side effects of statin therapy. Evidence was found indeed that higher oxidative stress in membranes may activate HMGCoA-reductase, accounting for the age-related increase in the plasma level of cholesterol and in two tissue antioxidants, the biomarkers of aging dolichol and ubiquinone. The induction of autophagy by the administration of Acipimox did prevent these changes. Incidentally, data may clarify also the mechanisms of the beneficial effects of red wine polyphenols and resveratrol on cholesterolemia, and of the toxicity of statins (together with plasma cholesterol statins may decrease tissue dolichol and ubiquinone thus increasing risks of free radical-mediated tissue injury: rhabdomyolysis).

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The authors declare no conflicts of interest.

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Diagnostic and management challenges in chronic obstructive pulmonary disease and heart failure: the need for an interdisciplinary approach

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Patients with *chronic obstructive pulmonary disease* (COPD) and heart failure can be challenging in terms of diagnosis and management, requiring an interdisciplinary approach. Vitale and colleagues indicated the value of collaboration between cardiologist, pulmonologists and general practitioners. Comprehensive Geriatric Assessment (CGA) may identify other needs requiring allied health professional input, while for those with complex needs, geriatrics and palliative care input may also be appropriate.

Key words: COPD, Heart failure, Interdisciplinary, Geriatrics, Palliative

In their recent paper, Vitale and colleagues highlighted the frequent co-existence of chronic obstructive pulmonary disease (COPD) and heart failure, posing diagnostic challenges to clinicians¹. The authors emphasised the importance of confirming the diagnosis of each condition. This requires assessment of left ventricular function using echocardiography or cardiac MRI, and pulmonary function tests to confirm airflow obstruction. In older people, there are limitations to investigating concurrent heart failure and COPD. The BED study showed that in dyspnoeic patients age 80 years or older, BNP was unable to discriminate between cardiac or respiratory causes². Echocardiography has limited sensitivity in confirming heart failure, as up to 50% patients aged 65 years or older with heart failure have preserved ejection fraction (HFPEF)³. The main utility of echocardiography in the acute setting is to rule out other differential diagnoses or precipitants for heart failure, such as myocardial infarction, pericardial effusions or cardiac tamponade. While cardiac MRI is useful in COPD patients with limited echocardiogram views, it may not be tolerated due to orthopnoea in heart failure. In older people, performance in pulmonary function tests

may be affected by physical and cognitive abilities. For patients with dyspnea, these tests may be too physically demanding. Interpretation of results should take into account patient factors such as spinal changes from osteoporosis, body habitus, or cardio-respiratory comorbidities in older people. Guidelines also recommend against testing patients within a month of myocardial infarction, which is relevant in patients with COPD and heart failure⁴. These limitations usually require clinicians to initiate expectant management based on the acute presentation and offer a presumed diagnosis based on treatment response.

For patients with multiple comorbidities, polypharmacy and potential drug interactions are common. Beta-agonists for COPD treatment may induce tachycardia, fast ventricular rate in atrial fibrillation and hypokalaemia, which are common in heart failure. Beta-agonists are also associated with adverse outcomes for patients with pulmonary disease, including risk of heart failure hospitalisation, major adverse cardiovascular events, cardiovascular death and mortality⁵. It remains unclear whether these adverse outcomes are related to bronchodilator toxicity or underlying pulmonary disease. As

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studies have consistently showed no benefit of nebulisers over standard pressurised metered-dose inhaler (MDI) with spacer ⁶, it may be preferable to use MDI to reduce the exposure of beta-agonists to patients in heart failure.

For patients with possible conflicting treatment goals due to polypharmacy, applying concepts of comprehensive geriatric assessment (CGA) is beneficial. CGA requires a multidimensional, interdisciplinary approach to take into account the patient's medical, psychosocial and functional abilities. A meta-analysis showed that comprehensive discharge planning with post-discharge support for older people with heart failure significantly reduced readmission rates and improves health outcomes, such as survival and quality of life, without increasing costs ⁷.

In my experience, common issues identified through CGA include nutritional deficiencies and deconditioning requiring rehabilitation. If these are identified, involvement of dietician or physiotherapist respectively early on in the admission would be useful. In addition, both heart failure and COPD are associated with poor cognition. Heart failure is associated with significant impairment in executive function and psychomotor speed, poor immediate memory and global cognition when compared to patients with cardiovascular disease only ⁸. COPD is associated with global cognitive impairment, especially perception, memory and motor function, and is worse in those with hypoxaemia, smoking and cardiac comorbidities ⁹.

Cognitive assessment is crucial as it impacts self-management. It is important to assess the patient's knowledge and technique of using MDI with spacers. If treatment compliance is an issue due to cognitive impairment, sufficient support is necessary to monitor medication use to avoid exacerbations or relapse.

Finally, patients with multiple co-morbidities tend to have high symptom burden and mortality, contributing to palliative care needs such as managing refractory multi-faceted symptoms, communication, decision making issues and requirement for family support ⁹. Symptom fluctuation may require repeated evaluation of care goals during disease progression. The anticipated course of illness, treatment options, patient preferences and advance directives may need further exploration with patients and family. Palliative care involvement should be considered, preferably during the early stage of the disease. The roles of geriatric medicine, palliative care, cardiology or pulmonology are not mutually exclusive but each specialty offers a unique perspective on management of these patients, particularly in older people with peculiarities in disease presentation and treatment response.

In summary, patients with COPD and heart failure can be challenging in terms of diagnosis and management, requiring an interdisciplinary approach. Vitale and colleagues indicated the value of collaboration between cardiologist, pulmonologists and general practitioners ¹. CGA may identify other needs requiring allied health professional input, while for those with complex needs, geriatrics and palliative care input may also be appropriate.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Original Investigation

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Nutritional interventions in patients with Alzheimer's disease and other late-life cognitive disorders

P. Agosti, C. Custodero, A. Schilardi, V. Valiani, A. D'Introno, M. Lozupone, F. Panza, V. Dibello, M. La Montagna, F. D'Urso, V. Solfrizzi, C. Sabbà 101

Effectiveness of a specific nutritional supplement on cognitive, behavioral and functional symptoms in mild cognitive impairment and Alzheimer's dementia: caregivers judgments. Results of an observational survey

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Background and aims. Caregivers play a central role in the evaluation of symptoms in mild cognitive impairment (MCI) and dementia, and in clinical practice their opinion is important in the definition of the effectiveness of pharmacological and not pharmacological intervention.

With the aim to explore the impact of a nutritional intervention by the use of a medical food on quality of life, cognitive and functional outcomes in large populations of Alzheimer's dementia (AD) and MCI subjects, we performed an observational survey (the MEMENTO study).

Methods. The study was carried out in 30 Italian outpatients clinics, based on patient and caregiver judgment.

Results. Five hundred patients (58.8% female, mean age 75.9 ± 7.1 SD) were included in the survey. The results confirmed the data from RCT about the effectiveness of dietary supplementation with a medical food on cognitive symptoms of AD and MCI and also the effectiveness on behavioral and functional deficits. In particular, the effectiveness was more evident in patients with higher MMSE score, and in MCI compared to AD. Interestingly, caregivers of MCI subjects reported better results than those of AD patients only in cognitive and functional domains but not in behavioral domain.

Conclusions. The study uses for the first time the subjective judgment of patients and caregivers as an outcome measure, by focusing on the cognitive aspects, and on functional status and behavior.

Key words: Nutritional supplement, Mild cognitive impairment, Alzheimer disease, Caregivers

INTRODUCTION

Several epidemiological and observational studies suggest that dietary habits, as well as physical and mental activity, and chronic diseases (e.g. hypertension, cardiovascular disease, diabetes mellitus and metabolic syndrome), are associated with cognitive impairment and increased risk of dementia ^{1,2}. Specific dietary pattern, and in particular, the so-called "Mediterranean diet", characterized by the presence of fruit and

vegetable, olive oil, fish, low animal fats, high content of vitamin C and vitamin E, is associated with a lower risk of developing Alzheimer's disease (AD) and cognitive impairment ^{3,4}, lower progression from mild cognitive impairment (MCI) to dementia ⁵ and better cognitive performances in the elderly ⁶. These evidences are supported by epidemiological data, showing that in healthy elderly subjects, elevated plasma levels of vitamin B (B1, B2, B6, folate, B12), C, D, and E, and higher levels of fatty acids ω -3, are associated with better cognitive

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performance and less brain atrophy on cerebral magnetic resonance imaging (MRI) ⁷.

Although epidemiological data are broadly in agreement, the studies that evaluated the efficacy of dietary supplements (vitamins or nutritional elements) on cognitive functions reported contrasting results: supplementation with high doses of vitamin B does not slow cognitive decline in healthy subjects and AD patients ^{8,9}; the addition of polyunsaturated fatty acids does not slow the decline in AD, except in very mild stages ¹⁰; vitamin E supplements in patients with cognitive impairment determines limited benefit on slowing the progression of AD ^{11,12} but no benefit in MCI patients ¹³. Even the use of a combination of antioxidant substances did not produce positive results; a mixture of vitamin E, C, α -lipoic acid, coenzyme Q has even shown an acceleration of the cognitive decline in people with AD ¹⁴.

The reasons for these unsatisfactory results may be various: insufficient doses or short duration of treatment, the advanced stage of the disease, or the need to combine different nutrients acting synergically against the pathophysiological process of neurodegeneration.

Recent randomized controlled clinical trials demonstrate that a dietary supplementation with a specific combination of nutrients (docosahexaenoic acid, eicosapentaenoic acid, uridine monophosphate and choline as precursors required to enhance neuronal membrane formation and B-vitamins, vitamin C, E, selenium and phospholipids as cofactors by enhancing the bioavailability of those precursors) improves memory complaints in patients with mild AD: subjects treated with dietary supplementation had better verbal memory performance than controls after 12 weeks of treatment ¹⁵ and best global memory after 24 weeks of treatment ¹⁶. The impact of the use of specific nutritional supplement on quality of life, and on cognitive and functional outcomes in large populations have not yet been evaluated, as well as the judgment of the caregiver. These points of view are important because they provide a measure of the impact of objective improvements assessed in randomized trials on the personal dimension of the disease on both patient and caregivers ¹⁷. Caregiver judgment is rarely considered in the definition of the effectiveness of treatment for AD, although in the "real world" the opinion of caregivers is important in collecting patient's clinical history and definition of cognitive, functional and behavioral changes holding treatment, and the opinion of patients is considered only as "secondary outcomes" although studies demonstrated that, in the mild/moderate stages of the disease, AD patients provide a reliable judgment of their cognitive and functional status ¹⁸.

For these reasons we performed an observational survey (the MEMENTO study) with the aim to collect

patient and caregiver judgment about changes in cognitive, behavioral and functional domains after a nutritional intervention.

MATERIALS AND METHODS

The MEMENTO study was conducted in 30 Italian outpatient clinics specifically devoted to the evaluation and treatment of Alzheimer's disease and other types of dementia (Alzheimer Evaluation Units) ¹⁹. We used a medical food (containing a specific nutrient combination named Fortasyn Connect) ²⁰ in addition to standard treatment in MCI and mild AD subjects. The diagnosis was made using standard criteria and shared protocols ²¹. Subjects receiving nutritional treatment were evaluated at baseline using standard protocols and at the follow-up visit (usually after 3 or 6 months) using in addition to usual assessment instruments a structured interview to explore modification of cognitive, behavioural and functional domains in "real life" situations ²². Data were collected anonymously.

The survey was carried out from June 2013 to March 2014.

COLLECTION OF CLINICAL DATA

Patients and caregivers judgment about changes in cognitive, behavioral and functional domains at follow-up visit after the assumption of the medical food supplement were collected by means of a 14-items clinical structured interview designed for the study, administered to the patient and to the caregiver, exploring cognitive, behavioral and functional domains in "real life" situations (Tab. I). The answers of each item were standardized using a hierarchical scale (from 1, worsened, to 5, improved). A single domain score and a global score were calculated for the analysis. Each variable was scored on the basis of the clinical judgment: 1 point was given for "worsened", 2 points for "slightly worsened", 3 points for "unchanged", 4 points for "slightly improved" and 5 points for "improved".

For the caregiver variables specific indices were obtained by summing up the score of single variables: 1) "cognitive index" (sum of the score of "memory for appointments", "memory for name of people" and "orientation"); 2) "functional index" (sum of the score of "domestic activities", "outside activities" and "reading"); 3) "behavioral index" (sum of score of "apathy", "agitation", "sleep disturbances" and "feeding behavior"). A "patient index" was calculated by summing the score of all patient variables ("memory", "orientation", "activities" and "mood"). A "global index" was obtained from the sum of all caregivers and patients variables.

The interview scale was fielded twice (the second after

Table I. Variables investigated in the structured interview used to explore the modification of cognitive, behavioral and functional domains in a 'real life' situation.

Domain	Caregiver interview	Patient interview
Cognition	Remember appointments/commitments/dates Identify persons/remember names Orientation in new places	Subjective memory Orientation in and out home
Behavior	Apathy/loss of interest Agitation/irritability Sleep disturbances Eating behavior	Depression complain
Function	Household activities/hobbies Outdoor activities Reading books/newspaper	Household activities/hobbies

two weeks by the same researcher) in a sample of 30 patients (60% female, mean age was 77.5 ± 7.5) and their caregivers. The internal consistency reliability (Cronbach's alpha coefficient) was good for both patient (0.86) and caregiver (0.83) report. Pearson correlation coefficient for the two-week retest was 0.78 ($p < .001$) for patients and 0.76 ($p < .001$) for caregivers.

STATISTICAL ANALYSIS

Differences among groups (AD and MCI) were measured by means of chi-square for categorical variables and unpaired student t-test for continuous variables. The linear dependence between two variables was assessed by determining Pearson's correlation coefficient 'r' values. The level of statistical significance was defined as $p < 0.05$.

RESULTS

Five hundred patients (58.8% female, mean age 75.9 ± 7.1 SD) were included in the survey. The subjects received nutritional supplement for an average of 4 months with a range from 1 to 12 months. The majority of the subjects were suffering from AD (45.2%) or MCI (33.8%), the remaining patients had other forms of cognitive impairment (i.e.: vascular cognitive decline, Lewy body dementia, fronto temporal dementia). The mean baseline MMSE of the whole sample was 21.8 ± 4.6 SD; in 144 (28.8%) patients MMSE score was greater than 24, in 276 (55.2%) between 18 and 24 and in 80 (16%) less than 18. Only 27 subjects (5.4% of the sample) symptoms of intolerance were reported, mainly diarrhea and nausea; 112 patients (22.4%) completed the treatment period but reported difficulties related to the cost of treatment.

Concomitant medications were: acetylcholinesterase inhibitors (32%), memantine (14.4%), antidepressants (29.2%) and nootropic drugs (8.4%).

Table II shows the results of patients and caregivers interview in the whole sample. From 28.6% to 49.6% of caregivers provided a positive judgment on the effectiveness of the treatment (slightly improved/improved); apathy and memory about appointments are the variables with higher frequency of positive judgment; orientation and sleeping disturbances showed less relevant improvement. From 36.2% to 46.2% of patients provide a positive judgment (maximum for memory and mood, minimum for orientation and activities).

To explore more deeply the relationship between severity of disease and response to treatment a comparison between AD ($n = 226$) and MCI ($n = 169$) subjects was performed. The groups did not differ for mean age (MCI: 75 years ± 7.1 SD; AD: 76.2 years ± 6.9 SD); MCI subjects had a significantly higher MMSE mean score than AD patients (MCI: 24.6 ± 2.9 SD; AD: 19.9 ± 4.6 SD; $F = 23.5$, $p < 0.0001$).

The efficacy judgments were then grouped into three levels: 1 = worsened (including the judgments "slightly worsened" and "worsened"); 2 = unchanged (including the judgment "unchanged"); 3 = improved (including the judgment "slightly improved" and "improved") and the results in MCI and AD compared (see Table III). Caregivers of MCI patients reported better positive judgments of effectiveness compared to caregivers of AD patients, with statistically significant differences for the items exploring household activities ($p = 0.005$), memory for appointments ($p = 0.002$), remember person's name ($p = 0.023$) and orientation in new places ($p = 0.023$). Patients with MCI reported a better positive judgment for subjective memory ($p = 0.017$).

Table IV shows linear correlations among efficacy indices, months of treatment, age of patients, basal MMSE scores, follow-up MMSE scores and delta MMSE scores (difference between MMSE at follow-up and MMSE at baseline). All clinical indices were positively correlated with months of treatment and delta MMSE and inversely correlated with age of patients. The score of MMSE,

Table II. Distribution of the efficacy judgment of nutritional supplement treatment by caregivers and patients. Data obtained in the whole sample.

	Worsened n (%)	Slightly worsened n (%)	Unchanged n (%)	Slightly improved n (%)	Improved n (%)
Caregivers interview					
Apathy	0 (0)	31 (6.2)	221 (44.2)	202 (40.4)	46 (9.2)
Agitation	0 (0)	40 (8.0)	300 (60.0)	136 (27.2)	24 (4.8)
Sleep disturbances	0 (0)	24 (4.8)	327 (65.4)	129 (25.8)	20 (4.0)
Feeding behavior	0 (0)	22 (4.4)	310 (62.0)	146 (29.2)	22 (4.4)
Domestic activities	1 (0.2)	36 (7.2)	249 (49.8)	183 (36.6)	31 (6.2)
Outside activities	1 (0.2)	30 (6.0)	288 (57.6)	161 (32.2)	20 (4.0)
Reading	2 (0.4)	34 (6.8)	302 (60.4)	140 (28.0)	22 (4.4)
Memory for appointments	6 (1.2)	41 (8.2)	235 (47.0)	185 (37.0)	33 (6.6)
Memory for name of people	3 (0.6)	32 (6.4)	271 (54.2)	168 (33.6)	26 (5.2)
Orientation	1 (0.2)	38 (7.6)	318 (63.6)	129 (25.8)	14 (2.8)
Patients interview					
Memory	1 (0.2)	32 (6.4)	236 (47.2)	203 (40.6)	28 (5.6)
Orientation	1 (0.2)	18 (3.6)	294 (58.8)	166 (33.2)	21 (4.2)
Activities	0 (0)	25 (5.0)	294 (58.8)	166 (33.2)	15 (3.0)
Mood	1 (0.2)	26 (5.2)	246 (49.2)	196 (39.2)	31 (6.2)

Table III. Comparison between MCI and AD group (caregivers and patients efficacy judgment).

	MCI			AD			X²	p
	Worsened n (%)	Unchanged n (%)	Improved n (%)	Worsened n (%)	Unchanged n (%)	Improved n (%)		
Caregivers interview								
Apathy	6 (3.6)	69 (40.8)	94 (55.6)	19 (8.4)	102 (45.1)	105 (46.5)	5.628	0.060
Agitation	11 (6.5)	101 (59.8)	57 (33.7)	26 (11.5)	130 (57.5)	70 (31)	2.887	0.236
Sleep disturbances	9 (5.3)	112 (66.3)	48 (28.4)	12 (5.3)	146 (64.6)	68 (30.1)	0.135	0.935
Eating behavior	7 (4.1)	110 (65.1)	52 (30.8)	10 (4.4)	136 (60.2)	80 (35.4)	1.013	0.603
Household activities	6 (3.6)	83 (49.1)	80 (47.3)	29 (12.8)	107 (47.3)	90 (39.8)	10.732	0.005*
Outdoor activities	10 (5.9)	90 (53.3)	69 (40.8)	18 (8)	137 (60.6)	71 (31.4)	3.901	0.142
Reading	10 (5.9)	102 (60.4)	57 (33.7)	19 (8.4)	129 (57.1)	78 (34.5)	1.011	0.603
Memory for appointments	9 (5.3)	72 (42.6)	88 (52.1)	34 (15)	104 (46)	88 (38.9)	12.386	0.002*
Remember persons name	6 (3.6)	89 (52.7)	74 (43.8)	24 (10.6)	119 (52.7)	83 (36.7)	7.575	0.023*
Orientation	8 (4.7)	108 (63.9)	53 (31.4)	29 (12.8)	135 (59.7)	62 (27.4)	7.555	0.023*
Patients interview								
Memory	9 (5.3)	68 (40.2)	92 (54.4)	22 (9.7)	112 (49.6)	92 (40.7)	8.152	0.017*
Orientation	5 (3)	98 (58)	66 (39.1)	12 (5.3)	127 (56.2)	87 (38.5)	1.304	0.521
Activities	6 (3.6)	99 (58.6)	64 (37.9)	14 (6.2)	133 (58.8)	79 (35)	1.563	0.458
Mood	7 (4.1)	85 (50.3)	77 (45.6)	15 (6.6)	106 (46.9)	105 (46.5)	1.328	0.515

MCI: mild cognitive impairment; AD: Alzheimer's disease; * statistically significant difference between AD and MCI group

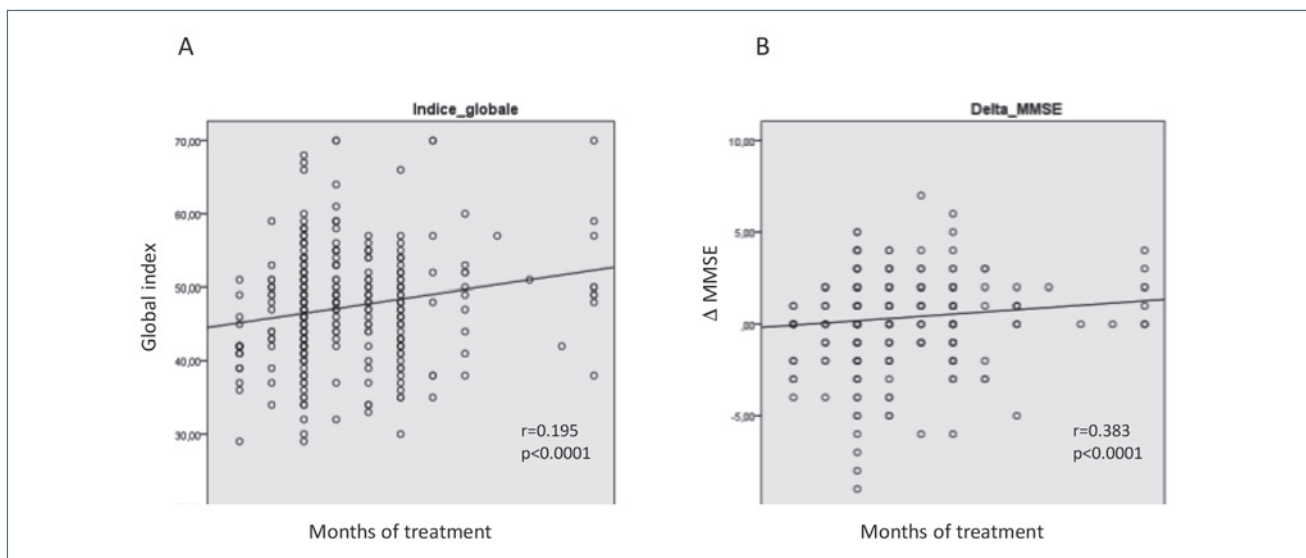
at follow-up visit was positively correlated with clinical indices except for caregiver behavioral index. Among symptoms belonging to the behavioral index,

we performed a sub-analysis exploring the correlation between the symptom "apathy" and MMSE follow-up scores: a correlation between the two variables was

Table IV. Correlations among efficacy indices and clinical variables in the whole group of MCI and AD patients.

	Months of treatment	Age of patient	MMSE at baseline	MMSE at follow-up	Δ MMSE (MMSE at follow-up – MMSE at baseline)
Cognitive index – caregiver	$r = 0.181$ $p < 0.0001^*$	$r = -0.209$ $p < 0.0001^*$	$r = 0.064$ $p = 0.205$	$r = 0.226$ $p < 0.0001^*$	$r = 0.371$ $p < 0.0001^*$
Functional index – caregiver	$r = 0.183$ $p < 0.0001^*$	$r = -0.162$ $p = 0.001^*$	$r = 0.059$ $p = 0.240$	$r = 0.196$ $p < 0.0001^*$	$r = 0.312$ $p < 0.0001^*$
Behavioral index - caregiver	$r = 0.135$ $p = 0.007^*$	$r = -0.114$ $p = 0.024^*$	$r = 0.064$ $p = 0.205$	$r = 0.071$ $p = 0.160$	$r = 0.305$ $p = 0.0001^*$
Patient index	$r = 0.183$ $p < 0.0001^*$	$r = -0.182$ $p < 0.0001^*$	$r = 0.054$ $p = 0.282$	$r = 0.209$ $p < 0.0001^*$	$r = 0.354$ $p < 0.0001^*$
Global index	$r = 0.195$ $p < 0.0001^*$	$r = -0.190$ $p < 0.0001^*$	$r = 0.030$ $p = 0.556$	$r = 0.198$ $p < 0.0001^*$	$r = 0.383$ $p < 0.0001^*$

R: Pearson's correlation; * statistically significant

**Figure 1.** Relationship among global index (figure A) and delta MMSE (figure B) in MCI and AD patients.

found ($r = 0.147$, $p = 0.003$); on the contrary no correlation between MMSE baseline score and clinical indices was found.

Figure 1 shows the correlation between the duration of treatment and the response to treatment (the global index of efficacy) ($r = 0.195$; $p < 0.0001$; Figure A) and the delta MMSE score ($r = 0.383$; $p = 0.0001$; Figure B) in the whole group of MCI and AD patients.

DISCUSSION

The role of nutritional factors for the prevention and for the treatment of neurodegenerative diseases is based on biological observation, and confirmed by epidemiological and clinical data.

In recent years products containing substances with mutually reinforcing actions on mechanisms underlying

cognitive impairment have been developed and evidences of efficacy in AD and MCI were demonstrated²². A medical nutrition containing a specific nutrient combination (Fortasyn Connect) designed to support synapse formation, demonstrated efficacy on memory deficit in mild AD subjects in RCT²³.

With the aim to evaluate the effectiveness of this medical food in clinical practice, we explored the opinion of patients and caregivers in a “real world” situation. Our survey was based on a questionnaire administered to caregivers and patients during a clinical interview with the aim of investigating those cognitive, behavioral and functional symptoms that are most prevalent in MCI and mild AD (i.e. cognitive: episodic memory and orientation; behavioral: apathy, sleep disorders and depression; functional: instrumental activities of daily living)²⁴⁻²⁶.

Caregivers of patients with dementia have to perform many different tasks and roles as the disease

progresses and frequently experience stress and physical and emotional burden and their involvement in the care plan of patients is fundamental in all the stages of the disease. Family caregivers are central to the assessment and care of the patient with dementia and establishing and maintaining collaboration with caregivers is critical for care of the patient²⁷. For these reasons in our survey we evaluated caregivers' judgment in the assessment of the modification of cognitive, behavioral symptoms of dementia and functional status after a non-pharmacological intervention (supplementation of diet with a medical food).

Recent studies demonstrated that patients with dementia may evaluate properly their symptoms of cognitive decline and gathering information from both patients and caregivers may be considered an ameliorative element for the interpretation of dementia progression, since the two sources of information increase the quality of evaluation^{28,29}.

In our survey we analyze caregiver and subjects' judgment about the evolution of cognitive, behavioral and functional symptoms after a nutritional intervention and found three important clinical results: 1) both patients and caregivers provided an overall positive opinion about the effectiveness of the dietary supplementation on cognitive, behavioral and functional domains explored using "real life" situations; 2) the level of satisfaction was higher for patients with higher MMSE score and in those with MCI compared to AD, and 3) patients with higher duration of treatment reported higher benefit from the treatment.

Our survey also demonstrated that the medical food is well tolerated in clinical practice (only 6.5% of patients discontinued) confirming data from RCT.

Our results confirmed the data from RCT about the effectiveness of this nutraceutical product on cognitive symptoms of AD and MCI and also the effectiveness on behavioral and functional deficits. In particular, the effectiveness was more evident in patients with higher MMSE score, and in MCI compared to AD, as demonstrated in clinical trials. Interestingly, caregivers of MCI subjects reported better results than those of AD patients only in cognitive and functional domains but not in behavioral domain. Among symptoms included in behavioral domain, we analyzed the symptom "apathy" alone due to its higher prevalence in MCI and mild AD patients and the role as risk factor for conversion from MCI to dementia^{30,31}. As we expected, differently from other behavioral symptoms, apathy improvement was strictly correlated with MMSE score, with better results in subjects with higher MMSE scores.

An important aspect is represented by the fact that the supplementation was significantly more effective if administered in the earliest stages of the disease (MMSE greater) and for a longer duration of treatment (number of months).

The study uses for the first time the subjective judgment of patients and caregivers as an outcome measure, by focusing not only on the cognitive aspects, but also on functional status and behavior. It is interesting to observe that apathy, together with memory, is the neuropsychiatric symptom that most improves in our investigation.

One possible explanation for results reported in this study is that in Alzheimer's disease the synaptic damage is the pathogenic element mostly correlated with the extent of cognitive decline³². In the course of a neurodegenerative disease, characterized by a progressive extent and spread of the synaptic damage, a product able to increase the synthesis of synaptic membrane precursors has a greater likelihood of effectiveness and consequently clinical evidence when administered in the earliest stages of the disease.

The study has limitations due to the observational design and to the lack of a control group. The strength of the study is that the results have been obtained in the real world; they should be read together with those derived from randomized trials to confirm the therapeutic role of a medical food in subjects affected by MCI or AD.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REVIEW

Dietary patterns, foods, and food groups: relation to late-life cognitive disorders

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The limited efficacy of disease-modifying therapeutic strategies for mild cognitive impairment (MCI) and Alzheimer's dementia (AD) underscores the need for preventive measures to reduce the burden of late-life cognitive impairment. The aim of the present review article was to investigate the relationship among dietary patterns, foods, and food groups and late-life cognitive disorders considering the results of observational studies published in the last three years (2014-2016). In the last decade, the association between diet and cognitive function or dementia has been largely investigated. However, more recently, the National Institute on Aging-Alzheimer's Association guidelines for AD and cognitive decline due to AD pathology introduced some evidence suggesting a direct relation between diet and changes in the brain structure and activity. Several studies focused on the role of the dietary patterns on late-life cognition, with accumulating evidence that combinations of foods and nutrients into certain patterns may act synergistically to provide stronger health effects than those conferred by their individual dietary components. In particular, higher adherence to a Mediterranean-type diet was associated with decreased cognitive decline, although the Mediterranean diet (MeDi) combines several foods, micronutrients, and macronutrients already separately proposed as potential protective factors against dementia and MCI. Moreover, also other emerging healthy dietary patterns such as the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) diets were associated with slower rates of cognitive decline and significant reduction in AD rate. Furthermore, some foods or food groups traditionally considered harmful such as eggs and red meat have been partially rehabilitated, while there is still a negative correlation of cognitive functions with added sugars and trans fatty acids, nutrients also increasing the cardiovascular risk. This would suggest a genesis for the same damage for aging brain.

Key words: Dementia, Alzheimer's disease, MCI, Dietary pattern, Mediterranean diet, Healthy diet, Foods, Food groups

INTRODUCTION

Currently, available drugs for the treatment of Alzheimer's disease (AD) have only symptomatic effects ¹, and there is an unmet need of preventing AD onset and delaying or slowing disease progression from mild cognitive impairment (MCI) in absence of disease-modifying

therapies. In the last ten years, a large number of studies have investigated the association between diet and cognitive function and dementia ²⁻⁴. However, in the last few years, some changes have emerged in approaching the relationship between diet and cognitive impairment. In fact, the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines for AD and cognitive decline due to AD pathology ⁵ introduced

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some evidence suggesting a direct relation between diet and changes in the brain structure and activity, opening the era of brain imaging biomarkers in nutrition epidemiology. Furthermore, some groups of foods traditionally considered harmful such as eggs and red meat have been partially rehabilitated. Conversely, there is still a negative correlation of cognitive functions with added sugars and trans fatty acids, the same nutrients that increase the cardiovascular risk, suggesting a genesis for the same damage for aging brain. Finally, many studies focused on the role of dietary patterns on late-life cognition, accumulating evidence that combinations of foods and nutrients into certain patterns may act synergistically to provide stronger health effects than those conferred by their individual dietary components. The aim of the present review article was to shed light on the relationship among dietary patterns, foods, and food groups and late-life cognitive disorders considering the results of observational studies published in the last three years (2014-2016).

DIETARY PATTERNS AND LATE-LIFE COGNITION

The Mediterranean diet (MeDi) is a typical dietary pattern of Mediterranean countries, characterized by high consumption of fruits, vegetables, legumes and cereals, olive oil as the main added lipid, moderate consumption of alcohol (mainly wine and during meals) and low consumption of red meat and dairy products. It is doubtless the most analyzed dietary pattern and accumulating evidence support a potential protective role against cognitive decline and dementia, although there are still inconsistencies in the reported data. In particular, the findings from prospective studies and very recent systematic reviews and meta-analyses suggested that adherence to the MeDi fulfilling the whole-diet approach may affect not only the risk of AD, but also of predementia syndromes and their progression to overt dementia ⁶. In the last two years, in the EPIC study, in a cohort of Greek elderly population that still adheres to the traditional MeDi, it was demonstrated that closer adherence to MeDi was associated with less decline in Mini Mental State Examination (MMSE) performance over a period of about 7 years, especially in individuals aged 75 years or older (Tab. I) ⁷.

Other emerging dietary patterns are the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) diets (Tab. I). The DASH diet is characterized by low consumption of saturated fat and commercial pastries and sweets, and higher intake of dairy than in the MeDi. In the last three years, in the Memory

and Aging Project (MAP) study, a prospective study on older adults with 4 years of follow-up, the DASH pattern was associated with slower rates of cognitive decline. In particular, a 1-unit-higher DASH score, was equivalent of being at least 4.4 years younger (Tab. I) ⁸. These results were in line with those of Morris and colleagues, in the same MAP study, in which higher adherence to DASH diet was related with greater reduction of incident AD rather than higher adherence to MeDi (54% and 39% reduction, respectively) (Tab. I) ⁹.

The MIND diet was based on the dietary components of the MeDi and DASH diet with modifications that highlight the foods and nutrients shown to be associated with dementia prevention. Among the MIND diet components, there are 10 brain healthy food groups (green leafy vegetables, other vegetables, nuts, berries, beans, whole grains, seafood, poultry, olive oil, and wine) and five unhealthy food groups (red meats, butter and stick margarine, cheese, pastries and sweets, and fried/fast food). Hence, MIND diet uniquely specifies consumption of berries and green leafy vegetables and does not specify high fruit consumption (both DASH and MeDi), high dairy (DASH), high potato consumption, or > 1 fish meal per week (MeDi). Other recent findings from the MAP study suggested that higher MIND diet score was associated with slower decline in cognitive abilities (Tab. I) ¹⁰. The rate reduction for persons in the highest tertile of diet scores compared with the lowest tertile was the equivalent of being 7.5 years younger. MIND diet score was also more predictive of cognitive decline than either of the other (DASH and MeDi) diet scores (Tab. I) ¹⁰. Furthermore, in a follow-up of 4.5 years of the MAP study, participants with higher and moderate adherence to MIND diet had statistically significant reduction in AD rate compared with those with lower adherence (53% and 35% respectively) ⁹. Instead only the highest tertiles of the DASH and MeDi scores were significantly associated with incident AD reduction (Tab. I) ⁹.

Despite the promising results of these two diets, to date, we have brain imaging data only on the correlation with the MeDi (Tab. I). The few cross sectional studies carried out on cognitively normal people showed that higher adherence to MeDi was related to greater magnetic resonance imaging (MRI)-based cortical thickness in AD-vulnerable regions and larger brain volumes. MeDi effects on MRI biomarkers were significant in the left, but not in the right hemisphere, and were most pronounced in entorhinal cortex, orbito-frontal cortex and posterior cingulate cortex (Tab. I) ¹¹. Higher adherence to a Mediterranean dietary pattern was associated with larger MRI measures of cortical thickness and with several individual region of interests (ROIs) that undergo age-related or AD-related neurodegeneration, was

marginally associated with temporal and AD signature cortical thickness and was not associated with hippocampal volume (Tab. I) ¹². This finding may be explained with the observation from the Alzheimer's Disease Neuroimaging Initiative in which presymptomatic individuals had significantly reduced cortical thickness in AD vulnerable regions compared to controls but did not differ in regard to hippocampal volume ¹³. In the Washington Heights-Inwood Community Aging Project (WHICAP), higher MeDi adherence was associated with less brain atrophy (larger total brain volume, total gray matter volume, total white matter volume), with an effect similar to 5 years of aging (Tab. I) ¹⁴.

To date, only one prospective imaging-diet study on older adults was conducted (Tab. I) ¹⁵, confirming other results coming from cross-sectional studies. In fact, Jacka and colleagues, in the Personality and Total Health Through Life Study found that healthy "prudent" dietary pattern characterized by intake of fresh vegetables, salad, fruit and grilled fish was associated with a larger left hippocampal volume on MRI over 4 years of follow-up (Tab. I) ¹⁵. In particular, every one standard deviation (SD) increase in healthy "prudent" dietary pattern was associated with a 45.7 mm³ larger left hippocampal volume ¹⁵. While higher consumption of an unhealthy "Western" dietary pattern characterized by intake roast meat, sausages, hamburgers, steak, chips, crisps and soft drinks was independently associated with a 52.6 mm³ smaller left hippocampal volume ¹⁵. The difference in hippocampal volume between those classified with a healthy and or unhealthy diet was 203 mm³, a difference which corresponds to 62% of the average decline in left hippocampal volume observed over the 4-year period. It was found no interaction between right hippocampus volumes and the two dietary factor scores (Tab. I) ¹⁵.

Other studies suggested a strong impact of healthy diets on structural connectivity in older subjects, rather than gray and white matter volumes. In fact, through diffusion tensor imaging (DTI) at MRI examination was seen that higher adherence to the MeDi was associated with preserved white matter microstructure in multiple brain areas and appeared to delay cognitive aging by up to 10 years (Tab. I) ¹⁶. None of the individual components was strongly associated with DTI parameters, supporting the hypothesis that overall diet quality may be more important to preserve brain structure than any single food. These results suggested the involvement of vascular pathways rather than neurodegenerative mechanisms in the link between the MeDi and lower risks of cognitive decline and related diseases (Tab. I) ¹⁶.

The importance of components of prudent dietary pattern (vegetables, fruit, cooking/dressing oil, cereals and legumes, whole grains, rice/pasta, fish, low-fat dairy,

poultry and water) was confirmed by the observation that the MMSE decline associated with Western diet may be attenuated by high adherence to prudent pattern (Tab. I) ¹⁷. In fact, the decline became less pronounced (53.5%) and non-significant among people who had a high adherence to both the prudent and Western patterns. Furthermore, Western dietary pattern score was significantly associated with all-cause mortality in the older age cohorts (Tab. I) ¹⁷. Instead, people who followed healthiest diet were slightly older, more active, less likely to smoke, had a lower body mass index (BMI), normal serum creatinine, and had higher MMSE score (Tab. I) ¹⁸. The healthiest diet was associated with a reduction of about 24% in risk of cognitive decline and in particular was shown a significant association between higher diet quality and reduced risk of decline in 4 components of the MMSE including copying, attention and calculation, registration and writing (Tab. I) ¹⁸. The brain damage related to an unhealthy diet may be based on a pro-inflammatory mechanism. Ozawa and colleagues detected an inflammatory dietary pattern (IDP) characterized by higher intake of red meat, processed meat, peas and legumes and fried food, and lower intake of whole grains which correlated with elevated interleukin(IL)-6 (Tab. I) ¹⁹. It was related with greater decline in reasoning and in global cognition and, in a cross-sectional analysis at baseline, a two times greater risk of having a decline of 3 points or more in MMSE (Tab. I) ¹⁹.

FOODS, FOOD GROUPS, AND LATE-LIFE COGNITION

FISH AND SEAFOOD

The emerging data from the last studies on the correlation between fish and seafood consumption and cognitive decline are conflicting. Significant correlations were found in some particular population subgroups [≥ 65 years and apolipoprotein E (*APOE*) $\epsilon 4$ carriers]. Age significantly modified the association between fish consumption and cognitive change (Tab. II) ²⁰. In fact, no association was observed among adults aged 55-64 years. Conversely, adults aged ≥ 65 years, that consuming ≥ 1 servings/week fish (i.e., 100 g) had a reduction of cognitive decline rate ²⁰. Compared with individuals who consumed < 1 serving/week fish, the mean annual rate of global cognitive decline was reduced by 0.35 point equivalent to the disparity associated with 1.6 years of age. Removing shellfish and/or preserved fish from the total fish did not appreciably alter the results (Tab. II) ²⁰.

Interestingly, Morris and colleagues showed that, in *APOE* $\epsilon 4$ carriers, seafood consumption ≥ 1 meals/

Table 1. Observational studies on the relationship among dietary patterns and late-life cognitive disorders (2014-2016).

References	Study design	Sample	Outcome	Cognitive and nutritional assessment	Principal results
Dietary patterns					
Trichopoulou et al., 2015 ⁷	Prospective cohort study Follow-up: average 6.6 years	n = 401 older subjects from EPIC-Greece cohort (mean age 74 years)	Association of MeDi or any particular MeDi component with cognitive decline	FFQ (150 items) MeDi score MMSE; MMSE change (cMMSE)	Decline in MMSE performance inversely associated with adherence to traditional MeDi. Only vegetable consumption, showed significant inverse association with cognitive decline
Tangney et al., 2014 ⁸	Prospective cohort study Follow-up: mean of 4.1 years	n = 826 older persons (mean age 81.5 years)	Association between DASH diet or MeDi and cognitive decline	MAP FFQ (144 item) DASH diet MeDi Score Global composite score of 19 cognitive tests	DASH and MeDi patterns associated with a slower rate of global cognitive decline
Morris et al., 2015 ⁹	Prospective cohort study Follow-up: mean of 4.5 years	n = 923 participants (58 to 98 years old)	Association of MIND diet, DASH diet and MeDi with incident AD	AD diagnosis at each annual evaluation FFQ (144 items) MIND diet score DASH diet score MeDi score	High adherence to all three diets may reduce AD risk. Moderate adherence to the MIND diet may also decrease AD risk
Morris et al., 2015 ¹⁰	Prospective cohort study Follow-up: mean of 4.7 years	n = 960 participants (mean age 81.4 years)	Association of MIND diet score with cognitive decline Comparing the estimated effects of MIND diet to those of the MeDi and DASH diet	Annual cognitive assessments, global and composite scores of 5 domains FFQ (144 items) at each annual clinical evaluation MIND diet score DASH diet score MedDiet score	The MIND score positively associated with slower decline in global cognitive score and with each of five cognitive domains. The MIND diet score more predictive of cognitive decline than either of the other diet scores
Mosconi et al., 2014 ¹¹	Cross-sectional study	n = 52 clinically and cognitively normal subjects (mean age 54 years)	Associations between adherence to a MeDi and structural MRI-based brain atrophy in key regions for AD	Semiquantitative FFQ (61-item) MeDi score MRI CT measures for 5 ROIs	Subjects with higher MeDi adherence showed greater thickness of AD-vulnerable ROIs as compared to subjects with lower MeDi adherence
Staubo et al., 2016 ¹²	Cross-sectional study	n = 672 cognitively normal participants (mean age: 79.8 years)	Association of MeDi score and MeDi components with MRI measures of CT for the four lobes separately and averaged	FFQ (128 items) MeDi score MRI CT measures	Higher MeDi score associated with larger CT. Higher legume, fish, vegetables, whole grains or cereals intakes were associated with larger CT
Gu et al., 2015 ¹⁴	Cross-sectional study	n = 674 elderly adults without dementia (mean age 80.1 years)	Association between higher adherence to MeDi with larger MRI measured brain volume or CT	FFQ MeDi score MRI scans for TBV, TGMV, TWMV and mCT	Higher MeDi adherence associated with larger TBV, TGMV and TWMV. Higher fish intake associated with larger TGMV and mCT. Lower meat intake associated with larger TGMV and TBV



References	Study design	Sample	Outcome	Cognitive and nutritional assessment	Principal results
Dietary patterns					
Jacka et al., 2015 ¹⁵	Prospective cohort study Follow-up: 4 years	n = 255 older adults (mean age 62.6 years)	Association between dietary patterns and hippocampal volume Association between diet and differential rates of hippocampal atrophy over time	FFQ “Prudent” (healthy) diet and “Western” (unhealthy) diet. Two MRI scans	Lower intakes of nutrient-dense foods and higher intakes of unhealthy foods each independently associated with smaller left hippocampal volume. No evidence that dietary patterns influenced hippocampal volume decline
Pelletier et al., 2015 ¹⁶	Prospective cohort study Follow-up: MRI performed mean of 8.9 years after dietary assessment	n = 146 non-demented participants (mean age 73.0 years)	Association between higher adherence to the MeDi and preserved brain GM volume and WM microstructure	FFQ (148 items) MeDi score MRI Brain GM and WM volumes, and WM microstructure Cognitive assessment	Adherence to the MeDi significantly associated with preserved WM microstructure in extensive areas, a gain in structural connectivity related to strong cognitive benefits
Shakersain et al., 2016 ¹⁷	Population-based longitudinal study Follow-up: 6 years.	n = 2223 dementia-free older adults (mean age 70.6 years)	Impact of dietary patterns on cognitive decline	MMSE Semiquantitative FFQ (98 items) Two dietary patterns: 1) the “Western”, 2) the “prudent”; factor scores for each dietary pattern categorized into quintiles	Highest adherence to prudent pattern related to less MMSE decline, whereas the highest adherence to Western pattern was associated with more MMSE decline. Decline associated with Western diet, attenuated by high adherence to prudent pattern
Smyth et al., 2015 ¹⁸	Prospective cohort study Follow-up: 56 months	n = 27860 patients (mean age 66.2 years)	Association of dietary factors and cognitive decline in a population at high risk of cardiovascular disease	MMSE FFQ (20 items) mAHEI	Highest quintile of mAHEI (healthiest diet) associated with a reduced risk of cognitive decline
Ozawa et al., 2016 ¹⁹	Prospective cohort study Follow-up: 10 years	n = 5083 patients (mean age 56 years)	Investigate dietary patterns associated with inflammation Association of such diet with cognitive decline	Alice Heim 4-I, short-term verbal memory, phonemic and semantic fluency, MMSE FFQ (127 item) Serum IL-6 IDP	Dietary pattern with higher intake of red and processed meat, peas, legumes and fried food, and lower intake of whole grains associated with higher inflammatory markers and accelerated cognitive decline

Abbreviation: MeDi: mediterranean diet; FFQ: food frequency questionnaire; MMSE: mini-mental state examination; DASH: dietary approach to stop hypertension; MIND: mediterranean-DASH diet intervention for neurodegenerative delay; AD: Alzheimer's disease; MRI: magnetic resonance imaging; CT: cortical thickness; ROI: region of interest; TBV: total brain volume; TGMV: total gray matter volume; TWMV: total white matter volume; mCT: mean cortical thickness; GM: gray matter; WM: white matter; mAHEI: modified alternative healthy eating index; IL-6: interleukin-6; IDP: inflammatory dietary pattern

week was correlated with lesser burden of brain AD neuropathology, including lower density of neuritic plaques, less severe and widespread neurofibrillary tangles, and lower neuropathologically defined AD (Tab. II)²¹. Furthermore, some studies demonstrated an association between fish consumption and MRI biomarkers

(Tab. I)^{12,14}. In the Mayo Clinic Study of Aging, higher fish intake was associated with larger cortical thickness summary measures for parietal and average lobar cortical thickness and marginally associated with AD signature cortical thickness, temporal and frontal cortical thickness, and also associated with several individual

Table II. Observational studies on the relationship among foods, food-groups, and late-life cognitive disorders (2014-2016).

References	Study design	Sample	Outcome	Cognitive and nutritional assessment	Principal results
Foods and food-groups					
Qin et al., 2014 ²⁰	Prospective cohort study Follow-up: mean 5.3 years.	n = 1566 community-dwelling adults (mean age 63 years).	Association of fish consumption with decline in cognitive function.	Diet measured by 3-d 24-h recalls TICSm: global and composite cognitive scores	Age significantly modified the association between fish consumption and cognitive change. At least 1 serving/wk fish predicted slower cognitive decline among ≥ 65 years
Morris et al., 2016 ²¹	Cross-sectional analyses	n = 286 autopsied brains (mean age at death 89.9 years)	Relation of seafood consumption with brain mercury levels Association of seafood consumption or brain mercury levels with brain neuropathologies	Brain autoptical assessment Mercury and selenium brain tissue concentrations FFQ for consumption of seafood and n-3 fatty acids in the 4.5 years before death	Seafood consumption (> 1 meal[s]/week) significantly correlated with less AD pathology. Seafood consumption correlated with higher brain levels of mercury, these levels not correlated with brain neuropathology
Danthiir et al., 2014 ²²	Cross-sectional study	n = 390 community-dwelling cognitively normal older adults (mean age 73.1 years)	Associations between multiple domains of cognition and erythrocyte membrane n-3 PUFA proportions and historical and contemporary fish intake in older adults	n-3 FA analysis in erythrocyte membranes Fish consumption (current: FFQ, historical: LDQ) Cognitive tests	No evidence that higher proportions of long-chain n-3 fatty acids or fish intake benefits cognitive performances. Negative effect of fish intake in childhood and older age on older-age cognitive functions
Dong et al., 2016 ²³	Cross-sectional study	n = 894 Chinese adults, normal and with mild cognitive impairment (mean age 62.9 years)	Association between nuts, vegetables and fruit-rich diet and the risk of cognition impairment	MoCA FFQ of 13 food groups totally 41 items	The nuts and cooking oil intake of MCI patients were less than the normal subjects. Fruit and vegetable intake will benefit orientation, name and attention ability. Fruit and vegetable juice drinking will benefit abstraction ability
Pastor-Valero et al., 2014 ²⁴	Cross-sectional population-based study	n = 1849 low-income elderly subjects with CI (n = 147, mean age 77.5 years) and without (n = 1702, mean age 71.5 years)	Association between fruit and vegetable intake and cognitive impairment	CSI-D FFQ: 10 vegetables items, and 17 fruit and natural juices items Monthly consumption of fish	Daily intakes of fruit and vegetable ≥ 400 grams/day associated with decreased prevalence of cognitive impairment. Fish consumption not associated with cognitive impairment
Zhao et al., 2015 ²⁵	Cross-sectional study	n = 404 patients, aged 60 years old or above, with or without MCI	Association of dietary and lifestyle patterns with MCI	MoCA FFQ	Higher daily intake of eggs and marine products significantly decreased odds of suffering from MCI



References	Study design	Sample	Outcome	Cognitive and nutritional assessment	Principal results
Foods and food-groups					
Xu et al., 2015 ²⁶	Cross-sectional study	n = 517 Chinese elderly with possible dementia (22.1%, mean age 73.8 years) and without CI (77.9% mean age 65.7 years)	Effect of weekly tofu intake on cognitive performance	HVLT IR FFQ	High intake of tofu negatively related to cognitive performance. Consumption of meat and green vegetables independently associated with better memory function
O'Brien et al., 2014 ²⁸	Population-based prospective cohort study. Follow-up: 6 years	n = 16010 women without a history of stroke (mean age 74 years); final sample n = 15467	Association of long-term intake of nuts with cognition	FFQ TICS, immediate and delayed recalls, category fluency, delayed recall of the TICS 10-word list and the digit span backwards test	Increasingly higher total nut intake (≥ 5 nuts/week vs never < 1/month) related to increasingly better overall cognition at older ages
Solfrizzi et al., 2015 ³⁰	Population-based prospective cohort study Follow-up: 3.5 years	5632 subjects, aged 65-84 year old; final sample n = 1445	Association between change or constant habits in coffee consumption and the incidence of MCI	FFQ MCI diagnosis	Cognitively normal older individuals who increased their coffee consumption had a higher rate of developing MCI, while a constant in time moderate coffee consumption was associated to a reduced rate of the incidence of MCI
Araújo et al., 2015 ³¹	Cross-sectional study	n = 14563 public service workers (mean age 51.9 years)	Relation of coffee consumption to performance on specific domains of cognition	Cognitive tests from CERAD battery FFQ Type of coffee, caffeine content, additional items added	Coffee consumption associated with better cognitive performance on memory and efficiency of searching in long-term memory only in elderly, but without a dose response relationship
Beydoun et al., 2014 ³²	Prospective cohort study Follow-up: ~2 visits/person each ~2 years intervals	n= 628-1305 subjects free of dementia (mean age 66.8 years)	Association of caffeine and alcohol intake with cognitive performance	MMSE, BVRT, CVLT, VFT-L, VFT-C, TMT A and B, DS-F, DS-B 7-d dietary records for caffeine and alcohol intakes NAS	Stratum-specific associations by sex and baseline age, between caffeine and alcohol intake and cognition. Putative beneficial effects of caffeine and NAS on global cognition, verbal memory, and attention, and mixed effects of alcohol on letter fluency, attention, and working memory



References	Study design	Sample	Outcome	Cognitive and nutritional assessment	Principal results
Foods and food-groups					
Travassos et al., 2015 ³³	Cross-sectional multicentre study	n = 88 patients with AD (58%) or MCI (42%) (mean age 66.3 years)	Association of caffeine consumption with the CSF biomarkers, particularly A β	FFQ Caffeine and main active metabolites in the CSF and plasma A β ₁₋₄₂ , total tau and phosphorylated tau in the CSF	Caffeine consumption not modify the levels of CSF biomarkers. Theobromine associated with a favorable A β profile in the CSF
Kesse-Guyot et al., 2014 ³⁴	Prospective cohort study Follow-up: mean 13.6 years	n = 2983 middle-aged adults from the SU.VI.MAX 2 study (mean age at cognitive evaluation 65.5 years)	Association between a CDP and cognitive performance	Plasma concentrations of carotenoids 24 h dietary record every 2 months RRR statistical method 6 neuro-psychological tests	Positive correlation between CDP and consumption of orange- and green-coloured fruits and vegetables, vegetable oils and soup. Positive association between a CDP and cognitive function (executive functioning and episodic memory)

Abbreviation: TICSm: telephone interview of cognitive status modified; FFQ: food frequency questionnaire; AD: Alzheimer's disease; PUFA: polyunsaturated fatty acids; LDQ: lifetime diet questionnaire; MoCA: Montreal cognitive assessment; MCI: mild cognitive impairment; CSI-D: community screening instrument for dementia; HVLIT IR: Hopkins verbal learning test immediate recall; CERAD: consortium to establish a registry for Alzheimer's disease; MMSE: mini-mental state examination; BVRT: Benton visual retention test; CVLT: California verbal learning test; VFT-L and VFT-C: verbal fluency tests - letter and categorical; TMT A and B: trail making test parts A and B; DS-B and DS-F: digit span forward and backward tests; NAS: nutrient adequacy score; CSF: cerebrospinal fluid; A β : β -amyloid; CDP: carotenoid-rich dietary pattern; RRR: reduced rank regression

cortical thickness measures: precuneus, superior parietal, posterior cingulate, supramarginal, middle temporal, and inferior parietal and marginally associated with fusiform CT¹². Higher fish consumption was also related with larger total gray matter volume¹⁴. Fish consumption was associated with a slower decline in composite and verbal memory scores (Tab. II)²⁰. Other studies did not suggest evidence that higher fish intake may impact positively cognitive performance in cognitively normal older adults^{24 25} or in those with cognitive impairment (Tab. II)^{23 24}. However, Dong and colleagues found that cognitively normal Chinese older subjects consumed more fish than mild cognitive impairment (MCI) subjects²³ and Zhao and colleagues found that higher consumption of marine products was associated with a significantly decreased probability of suffering from MCI (Tab. II)²⁵. Of note, Danthiir and colleagues demonstrated that more frequent consumption of total fish (oily and white) was associated with slower cognitive speed for the constructs of inhibition, simple/choice reaction time, reasoning speed, and memory scanning (Tab. II)²². More frequent consumption of oily fish significantly associated with worse inhibitory processes, similarly, consumption of white fish significantly and negatively predicted simple/choice reaction time (Tab. II)²². Danthiir and colleagues²² hypothesized that

the negative trends observed between cognitive performance and fish consumption were due to neurotoxic contaminants in fish, such as methylmercury. However, as seen above, Morris and colleagues found that higher brain levels of mercury were not correlated with brain neuropathology (Tab. II)²¹.

FRUIT AND VEGETABLES

In Greece, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, among the components of MeDi, only vegetable consumption exhibited a significant inverse association with cognitive decline (Tab. I)⁷. The diet-low in fruit and vegetable might increase the risk of cognitive function decline in older adults (Tab. II)²³. In fact, adherence to WHO recommendations for daily intakes of fruit and vegetable, that are eating 5 or more portions of fruit and/or vegetables a day (≥ 400 g/day), were significantly associated with a 47% decreased prevalence of cognitive impairment (Tab. II)²⁴. In contrast to these findings, Xu and colleagues found that among older adults (≥ 68 years of age) being vegetarian (not eating meat), the risk for cognitive impairment increased almost 4-fold (Tab. II)²⁶. Imaging data in older cohort showed that higher intake of total vegetables was associated with larger dorsolateral prefrontal and superior parietal cortical thickness,

while vegetables without legumes were associated with larger middle temporal, superior parietal, and dorsolateral prefrontal cortical thickness (Tab. I) ¹². In contrast, fruit consumption was negatively associated with inferior parietal, supramarginal, superior parietal, parietal, and precuneus cortical thickness (Tab. I) ¹². These findings are in keeping with result of another study in which higher fruit intake was associated with lower temporal and hippocampal volumes (Tab. I) ¹⁴. This is probably due to high content of simple sugars and a high glycemic index of several fruits and so the effects of carbohydrate component on increased risk of MCI ²⁷. In older adults, fruit intake would benefit name ability and attention level, while vegetables intake would benefit orientation ability (Tab. II) ²³. Finally, consumption of green vegetables was independently associated with better memory function and among older elderly (≥ 68 years of age) it reduced the risk for cognitive impairment by almost 20% (Tab. II) ²⁶.

NUTS

Nuts are rich in polyunsaturated fatty acids (PUFA) (omega 3 and 6) and monounsaturated fatty acids (MUFA), and also contain a significant amount of minerals such as phosphorus, potassium, magnesium, calcium, iron and sulfur, and vitamin such as B1, B2, B6 and E. It was found the nut intake of MCI patients was less than that of cognitively normal subjects (Tab. II) ²³. In fact, a study performed on older women found that higher total nut intake (i.e., ≥ 5 /week) over the long term was associated with modestly better cognitive performance (Tab. II) ²⁸. Increasingly higher total nut intake was related to increasingly better overall cognition at older ages. Considering that one year of age was associated with a mean decline of 0.04 standard units on both the global and verbal composite scores, therefore, the mean differences comparing the highest to lowest categories of nut intake were equivalent to approximately two years of cognitive aging (Tab. II) ²⁸. In the same study, it was found a suggestion that those who consumed walnuts 1 to 3 times per month had better cognition than those who consumed walnuts less than once per month, but there was no overall trend of increasingly better cognitive performance with increasing walnut intake (Tab. II) ²⁸. Dong and colleagues also showed that nut intake would benefit delayed memory (Tab. II) ²³.

COFFEE AND CAFFEINE INTAKE

As summarized in a recent systematic review, several cross-sectional and longitudinal population-based studies suggested a protective effect of coffee, tea, and caffeine use against late-life cognitive impairment/decline, although the association was not found in all cognitive domains investigated and there was a lack of

a distinct dose-response association, with a stronger effect among women than men ²⁹. The findings on the association of coffee, tea, and caffeine consumption or plasma caffeine levels with incident MCI and its progression to dementia were too limited to draw any conclusion ²⁹. Furthermore, for dementia and AD prevention, some studies with baseline examination in midlife pointed to a lack of association, although other case-control and longitudinal population-based studies with briefer follow-up periods supported favorable effects of coffee, tea, and caffeine consumption against AD ²⁹. Recent findings from the Italian Longitudinal Study on Aging (ILSA) suggested that cognitively normal older individuals who increased their coffee consumption had a higher rate of developing MCI, while a constant in time moderate coffee consumption was associated to a reduced rate of the incidence of MCI (Tab. II) ³⁰. Among older adults in Brasil, coffee consumption was associated with better cognitive performance on memory and efficiency of searching in long-term memory (drinking 2-3 cups of coffee per day was associated with about a 3% increase in the mean number of words remembered on the learning, recall and word recognition tests) (Tab. II) ³¹. Also, drinking ≥ 3 cups/day of coffee was associated with an increase of about 1.23 words in the mean number of words pronounced in the semantic verbal fluency test ³¹. However, in this Brazilian study, Araujo and colleagues did not find indication of a dose response relationship in these associations ³¹. In another Chinese study on cognitively normal and MCI adults, no significant association was detected between drinking of coffee and cognitive function (Tab. II) ²³. Another aspect of coffee assumption is the role of its component such as the caffeine. Coffee is a rich source of caffeine, which acts as a psychoactive stimulant. In a cross sectional analysis, Beydoun and colleagues found that caffeine intake was associated with better global cognitive function (MMSE) at baseline for patients ≥ 70 years (Tab. II) ³². However, in a study that evaluated the association of caffeine consumption with the cerebrospinal fluid (CSF) biomarkers, particularly β -amyloid ($A\beta$), in AD and MCI patients, no significant difference was found in daily consumption of caffeine between MCI and AD patients, with no correlation between caffeine consumption and $A\beta_{42}$ in the CSF (Tab. II) ³³. In the same study, theobromine, xanthine formed upon caffeine metabolism and also directly ingested from chocolate products, was associated with a favorable $A\beta$ profile in the CSF (Tab. II) ³³. Interestingly, theobromine in the CSF did not correlate with caffeine consumption, theobromine consumption, or the levels of caffeine and other xanthines in the plasma, but instead it correlated with levels of caffeine, theophylline, and paraxanthine in the CSF, suggesting that it may be formed by central metabolic pathways ³³.

Eggs

Eggs have a high content of proteins and lipids in particular cholesterol. For this reason, they are traditionally considered an unhealthy food. However, eggs have also a significant amount of vitamins A, B6, B12, riboflavin, folic acid, choline, iron, calcium, phosphorus and potassium.

In a recent study, higher daily intake of eggs reduced of about 3% the odds of suffering from MCI (Tab. II)²⁵. Instead, in the Chinese study of Dong and colleagues, no significant association was detected between intake of eggs with cognitive function in normal and MCI adults (Tab. II)²³.

TOFU

Tofu is a common food in most of the Far East. It is obtained from curdling of the juice extracted from soybeans. It has a high proteins and PUFA content. Higher weekly intake of tofu was associated with worse memory performance, furthermore among older elderly (≥ 68 years of age), high tofu intake increases the risk (of almost 30%) of cognitive impairment indicative of dementia (Tab. II)²⁶.

MEAT

Red meat is a classical element of Western diet that, as mentioned previously, was associated with worse cognitive performance in several studies (Tab. I)^{15 17 19}. Consistent with these findings, a negative association of red meat with inferior and superior parietal cortical thickness was found (Tab. I)¹². However, this concept should be partially reviewed. In fact, in the last years, eating meat (not being vegetarian) was independently associated with better memory function and in older age (≥ 68 years of age) with a four-fold decrease in risk of possible dementia (Tab. II)²⁶. Furthermore, Staubo and colleagues also observed that higher red meat intake was associated with larger entorhinal cortical thickness (Tab. I)¹². This it could relate to some beneficial components of lean red meat (iron, protein, MUFA, PUFA, cobalamine) and beneficial effects in increasing satiety and reducing weight gain. In the Chinese study of Dong and colleagues, no significant association was detected between intake of light or red meat with cognitive function in normal and MCI adults (Tab. II)²³.

OIL

Dong and colleagues, in their Chinese cohort, found that oil intake of MCI patients was less than the normal subjects (29.76 vs 35.20 mL cooking oil per day), in particular would have a positive impact on visual-spatial ability (Tab. II)²³. Vegetable oils are rich in carotenoids, and in the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study carotenoids were

associated with higher cognitive performance (Tab. II)³⁴. Extra-virgin olive oil (EVOO) is one of the main elements of MeDi, and clinical trials and population studies indicated that this dietary pattern and its main lipid component EVOO could have a protective role against AD³⁵.

LEGUMES

Dong and colleagues, in their Chinese cohort, showed that normal subjects consumed more legumes and legume products than MCI subjects, demonstrating that intake of legumes and legume product would benefit overall cognition level (Tab. II)²³. These data were confirmed by imaging biomarkers, in fact, Staubo and colleagues also found that higher intake of legumes was associated with larger parietal and occipital cortical thickness, and with larger thickness in ROIs for superior parietal, inferior parietal, precuneus, and lingual cerebral cortex (Tab. I)¹².

GRAIN

In their imaging biomarker study, Staubo and colleagues also showed that intake of whole grains or cereals was associated with larger temporal pole and superior temporal cortical thickness (Tab. II)¹². Conversely, lower intake of whole grains was associated with higher inflammatory markers (IL-6) and accelerated cognitive decline at older age in the Whitehall II prospective cohort study (Tab. II)¹⁹. However, in the Chinese cohort of Dong and colleagues, no significant association was detected between intake of whole grain and cognitive function in normal and MCI adults (Tab. II)²³.

ALCOHOL

Recent findings from the Baltimore Longitudinal Study of Aging suggested that alcohol intake was associated with slower improvement on letter fluency and global cognition among those aged < 70 years at baseline (Tab. II)³². Conversely, alcohol intake was associated with better attention and working memory performance, particularly among men and individuals ≥ 70 years at baseline (Tab. II)³². Compared with moderate consumption (14 to 28 g/d), individuals with higher alcohol intake (> 28 g/d) had faster decline or slower improvement on the MMSE, particularly among women and in the older group. Overall, among men, and for those aged ≥ 70 years, lower alcohol intake (< 14 g/d) compared with moderate consumption (14 to 28 g/d) was associated with poorer performance in working memory (Tab. II)³². In the younger group, consuming < 14 g/day was associated with slower decline or faster improvement in the letter fluency compared with a moderate intake of 14 to 28 g/day. Similar pattern was showed also for attention and executive functioning (Tab. II)³².

CONCLUSIONS AND FUTURE DIRECTIONS

In the last three years, the association between diet and cognitive function or dementia has been largely investigated. However, more recently, the NIA-AA guidelines for AD and cognitive decline due to AD pathology introduced some evidence suggesting a direct relation between diet and changes in the brain structure and activity. Several studies focused on the role of the dietary patterns on late-life cognition, with accumulating evidence that higher adherence to a Mediterranean-type diet was associated with decreased cognitive decline, although the MeDi combines several foods, micronutrients, and macronutrients already separately proposed as potential protective factors against dementia and MCI. Moreover, also other emerging healthy dietary patterns such as the DASH and the MIND diets were associated with slower rates of cognitive decline and significant reduction in AD rate. Furthermore, some food groups traditionally considered harmful such as eggs and red meat have been partially rehabilitated, while there is still a negative correlation of cognitive functions with added sugars and trans fatty acids, nutrients also increasing the cardiovascular risk.

However, some limits should be reported for this review article. Heterogeneity exists in the quantification of individual items as well among the different diets background of the populations investigated, especially in view of different geographical areas, setting of dietary patterns such as the Mediterranean countries in which a large segment of the population still adheres to MeDi. Heterogeneity in time between the two assessments, among studies using paired assessments (or a single assessment) several years after study population enrollment. Nevertheless, these data represent a brick in the construction of the building of the causal link between dietary habits and cognitive impairment.

The absence of causal etiological therapies against AD leads to seek multimodal alternative strategies, increasing the interest in the potential for prevention of dementia by targeting modifiable risk factors. It is now evident that dietary habits influence diverse cardiometabolic risk factors, including not only obesity and low-density lipoprotein cholesterol, but also blood pressure, glucose-insulin homeostasis, lipoprotein concentrations and function, oxidative stress, inflammation, endothelial health, hepatic function, adipocyte metabolism, pathways of weight regulation, visceral adiposity, and the microbiome. Whereas decades of dietary recommendations focused on dietary fat and single vascular risk factors (e.g., hypertension, blood cholesterol etc.) and current dietary discussions are often worried about total calories and obesity, the full health impact of diet extends far beyond these pathways. Considering strategies of

prevention of AD could be complicated and take to negative results. A second key lesson is the importance to point out on specific foods and overall diet patterns, rather than single isolated nutrients, for cognitive impairment. A food-based approach also better facilitates public guidance and minimizes industry manipulation. Nevertheless the complexity of the stake, the correction of modifiable risk factors to expect 'the compression of cognitive morbidity' still remains a desirable goal of public health. Larger observational studies with longer follow-up periods should be encouraged, addressing other potential bias and confounding sources, so hopefully opening new ways for diet-related prevention of dementia and AD.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REVIEW

Dietary intervention and prevention of cognitive-related outcomes in healthy older adults without cognitive dysfunction

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In the last decade, the association between diet and cognitive function/dementia has been largely investigated in observational studies, while there was a lack of evidence from randomized clinical trials (RCTs) on the prevention of late-life cognitive disorders through dietary intervention in cognitively healthy older adults. In the present article, we reviewed RCTs published in the last three years (2014-2016) exploring nutritional intervention efficacy in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years using different levels of investigation (i.e., dietary pattern changes/medical food/nutraceutical supplementation/multidomain approach and dietary macro- and micronutrient approaches). From the included RCTs, there was moderate evidence that intervention through dietary pattern changes, medical food/nutraceutical supplementation, and multidomain approach improved specific cognitive domains or cognitive-related blood biomarkers. Moreover, there was high evidence that protein supplementation improved specific cognitive domains. For fatty acid supplementation, mainly long-chain polyunsaturated fatty acids, there was emerging evidence suggesting an impact of this approach in improving specific cognitive domains, MRI findings, and/or cognitive-related biomarkers also in selected subgroups of older subjects although some results were conflicting. Moreover, there was convincing evidence of an impact of non-flavonoid polyphenol and flavonoid supplementations in improving specific cognitive domains and/or MRI findings. Finally, there was only low evidence suggesting efficacy of intervention with homocysteine-related vitamins in improving cognitive functions, dementia incidence, or cognitive-related biomarkers in cognitively healthy older subjects.

Key words: Alzheimer's disease, Dementia, Dietary pattern, Medical food, Nutraceuticals, Healthy diet, Mediterranean diet, Macronutrients, Micronutrients, Mild cognitive impairment, Prevention

INTRODUCTION

Given the absence of available disease-modifying therapies for the treatment of Alzheimer's disease (AD) ¹, there is a great need in preventing and delaying the onset of cognitive impairment in healthy

older subjects. In the last decade, many observational studies have shown a wide variety of potentially modifiable risk factors for cognitive impairment, that have been proposed as targets for preventive strategies ². In addition to cardiovascular risk factors, psychological conditions, education level, engagement

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in social and mentally stimulating activities, sensory changes, lifestyle including diet, physical activity and voluptuary habits has obtained a crucial role^{2,3}. In particular, in the last years, a growing body of evidence has been focused on the association between dietary habits and cognitive performance³. Several nutritional supplements have been studied for their potential role as neuroprotective interventions useful in delaying the onset of cognitive decline in older adults⁴⁻⁷. Observational studies have showed that specific micro- or macronutrients such as polyunsaturated fatty acids (PUFAs), vitamins, flavonoids are associated with a significantly reduced risk of dementia^{3,8}. This protective effect could be mediated by several pathobiological pathways involved in AD development as amyloid- β (A β) deposition, neurofibrillary degeneration, synapse loss, inflammation, oxidative stress, mitochondrial dysfunction, loss of vascular integrity and neuronal injury⁸. Furthermore, several evidences underlined that foods and nutrients properly combined into specific dietary patterns may act synergistically amplifying the health effects of single components^{3,9-14}. In particular, the Mediterranean dietary pattern has been the first and widely well studied and proposed in epidemiological studies, showing a strong protective role in cardiovascular and cognitive aging^{3,9-11}. Considering these promising results and the growing interest in this field, several randomized clinical trials (RCTs) investigated nutritional interventions as preventive or therapeutic approaches for cognitive function obtaining contrasting results. Furthermore, in the last few years, the approach to the study of the relationship between diet and cognitive impairment has been changed. In fact, according to the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines for AD and cognitive decline due to AD pathology¹⁵, it has been suggested a direct impact of nutrition to brain structure and activity changes. This consideration in addition to the need to objectively quantify the effects of nutrients on cognitive outcomes not only in terms of neuropsychological test scores or clinical scales, has opened the era of brain imaging biomarkers in nutritional research. Another feature to underline was the emerging use of objective measures of dietary habits, not only in terms of daily questionnaires, but also biomarkers in order to achieve more reliable findings. The aim of the present article was to provide a comprehensive and updated review focusing on the RCTs published in the past 3 years (2014-2016) exploring nutritional interventions efficacy in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged 60 years and older.

NUTRITIONAL INTERVENTION THROUGH DIETARY PATTERN CHANGES, MEDICAL FOOD/NUTRACEUTICAL SUPPLEMENTATION AND MULTIDOMAIN APPROACH

DIETARY PATTERN CHANGES

We used a narrative synthesis to summarize the findings of the included studies, subdividing the articles for the three principal diet-based approaches (dietary patterns/medical food/nutraceutical supplementation/multidomain approach, macronutrients, and micronutrients), specifying sample size and the cognitive outcomes of the included studies (Tabs. I-III)¹⁶⁻⁴³. Table I shows selected RCTs published in the last three years (2014-2016) that evaluated the efficacy of nutritional intervention through dietary pattern changes, medical food/nutraceutical supplementation, and multidomain approach in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years¹⁶⁻²³. The Mediterranean diet (MeDi), the typical dietary pattern of Mediterranean countries, has been the most studied dietary pattern, with a proposed protective role against cognitive decline and dementia. The main components of the MeDi pattern are fruits, vegetables, legumes, cereals and olive oil as the main added lipid, associated with a moderate consumption of red wine and low consumption of red meat and dairy products. In particular, the findings from prospective observational studies and very recent systematic reviews and meta-analyses of pooled studies suggested that higher adherence to the MeDi fulfilling the whole-diet approach was associated with a reduced risk of cognitive impairment, MCI and AD, as well as the transition from MCI to AD^{3,9-11}. Moreover, a recent systematic review on this issue suggested that also other emerging healthy dietary patterns such as the Dietary Approach to Stop Hypertension (DASH) and the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND) diets were associated with slower rates of cognitive decline and significant reduction of AD rate³. Despite observational studies showed a positive significant association of certain healthy dietary patterns with cognitive impairment, only few interventional studies have been conducted on dietary patterns, particularly on MeDi, reporting contrasting findings. In fact, in a RCT including 447 cognitively normal participants randomly assigned to a MeDi supplemented with extra-virgin olive oil (EVOO) or with mixed nuts, or a control diet for a 4.1 years follow-up, those allocated to a MeDi plus EVOO scored better on the episodic memory and attention tasks compared with the control group. Furthermore, compared with controls, this RCT showed a significant improvement in memory composite in the

MeDi plus nuts group and a significant improvement in frontal and global cognition composites in the MeDi plus EVOO group (Tab. I) ¹⁶. Furthermore, in a large RCT recruiting 48,835 women (50-79 years) for a follow-up of mean length of 8.1 years, dietary intervention based on caloric fat restriction and increasing consumption of vegetables, fruit and grain had no significant effects on cognition, with small significant improvements in three health-related quality of life subscales: general health, physical functioning, and vitality at one year follow-up (Tab. I) ¹⁷.

MEDICAL FOOD/NUTRACEUTICAL SUPPLEMENTATION

In the last decade, several RCTs have proposed medical foods/nutraceuticals as preventive or therapeutic approaches for cognitive decline and dementia, according to the increasing knowledge about the potential beneficial effect of specific nutrients properly combined in selected dietary patterns.⁴⁴ In the last three years, some medical foods/nutraceuticals have been tested in cognitively healthy subjects in order to delay cognitive impairment obtaining good results only in specific cognitive domains (Tab. I) ¹⁸⁻²¹. In a RCT, 105 cognitively intact adults were randomized to receive a pill-based nutraceutical (NT-020), a proprietary formulation of blueberry, green tea extract (95% polyphenols), carnosine, blueberry extract (40% polyphenolics, 12.5% anthocyanins), and vitamin D3 (2000 IU per serving) and also contains grape polyphenolics, including 5% resveratrol or placebo using a battery of neuropsychological tests assessing six broad cognitive domains (episodic memory, processing speed, verbal ability, working memory, executive functioning, and complex speed) at baseline and eight weeks later. The NT-020 group exhibited better performance on two measures of processing speed than the placebo group at eight weeks of follow-up (Tab. I) ¹⁸. Among nutraceutical compounds and combinatorial formulations, Ginkgo biloba extract is probably the most widely studied and used herbal-based medication for the prevention and treatment of AD and late-life cognitive decline ⁴⁵. Notwithstanding negative meta-analytic findings and the discouraging results of preventive trials against AD, some RCTs focusing particularly on dementia, AD, and MCI subgroups with neuropsychiatric symptoms and some recent meta-analyses have suggested a renowned role for Ginkgo biloba extract for cognitive impairment and dementia ⁴⁵. A RCT on 97 cognitively healthy older adults with no history of significant cognitive deficits reported modest effects of Ginkgo biloba plus choline-based formula on specific cognitive domains (executive functioning and verbal fluency) and immune functioning (Tab. I) ¹⁹. An interesting RCT including 116 healthy cognitively older participants investigated the effects of supplementation

with two multivitamin, mineral and herbal supplements, a women's formula and a men's formula in women and men, respectively. Assessments at baseline and post-supplementation included computerized cognitive tasks and blood biomarkers relevant to cognitive aging. After 16 weeks of follow-up, no cognitive improvements were observed after supplementation with either formula, while several significant improvements were observed in cognitive-related blood biomarkers including increased levels of vitamins B6 and B12 in women and men, reduced C-reactive protein in women, reduced homocysteine (Hcy) and marginally reduced oxidative stress in men, as well as improvements to the lipid profile in men (Tab. I) ²⁰. Finally, in one RCT, 27 postmenopausal women received either a combination of 1 g docosahexaenoic acid (DHA), 160 mg eicosapentaenoic acid (EPA), 240 mg Ginkgo biloba, 60 mg phosphatidylserine, 20 mg d- α tocopherol, 1 mg folic acid, and 20 μ g vitamin B12 per day or placebo for 6 months. The intervention resulted in significant effects in two of the four cognitive tests, with shorter mean latencies in a motor screening task, and more words remembered, and one of the three primary mobility measures with improved habitual walking speed. Compared with the placebo group, supplementation also resulted in significantly higher blood DHA levels (Tab. I) ²¹.

MULTIDOMAIN APPROACH

Considering the great interest on the relationships between an healthy lifestyle including optimal dietary habits and physical activity and an healthy cognitive aging, some studies have proposed a multidomain approach as an effective preventive approach for cognitive impairment or dementia (Tab. I) ^{22,23}. The findings of several RCTs have suggested that some single-domain interventions, i.e., antihypertensives, nutritional supplements, cognitive training, and physical activity, had protective effects on cognitive decline ⁴⁶, but these results have seldom been replicated in larger samples. In two 24-week RCTs carried out in parallel, 127 older subjects performed a resistance-type physical exercise program or not and, in both studies, subjects were randomly allocated to either a protein drink (2 \times 15 g daily) or a placebo one. In frail and pre-frail older adults, resistance-type exercise training combined with protein supplementation significantly improved information processing speed, whereas exercise training alone had significant good effects on attention and working memory. There were no significant differences among the intervention groups on the other cognitive tests or domain scores (Tab. I) ²². Finally, in 2015, a successful 2-year multi-domain lifestyle intervention was completed aiming at prevention of cognitive decline, the Finnish Geriatric Intervention Study to Prevent Cognitive

Table I. Randomized clinical trials evaluating the efficacy of nutritional intervention through dietary pattern changes, medical food/nutraceutical supplementation, and multidomain approach in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Dietary pattern changes					
Valls-Pedret et al., 2015 ¹⁶	447 cognitively healthy older subjects Mean age: 68.2 ± 6.3 years for the intervention group and 68.8 ± 6.5 years for the placebo group	MeDi + EVOO (1L/week) MeDi + mixed nuts (30 g/day) Control diet (advice to reduce dietary fat)	4.1 years (median)	MMSE, AVLT, ASF, DS-WAIS, VPA-WAIS, CTT	In an older population, a MeDi supplemented with EVOO or nuts was associated with improved episodic memory and frontal and global cognition
Assaf et al., 2016 ¹⁷	48.835 older women Aged: 50-79 years	Intervention group: reduced calories from fat to 20%, increased vegetables and fruit to 5+ servings, and increased grain servings to 6+ servings a day Placebo	8.1 ± 1.7 years (max. 11.2 years)	3MSE, RAND36 WHI FFQ.	No significant improvement in cognitive functions. Small significant improvements in three health-related quality of life subscales: general health, physical functioning, and vitality at 1 year follow-up
Medical food/nutraceutical supplementation					
Small et al., 2014 ¹⁸	105 cognitively intact adults Aged: 65-85 years	Nutraceutical NT-020 Placebo	8 weeks	MMSE, AVLT, IPT, NC, TMT-A and -B, FBDS-WAIS, CF, COWAT, DST	Better performance for the NT-020 group in two measures of processing speed (IPT and NC) compared to placebo group
Lewis et al., 2014 ¹⁹	97 cognitively healthy older subjects MMSE ≥ 23 Aged ≥ 60 years	Nutraceutical formulation with: Ginkgo biloba leaf (120 mg/day), Ginkgo biloba whole extract (80 mg/day), grape seed extract (40 mg/day), Gotu kola leaf (Centella asiatica), dried buckwheat leaf juice, buckwheat seed, and soybean lecithin powder + Choline (700 mg/day) Nutraceutical formulation with: grape seed extract (100 mg/day), green tea extract (50 mg/day, 60% catechins), bilberry fruit (50 mg/day, 25% anthocyanins), dried buckwheat leaf and juice, green tea leaf powder, and dried carrot root + nutraceutical formulation with: vitamin D (312 IU/day), vitamin A (1,600 IU/day), vitamin C (5.3 mg/day), thiamine (0.3 mg/day), riboflavin (0.3 mg/day), vitamin B6 (1.3 mg/day), defatted wheat germ, carrot (root), calcium lactate, nutritional yeast, bovine adrenal, bovine liver, magnesium citrate, bovine spleen, ovine spleen, bovine kidney, dried pea (vine) juice, dried alfalfa (whole plant) juice, mushroom, oat flour, soybean lecithin, and rice bran Placebo	6 months	MMSE, SCWT, TMT-A and -B, COWAT, DS-WAIS-III, HVLT-R Immune function markers	Isolated and modest effects of a Ginkgo biloba plus choline-based formula on cognitive (executive functioning and verbal fluency) and immune functioning among healthy older adults with no history of significant cognitive deficits



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Multidomain approach					
Harris et al., 2015 ²⁰	116 healthy older participants Aged: 55-65 years	Multivitamin, mineral and herbal supplements Placebo	16 weeks	CRT, IDRM, SI, SWM, and CM, blood biomarkers relevant to cognition	In cognitively healthy older people, multivitamin supplementation improved a number of cognitive-related blood biomarkers, but these biomarker changes were not accompanied by no significant improvement in cognitive functions
Strike et al., 2016 ²¹	27 postmenopausal women Aged: 60-84 years	Nutraceutical formulation providing: DHA (1 g/day), EPA (160 mg/day), Ginkgo biloba, phosphatidylserine, α -tocopherol, folic acid, and vitamin B12 Placebo	6 months	MOT, VRM, and PAL, mobility was assessed by VICON 9 motion capture camera system synchronized with Kistler force plates; blood fatty acid levels by pin-prick analysis	In this RCT, multivitamin supplementation improved cognition and mobility in healthy older females suggesting a potential role in reducing the decline to frailty
Van de Rest et al., 2014 ²²	127 frail or pre-frail older subjects Mean age: 79 years	Protein (30g/day) Protein + physical exercise Placebo Placebo + physical exercise	24 weeks	MMSE, TMT-A and -B, WLT, SCWT, FBDS-WAIS, VFT, and reaction time tasks 3 day dietary record	Significant improvement of information processing speed in the protein plus physical exercise group
Ngandu et al., 2015 ²³	1260 nondemented older subjects Aged: 60-77 years	Multidomain lifestyle intervention Control group	2 years	A comprehensive NTB Z score	Findings from this long-term, RCT suggested that a multidomain intervention could improve or maintain cognitive functioning in at-risk older people

MeDi: Mediterranean diet; EVOO: extravirgin olive oil; MMSE: Mini-Mental State Examination; AVLT: Rey Auditory Verbal Learning Test; ASF: Animals Semantic Fluency; DS-WAIS: Digit Span subtest from the Wechsler Adult Intelligence Scale; VPA-WAIS: Verbal Paired Associates from the Wechsler Memory Scale; CTT: Color Trail Test; 3MSE: modified Mini-Mental State Examination; RAND36: RAND 36-Item Health Survey; WHI: Women's Health Initiative; FFQ: food frequency questionnaires; IPT: Identical Pictures Test; NC: Number Comparison task; TMT-A: Trail Making Test - A; TMT-B: Trail Making Test - B; FBDS-WAIS: Forward and Backward Digit Span task; CF: Category Fluency; COWAT: Controlled Oral Word Association Test; DST: Digit Symbol Tests; SCWT: Stroop Color-Word Test; DS-WAIS-III: Digit Symbol subtest from the Wechsler Adult Intelligence Scale- III; HVL-R: the Hopkins Verbal Learning Test-Revised; CRT: Choice Reaction Time; IDRM: Immediate and Delayed Recognition Memory; SI: Stroop Interference tasks; SWM: Spatial Working Memory; CM: Contextual Memory; MOT: psychomotor response latency; VRM: Verbal Recognition Memory; PAL: paired associate learning; WLT: Word Learning Test, SCWT: Stroop Color-Word Test, VFT: Verbal Fluency Test; PUFAs: polyunsaturated fatty acids; NTB: neuropsychological test battery

Impairment and Disability (FINGER) (Tab. I)²³, with dietary counselling as one of the intervention domains (diet, exercise, cognitive training, vascular risk monitoring) and a control group (general health advice). Intervention goals were based on Finnish dietary recommendations. This 2-year multidomain lifestyle intervention was conducted on 631 participants in the intervention and 629 in the control group, aged 60-77 years at baseline with an estimated mean change in neuropsychological test battery total Z score at 2 years of 0.2 in the intervention group and 0.16 in the control group. These findings from the FINGER suggested that a multidomain intervention could improve or maintain cognitive functioning in at-risk older people from the general population (Tab. I)²³.

NUTRITIONAL INTERVENTION THROUGH MACRONUTRIENT CHANGES

Table II shows selected RCTs published in the last three years (2014-2016) that evaluated the efficacy of nutritional intervention through supplementation of dietary macronutrients in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy

subjects aged over 60 years²⁴⁻³⁴. In particular, many interventional RCTs evaluated the cognitive impact of macronutrient intakes such as proteins and PUFAs with promising results.

PROTEINS

Many RCTs evaluated protein intake as a supplementation in nondemented older adults showing significant improvement in specific cognitive domains (Tab. II)²⁴⁻²⁷. Interestingly, these RCTs reported also promising results not only in terms of cognitive outcomes, but also magnetic resonance imaging (MRI) findings. In one RCT on 65 frail or pre-frail cognitively healthy older subjects randomly assigned to protein drink or placebo for 24 weeks, protein supplementation improved reaction time performance, but did not improve the cognitive domains of episodic memory, attention and working memory, information processing speed, and executive functioning (Tab. II)²⁴. Promising results have been reported in a trial including 51 cognitively healthy older subjects [Mini-mental State Examination (MMSE) > 15] randomly assigned to dietary carnosine and anserine (carnosine related compounds, CRC) supplementation (chicken meat extract) or placebo. In this trial, a significant improvement

Table II. Randomized clinical trials evaluating the efficacy of nutritional intervention using a macronutrient approach in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Main Results Cognitive results
Protein supplementation					
Van der Zwaluw et al., 2014 ²⁴	65 frail or pre-frail older subjects Mean age: 79 years	Proteins (30 g/day) Placebo	24 weeks	MMSE, TMT-A and -B, WLT, SCWT, FBDS-WAIS, VFT, and reaction time tasks 3 day dietary record	Protein supplementation improved reaction time performance in pre-frail and frail older adults, but did not improve other cognitive functions
Szcześniak et al., 2014 ²⁵	51 older subjects MMSE \pm 15 Mean age: 81 \pm 7 years in CRC group and 80.5 \pm 7.5 years in placebo group	CME containing 40% of CRC (2:1 ratio of anserine to carnosine) was administered 2.5 g/day Placebo	13 weeks	MMSE, STMS, and CDR	A significant improvement was found after supplementation in specific subscores of STMS, a test evaluating global cognitive functions, such as construction/copying, abstraction, and recall
Rokicki et al., 2015 ²⁶	31 cognitively healthy participants Aged: 42-78 years	Twice-daily doses of the imidazole dipeptide formula (500 mg) Placebo	3 months	ADAScog, WMSLM 1 and 2, and BDI Functional MRI	In the CRC group, better verbal episodic memory performance and decreased connectivity on functional MRI were found
Hisatsune et al., 2016 ²⁷	39 cognitively healthy participants Mean age: 69.2 years	Twice-daily doses of the imidazole dipeptide formula (500 mg) Placebo	3 months	ADAScog, WMSLM 1 and 2, BDI, SF-36, MMSE Serum concentrations of 27 cytokines Perfusion MRI	CRC supplementation showed a significant beneficial effect on verbal episodic memory and brain perfusion in older adults
Fatty acid supplementation					
Witte et al., 2014 ²⁸	65 cognitively healthy older subjects MMSE \pm 26 Mean Age: 63.9 \pm 6.6 years	n-3 PUFA group received fish oil capsules with 2.2 g of n-3 PUFAs (1320 mg EPA + 880 mg DHA, given as 1000 mg fish oil and 15 mg vitamin E) Placebo (sunflower oil)	26 weeks	VF, TMT-A and -B, SCWT, AVLT, FBDS-WAIS, STAI 1 and 2 Erythrocyte membrane fatty acid composition MRI	Supplementation with high levels of n-3-PUFAs demonstrated enhanced executive functions in healthy older adults after 26 weeks and improved white matter microstructural integrity, regional gray matter volume, and vascular parameters
Jaremkka et al., 2014 ²⁹	138 cognitively healthy older subjects Mean age: 51.0 \pm 7.8 years	1.25 g/day of n-3 PUFAs 2.50 g/day of n-3 PUFAs Placebo The fish oil supplements contained a 7:1 ratio of EPA to DHA	4 months	20-item UCLA loneliness scale, CVLT -II, DS-WMS-III, LNS-WMS-III, SS- WMS-III, TMT, COWAT Plasma levels of n-6 and n-3 PUFAs.	Lonelier people within the placebo condition had poorer verbal episodic memory post-supplementation, as measured by immediate and long-delay free recall, than their less lonely counterparts. The plasma n-6 PUFAs: n-3 PUFAs ratio data mirrored these results
Mahmoudi et al., 2014 ³⁰	199 older individuals with normal or mild to moderate cognition impairment Aged \geq 65 years	180 mg of DHA + 120 mg of EPA Placebo	6 months	MMSE, AMT Plasma cholesterol, CRP, fasting blood sugar	No significant effects on cognitive outcomes
Chew et al., 2015 ³¹	3741 participants Mean Age: 72.7 years	n-3 PUFAs (1 g) and/or lutein (10 mg)/zeaxanthin (2 mg) Placebo All participants were also given varying combinations of vitamins C, E, beta carotene, and zinc	5 years	HHI, CES-D, TICS-M, TICS-M Recall, AC, LF, AF, LM-WMS-III-1 & 2, DB, and DR-WMS-III-RP	No significant effects on cognitive outcomes



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Main Results Cognitive results
Fatty acid supplementation					
Pase et al., 2015 ³²	160 cognitively healthy older volunteers Aged: 50-70 years	Multivitamin combined with fish oil (3 g) Multivitamin combined with fish oil (6 g) Placebo multivitamin combined with fish oil (6 g) Placebo multivitamin combined with placebo fish oil (Sunola oil)	16 weeks	SUCCAB measuring reaction time, cognitive processing speed, short-term memory, and visual memory BP variables	Absolute increases in the red blood cell n-3/n-6 ratio were associated with improvements in spatial working memory. The 6 g fish oil without the multivitamin group displayed a significant decrease in aortic pulse pressure and aortic augmentation pressure, two measures of aortic BP and aortic stiffness
Tokuda et al., 2015 ³³	113 older nondemented Japanese men Mean age: 59.6 years	LC-PUFA-containing oil (including ARA 120 mg/die, DHA 300 mg/die and EPA 100 mg/die) Purified olive oil	4 weeks	Event-related potential P300 and POMS LC PUFA plasma analysis Diet history questionnaire, semi-quantitative FFQ, and study diary	Changes in P300 latency were significantly different between the placebo group and the LC PUFA group after supplementation
Külzow et al., 2016 ³⁴	44 cognitively healthy individuals Mean age: 62 ± 6 years	n-3 PUFAs (2.2 g/day) Placebo	26 weeks	LOCATO assessing OLM in older adults, AVLT, and PANAS Erythrocyte membrane fatty acid composition, serum biomarkers and APOE genotyping Dietary habit questionnaire	Performance in cued recall in a OLM task was sensitive in detecting beneficial effects of n-3 PUFA supplementation. Omega-3-index significantly increased in the n-3 PUFA group and decreased in the placebo group

MMSE: Mini-Mental State Examination; TMT-A: Trail Making Test - A; TMT-B: Trail Making Test -B; WLT: Word Learning Test; SCWT: Stroop Color-Word Test; FBDS-WAIS: Forward and Backward Digit Span task from the Wechsler Adult Intelligence Scale; VFT: Verbal Fluency Test; CRC: carnosine related compounds; CME: chicken meat extract; STMS: Short Test of Mental Status; CDR: Clinical Dementia Rating; ADAS-cog: Alzheimer's Disease Assessment Scale-Cognition; LM-1 & 2-WMS: Logical Memory 1 & 2 from Wechsler Memory Scale; BDI: Beck Depression Inventory; MRI: magnetic resonance imaging; SF-36: Medical Outcomes Study, 36-item Short Form; MCS: Mental Health Component Summary score; PCS: Physical Health Component Summary; n-3 PUFA: n-3 polyunsaturated fatty acids; VF: Verbal Fluency; AVLT: Auditory Verbal Learning Test; STAI 1 and 2: Spielberger's State-Trait Angst Inventar; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; CVLT: California Verbal Learning Test, Second Edition; DS-WMS-III: Digit Span subtest from the Wechsler Memory Scale – Third Edition; LNS-WMS-III: Letter-Number Sequencing subtest from the Wechsler Memory Scale – Third Edition; SS-WMS-III: Spatial Span subtest from the Wechsler Memory Scale – Third Edition; COWAT: Controlled Oral Word Association Test; AMT: Abbreviated Mental Test score; CRP: C-reactive protein; CES-D: Center for Epidemiologic Studies' Depression Scale; TICS-M: Telephone Interview Cognitive Status-Modified; AC: Animal Category; LF: Letter Fluency; AF: Alternating Fluency; LM-WMS-III-1 & 2: Logical Memory 1 & 2 from Wechsler Memory Scale – Third Edition; DB: Digits Backward; DR-WMS-III-RP: Delayed Recall from Wechsler Memory Scale – Third Edition Recall Paragraph; SUCCAB: Swinburne University Computerised Cognitive Assessment Battery; BP: blood pressure; LC PUFA: long-chain polyunsaturated fatty acids; ARA: arachidonic acid; POMS: Profile of Mood Status; FFQ: food frequency questionnaires; OLM: object-location memory; PANAS: Positive and Negative Affect Schedule; APOE: apolipoprotein E

after supplementation was found in specific subscores of a test evaluating global cognitive functions, such as construction/copying, abstraction, and recall (Tab. II)²⁵. After 3 months of imidazole dipeptide formula supplementation containing 500 mg of CRC supplementation (carnosine and anserine, ratio 1/3) to 31 healthy participants, the CRC group had not only a better verbal episodic memory performance but also, at functional MRI, a decreased connectivity in the default mode network, the posterior cingulate cortex and the right fronto-parietal network, as compared with the placebo group. Furthermore, there was a correlation between the extents of cognitive and neuroimaging changes suggesting that daily CRC supplementation could impact cognitive function and that network connectivity changes may be associated with its effects (Tab. II)²⁶. These findings were confirmed in another RCT including 39 healthy older adults assigned to a CRC supplementation (carnosine and anserine) or

placebo for three months. CRC group showed significant preservation in delayed recall verbal memory compared to the placebo group, but not in the immediate recall test, suggesting that CRC supplementation may have a beneficial effect on verbal memory registration, but not on short-term working verbal memory. Blood analysis revealed a decreased secretion of inflammatory cytokines in the CRC group, including CCL-2 (MCP-1) and interleukin (IL)-8. Furthermore, perfusion MRI analysis using arterial spin labeling showed a suppression of the age-related decline in brain blood flow in the posterior cingulate cortex area in the CRC group compared to the placebo group suggesting a protective role of CRC supplementation on brain perfusion (Tab. II)²⁷.

FATTY ACIDS

In AD brains, it has been reported the lack of enzyme responsible for converting choline into acetylcholine,

therefore, the first dietary lipids proposed as potential therapeutic agents in AD were lecithin, the major dietary source of choline, and alpha-lipoic acid, both able to increase acetylcholine production⁴⁷. However, results from clinical trials were contrasting and further RCTs are required to evaluate their role as therapeutic supplements in order to delay cognitive impairment. Many epidemiological studies have demonstrated that dietary fatty acids may play a key role in several pathological conditions. Long-chain (LC) PUFAs, such as DHA, EPA, and arachidonic acid (ARA) are among the most studied macronutrients in late-life cognitive disorders and neurodegeneration⁴⁸. In particular, an increasing body of epidemiological evidence suggested that elevated saturated fatty acids (SFAs) could have negative effects on MCI, while a clear reduction of risk for cognitive decline has been found in population samples with elevated fish consumption, high intake of monounsaturated fatty acids (MUFAs) and LC PUFAs, particularly n-3 PUFAs⁴⁹. Despite the strong evidence in cognitive decline prevention coming from observational studies, findings coming from RCTs were controversial considering the great heterogeneity of samples and outcome measures as well as neuropsychological tools or MRI findings (Tab. II)²⁸⁻³⁴. Interesting data have been suggested from one RCT on 65 healthy subjects showing not only a significant increase in executive functions and letter fluency in the n-3-PUFA group compared with placebo, but also neuroimaging modifications after supplementation suggesting a pathobiological effect of n-3 PUFAs (Tab. II)²⁸. In fact, n-3 PUFA supplementation led to significant beneficial effects on white matter microstructural integrity and significant increases in regional gray matter volume compared with placebo in specific regions as left hippocampus, precuneus, superior temporal, inferior parietal and postcentral gyri, and in the right middle temporal gyrus and beneficial effects on carotid intima media thickness and diastolic blood pressure. Improvements in executive functions correlated positively with changes in omega-3-index and peripheral brain-derived neurotrophic factor, and negatively with changes in peripheral fasting insulin (Tab. II)²⁸. In another RCT, n-3 PUFA supplementation was effective on immediate and long-delayed free recall only in healthy lonelier participants. In fact, lonelier people within the placebo condition had poorer verbal episodic memory post-supplementation, as measured by immediate and long-delay free recall, than their less lonely counterparts. This effect was not observed in the n-3 PUFA 1.25 g/day and n-3 PUFA 2.5 g/day supplementation groups. The plasma n-6 PUFAs: n-3 PUFAs ratio data mirrored these findings (Tab. II)²⁹. However, findings from two RCTs showed that oral supplementation with n-3 PUFAs had no statistically significant

effect on cognitive functions (Tab. II)^{30,31}. In particular, in a RCT on 199 older subjects with normal or mild to moderate cognition impairment, low dose n-3 PUFAs (180 mg of DHA + 120 mg of EPA) for 6 months had no significant beneficial effects on improvement of cognition or prevention of cognitive decline in older people. However, considering only the cognitively healthy subjects, authors noticed near significant less decrement in global cognitive scores in n-3 PUFA group compared to placebo (Tab. II)³⁰. Moreover, in a large RCT including 3741 older participants, randomized to receive n-3 PUFAs (1 g) and/or lutein (10 mg)/zeaxanthin (2 mg) vs placebo for 5 years no statistically significant differences in change of cognitive scores between groups were reported (Tab. II)³¹. Furthermore, several RCTs reported promising findings only in specific cognitive domains evaluated with several neuropsychological tests. In fact, in a RCT including 160 healthy participants randomized to multivitamins with fish oil for 16 weeks, the red blood cell n-3/n-6 ratio increases were associated with improvements in spatial working memory (Tab. II)³². Some trials reported promising results in specific cognitive domains with higher doses of LC PUFAs compared to general dietary intake levels. Interestingly, a RCT suggested a potential role in improving cognitive function of LC PUFAs also at low doses of supplementation similar to general dietary intake. In fact, in 113 nondemented older Japanese participants, after 4 weeks of supplementation with LC PUFA-containing oil (DHA 300 mg/day, EPA 100 mg/day, and ARA 120 mg/day) or purified olive oil as placebo, changes in P300 latency, a measure of cognitive processes, were significantly different between the placebo group and the LC PUFA group. Significant increases in DHA and ARA contents in plasma phospholipids were observed in the LC PUFA group, while no changes were observed in the placebo group (Tab. II)³³. In another RCT conducted on 44 cognitively healthy individuals, the recall of object locations was significantly better after n-3 PUFA supplementation (daily dose of 1.320 mg EPA + 880 mg DHA for 26 weeks) compared with placebo. No significant correlation between changes in memory performance and omega-3-index were observed, suggesting that memory benefits were not associated in a simple linear fashion with changes in omega-3-index (Tab. II)³⁴.

NUTRITIONAL INTERVENTION THROUGH MICRONUTRIENT CHANGES

NON-FLAVONOID POLYPHENOLS

Table III shows selected RCTs published in the last three years (2014-2016) that evaluated the efficacy of

nutritional intervention through supplementation of dietary micronutrients in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years³⁵⁻⁴³. Several classes of polyphenols have been investigated for their potential anti-ageing and neuroprotective properties, including flavonoids, commonly found in berries, grapes and red wine, and non-flavonoids, i.e., curcumin from turmeric and resveratrol from grapes and red wine⁵⁰. An increasing body of evidence suggested that consumption of polyphenols such as resveratrol and flavonoids may have potential beneficial effects on cognition, particularly on declarative and spatial memory, mainly in cognitively healthy individuals⁵⁰. However, results from RCTs were contrasting considering also the methodological inconsistencies of studies. On the other hand, findings from observational studies suggested that moderate consumption of red wine, rich in specific polyphenolic compounds such as quercetin, myricetin, catechins, tannins, anthocyanidins, resveratrol, and ferulic acid, has been associated with a lower incidence of cognitive decline, suggesting a protective role against dementia⁵¹. These data were confirmed from a recent RCT (Tab. III)³⁵. In fact, a trial including 46 cognitively healthy older adults randomly assigned to receive a daily intake of 200 mg of resveratrol and 320 mg of quercetin or placebo showed that supplementary resveratrol over a period of 26 weeks improved retention of words over a 30 min delay and functional connectivity of the hippocampus with frontal, parietal, and occipital areas in healthy older overweight adults compared with placebo (Tab. III)³⁵. Among non-flavonoid polyphenols, curcumin has been extensively reported to demonstrate many beneficial biological effects including anti-cancer, anti-oxidant and anti-inflammatory activities⁵².

For the prevention of cognitive-related outcomes in older age, promising results were reported in a one-year RCT in 96 cognitively normal subjects randomized to receive placebo or 1500 mg/d of bioenhanced preparation of curcumin (BCM-95®CG). A significant time×treatment group interaction was observed for global cognitive function, explained by a function decline in the placebo group at 6 months that was not found in the intervention group (Tab. III)³⁶.

FLAVONOIDS

Flavonoids [flavanols (catechin, epicatechin, epigallocatechin, and epigallocatechingallate-EGCG), flavonols (quercetin and kaempferol), flavones (luteolin and apigenin), isoflavones (daidzein and genistein), flavanones (esperetin and naringenin), and anthocyanidins (pelargonidin, cyanidine, and malvidin) have also been proposed to prevent or treat cognitive impairment or dementia^{45 53}. Recent RCTs showed significant

improvements in some cognitive domains after flavonoid interventions⁵⁴. However, the great heterogeneity in sample, flavonoid dose, follow-up and cognitive tests used led to inconsistent findings⁵⁴. In a very interesting RCT on 37 healthy older adults who consumed a high cocoa flavanol-containing diet (900 mg cocoa flavanols and 138 mg of epicatechin) or a low-dose one (10 mg cocoa flavanols and < 2 mg epicatechin) with or without aerobic exercise for 12 weeks, the high-flavanol intervention was found to enhance dentate gyrus (DG) function measured by functional MRI and by cognitive testing, suggesting the crucial role of DG dysfunction in age-related cognitive decline and the potential beneficial effects of flavonoid supplementation on DG function (Tab. III)³⁷. On the contrary, in a trial including 300 cognitively healthy postmenopausal women randomized to receive 25 grams of isoflavone-rich soy protein for 2.7 years, long-term changes in isoflavonoids were not associated with global cognition and episodic memory, although greater isoflavonoid exposure was associated with decrements in general intelligence (Tab. III)³⁸. Promising results come from other two trials with a 8 week follow-up (Tab. III)^{39 40}. In particular, in a RCT including 37 healthy participants randomized to receive two different flavanone-rich supplementations, high flavanone and low flavanone orange juice drinks, global performance, executive function, and episodic memory, and immediate recall were significantly better after the high flavanone drink than the low flavanone drink (Tab. III)³⁹. Similar positive findings were found in the second RCT for a drink containing a high dose of cocoa flavanols (993 mg/day) compared to a low dose drink (993 mg/day) in cognitively healthy participants for specific cognitive domains (i.e., executive function and verbal fluency) suggesting a possible protective role in age-related cognitive dysfunction, possibly through an improvement in insulin sensitivity (Tab. III)⁴⁰.

HOMOCYSTEINE-RELATED VITAMINS

A possible modifiable risk factor of dementia is an elevated plasma Hcy level. In fact, Hcy may be toxic for neurons and vascular endothelial cells⁵⁵, and cross-sectional and prospective studies have shown associations between elevated Hcy levels and cognitive decline and dementia⁵⁶. Hcy levels can be lowered by supplementation with folic acid (vitamin B9) and vitamin B12⁵⁷. Although observational studies have shown a strong association between poor vitamin B6, B12, and folate levels and increased risk of dementia, suggesting a preventive and protective role of these micronutrients, evidence from RCTs appeared to be unclear (Tab. III)⁴¹⁻⁴³. In fact, in two RCTs, no significant effect of supplementation of Hcy-related vitamins on cognitive function were found (Tab. III)^{41 42}. In particular, in a large RCT

Table III. Randomized clinical trials evaluating the efficacy of nutritional intervention using a micronutrient approach in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Main results
Non-flavonoid polyphenols					
Witte et al., 2014 ³⁵	46 cognitively healthy overweight older individuals Aged: 50-75 years	Daily intake of four capsules (in total 200 mg of resveratrol and 320 mg of quercetin) Placebo All subjects received a 13 week supply of capsules and another 13 week supply after 3 months	26 weeks	AVLT Functional MRI and DTI MRI Lipid metabolism, inflammation, neurotrophic factors, and vascular parameters	Significant positive effect of resveratrol on retention of words over 30 minutes and functional connectivity of the hippocampus with frontal, parietal, and occipital areas in healthy older overweight adults compared with placebo
Rainey-Smith et al., 2016 ³⁶	96 community-dwelling older adults without significant cognitive impairments Mean age: 66 ± 6.6 years	1500 mg/day of bioenhanced preparation of curcumin (BCM-95®CG) Placebo	12 months	CCRT, DASS, SF-36, PRMQ-16, MoCA; AVLT, COWAT, WDSS-WAIS-R, and the computerized CogState battery APOE genotyping	A significant time×treatment group interaction for global cognition, explained by a function decline in the placebo group at 6 months that was not found in the intervention group. No differences for all other clinical and cognitive measures
Flavonoids					
Brickman et al., 2014 ³⁷	37 cognitively healthy, sedentary older subjects Aged: 50-69 years	High flavanol intake + aerobic exercise High flavanol intake Low flavanol intake + aerobic exercise Low flavanol intake	12 weeks	ModBent task, AVLT Functional MRI	High dietary flavanol consumption enhanced dentate gyrus function in the aging human hippocampal circuit, independently of exercise
St John et al., 2014 ³⁸	300 cognitively healthy women Mean age: 61 years	25 g of isoflavone-rich soy protein (91 mg of aglycone weight isoflavones: 52 mg genistein, 36 mg daidzein, and 3 mg glycitein) Milk protein-matched placebo provided daily	2.7 years	WTAR, CES-D; neuropsychological test battery evaluating general intelligence (executive/expressive/visuospatial tasks), verbal episodic memory (list learning/logical memory), and visual episodic memory Overnight urine excretion of isoflavonoids and fasting plasma levels of isoflavonoids	Long-term changes in isoflavonoids were not associated with global cognition. Increasing isoflavonoid exposure from dietary supplements was, however, associated with decrements in general intelligence but not memory
Kean et al. 2015 ³⁹	37 cognitively healthy older subjects Mean age: 66.7 years	High flavanone drink (305 mg/day) Low flavanone drink (37 mg/day)	8 weeks	CERAD immediate and delayed verbal recalls and serial sevens, SWM, DSST-WAIS, VPA-WMS-III, LM, LF, and Go-NoGo	Daily consumption of high dose flavanone-rich orange juice was associated with benefits for global cognitive function, executive function, and episodic memory, mainly immediate recall
Mastroiacovo D et al. 2015 ⁴⁰	90 cognitively healthy older subjects Mean age: 69.5 years	993 mg flavanols/day 520 mg flavanols/day 48 mg flavanols/day	8 weeks	MMSE, TMT-A and -B, and VFT	High dose flavanol consumption caused significant effects on executive function and verbal fluency
Van der Zwaluw et al., 2014 ⁴¹	2.919 older participants with Hcy levels between 12 and 50 µmol/L Mean age: 74.1 + 6.5 years	Daily either a tablet with 400 µg folic acid and 500 µg vitamin B12 Placebo Both tablets contained 15 µg vitamin D3	2 years	MMSE, AVLT, FBDS-WAIS, TMT-A and -B, SCWT, SDMT, and LF Blood biomarkers	This large RCT did not reveal beneficial effects of supplementation with vitamin B12 and folic acid on the cognitive domains of episodic memory, attention and working memory, information processing speed, and executive function



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Main results
Homocysteine-related and antioxidant vitamins					
Dangour et al., 2015 ⁴²	201 older subjects with moderate vitamin B-12 deficiency (serum vitamin B-12 concentrations: 107-210 pmol/L) in the absence of anemia Mean age: 80 years	1 mg crystalline vitamin B-12 Placebo	12 months	CVLT, SLMT, simple and choice reaction time, and VFT Peripheral motor and sensory nerve conduction and central motor conduction assessment	No evidence of an effect on peripheral nerve or central motor function outcome or on cognitive function
Cheng et al., 2016 ⁴³	104 older participants with hyperhomocysteinemia Mean age: 71.7 ± 8.8 years	Vitamin B group, which received 800 µg/day of folate, with 10 mg of vitamin B6 and 25 µg of vitamin B12 Placebo	14 weeks	BCATs Serum measure of tHcy, vitamin B6, vitamin B12, and folate	Improvement with vitamin B supplementation in global cognitive scores and four subtests (mental speed, visuo-spatial ability, working memory, and visual memory)

AVLT: Auditory Verbal Learning Test; DTI: diffusion tensor imaging; MRI: magnetic resonance imaging; CCRT: Cambridge Contextual Reading Test; DASS: Depression Anxiety Stress Scales; PRMQ-16: 16 item self-report Prospective and Retrospective Memory Questionnaire; MoCA: Montreal Cognitive Assessment; WDSS-WAIS-R: Wechsler Digit Symbol Scale from Wechsler Adult Intelligence Scale revised; APOE: apolipoprotein E; Mod Bent: modified Benton Visual Retention Test; WTAR: Wechsler Test of Adult Reading; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; SWM: Spatial Working Memory; DSST-WAIS: Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale; VPA-WMS-III: Verbal Paired Associates from the Wechsler Memory Scale—Third Edition; LM: Letter Memory; LF: Letter Fluency; TMT-A: Trail Making Test - A; TMT-B: Trail Making Test - B; VFT: Verbal Fluency Test; Hcy: homocysteine; FBDS-WAIS: Forward and Backward Digit Span task from the Wechsler Adult Intelligence Scale; SCWT: Stroop Color-Word Test; SDMT: Symbol Digit Modalities Test; CVLT: California Verbal Learning Test, Second Edition; SLMT: symbol letter modality test; BCATs: Basic Cognitive Aptitude Tests

on 2,919 older participants with elevated Hcy levels, a 2-year folic acid and vitamin B12 supplementation did not significantly improve cognitive performance in all four cognitive domains investigated (episodic memory, attention and working memory, information processing speed, and executive function). Interestingly it was reported a small difference in global cognition, that the authors concluded as attributable to chance (Tab. III)⁴¹. The other RCT included 201 healthy cognitive older adults with moderate vitamin B12 deficiency. In this one-year follow-up trial, there was no effect of B12 supplementation peripheral nerve or central motor function outcome or cognitive function (Tab. III)⁴². However, another RCT suggested more promising findings with a supplementation containing 800 µg/day of folate, 10 mg of vitamin B6 and 25 µg of vitamin B12 in 104 older patients with hyperhomocysteinemia. This supplementation improved cognitive function in terms of global cognitive scores and four subtests (mental speed, visuo-spatial ability, working memory, and visual memory) (Tab. III)⁴³.

CONCLUSIONS AND FUTURE DIRECTIONS

In the last decade, while the association between diet and cognitive function or dementia has been largely investigated in observational studies, there was a lack of evidence from RCTs dealing with the prevention of late-life cognitive disorders though dietary intervention in older adults without cognitive dysfunction. In

the present article, we reviewed RCTs published in the last three years (2014-2016) exploring nutritional intervention efficacy in preventing the onset of late-life cognitive disorders and dementia in cognitively healthy subjects aged over 60 years and using different levels of investigation (i.e., dietary pattern changes/medical food/nutraceutical supplementation/multidomain approach and dietary macro- and micronutrient approaches). From the reviewed RCTs, there was moderate evidence that nutritional intervention through dietary pattern changes, medical food/nutraceutical supplementation, and multidomain approach improved specific cognitive domains or cognitive-related blood biomarkers. Furthermore, there was convincing evidence that protein supplementation improved specific cognitive domains. For fatty acid supplementation, mainly LC PUFAs, there was emerging evidence suggesting an impact of this approach in improving specific cognitive domains, MRI findings, and/or cognitive-related biomarkers also in selected subgroups of older subjects although some results were conflicting. Among selected RCTs that evaluated the efficacy of nutritional intervention through supplementation of dietary micronutrients, there was evidence of an impact of non-flavonoid polyphenol and flavonoid supplementations in improving specific cognitive domains and/or MRI findings. Finally, there was only low evidence suggesting efficacy of intervention with homocysteine-related vitamins in improving cognitive functions, dementia incidence, or cognitive-related biomarkers in cognitively healthy older subjects.

In the last five years, several meta-analyses and systematic/scoping reviews investigated the efficacy of different nutritional supplementations in preventing late-life cognitive disorders in cognitively healthy older adults⁴⁻⁷. However, these meta-analyses and systematic/scoping reviews investigated also observational studies and not only RCTs^{4,7}, included also younger subjects⁵, and were limited to specific macronutrients (i.e., n-3 PUFAs)⁴⁻⁷, micronutrients^{5,6}, or dietary pattern changes/nutraceuticals^{4,7}. In particular, some of these studies found that n-3 PUFAs were associated with better global cognition and some specific cognitive domains^{4,6,7}. B vitamins, and vitamin E supplementations did not affect cognition⁵ or had limited efficacy^{6,7}, while adherence to the MeDi was significantly associated with better cognitive performance and less cognitive decline⁴.

The absence of disease-modifying treatment for AD patients leads to the investigation of a multimodal alternative therapeutic or preventive approaches by targeting modifiable risk factors. Therefore, in the last years, a growing interest has concerned the relation between nutrients and cognitive impairment in the earlier phases, considering the multifactorial effects of nutrition in human diseases. In fact, it is well known that dietary habits may influence several cardiometabolic risk factors, as visceral adiposity, blood pressure, glucose-insulin metabolism, lipids levels, but also hepatic function, endothelial health, microbiome function, and several biological processes as oxidative stress, inflammation, both involved in human aging. Despite several promising findings coming from observational studies³, evidence suggesting a potential preventive effectiveness of nutritional intervention in healthy elders to delay the onset of cognitive decline are still scarce and quite contrasting. Considering that is unlikely that a single nutrient could significantly improve cognition and delay cognitive impairment, several observational studies and RCTs proposed combination of micro/macronutrients or medical foods/nutraceuticals as potential preventive approaches in elders with promising results^{3,4,6,7}. Furthermore, a multidimensional approach consisting in healthy life style (healthy dietary habits in combination with physical activity) seems the best intervention in elders. In fact it is well known that there is a strong bidirectional interaction between cognitive performance and other main outcomes in elders that have to be considered as physical and cognitive frailty and disability⁵⁸. However, some limitations should be reported for the present systematic review article. An important limitation was linked to the great heterogeneity of included RCTs not only in terms of study samples and trial durations, but also in relation to the outcome measures and nutrients intake quantification. This heterogeneity made

really difficult to give clear answers about the efficacy of dietary intervention in older adults without cognitive dysfunction. However, there are several interesting concepts coming from the reviewed RCTs to underline. The first one was the emerging use of innovative measures of dietary habits, not only daily questionnaire but also biomarkers dosage as blood exams or urinary excretion. This resulted into an objective quantification of nutrient supplementation but also of nutritional status of patients at baseline. Furthermore, as shown in the present systematic review, recent RCTs underlined the importance to consider emerging cognitive-related outcomes in order to achieve more significant and objective results. Therefore, in addition to clinical scales and cognitive tests, serum and cerebrospinal fluid (CSF) biomarkers, neuroimaging and other cognitive-related biomarkers have been proposed. As a result, these findings could give us the possibility to better understand and quantify the nutrition-related impact on cognitive impairment and AD pathobiology. In conclusion, dietary pattern change/multidomain approaches, macronutrient (i.e., proteins and LC PUFAs) and micronutrient (i.e., non-flavonoid polyphenols and flavonoids) supplementations could be really effective in achieving cognitive-related outcomes in healthy older subjects without cognitive dysfunction. However, to obtain more statistically significant and reliable results, RCTs would be conducted in larger selected samples characterized by well defined cognitive function status, nutritional and dietary habits at baseline, with longer follow-up, and would include further objective measures of cognitive-related outcomes as blood or CSF biomarkers and neuroimaging findings.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REVIEW

Nutritional interventions in patients with Alzheimer's disease and other late-life cognitive disorders

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Given the impact of nutrition on neuroprotection largely investigated in observational studies, in the present article, we reviewed evidence from randomized clinical trials (RCTs) published in the last three years (2014-2016) exploring nutritional intervention efficacy in slowing cognitive impairment progression and achieving cognitive-related outcomes in patients aged 60 years and older with mild cognitive impairment (MCI), preclinical Alzheimer's disease (AD), prodromal AD, AD, unspecified dementia, and vascular dementia using different levels of investigation (i.e., medical food/nutraceutical supplementation/multidomain approach and dietary food/macro- and micronutrient approaches). From the reviewed RCTs, there was emerging evidence that nutritional intervention through medical food/nutraceutical supplementation (Fortasyn Connect[®] and another similar nutraceutical formulation) and multidomain approach improved magnetic resonance imaging findings and other cognitive-related biomarkers, but without clear effect on cognition in mild AD and MCI. Moreover, there was some evidence of a positive effect of antioxidant-rich foods (nuts) in improving specific cognitive domains and cognitive-related outcomes in MCI and mild-to-moderate dementia, but only in small samples. There was also convincing evidence for fatty acid supplementation, mainly n-3 polyunsaturated fatty acids (PUFAs), in improving specific cognitive domains and/or cognitive-related biomarkers in MCI and AD. Furthermore, antioxidant vitamin and trace element supplementations improved only cognitive-related outcomes and biomarkers, without effect on cognitive function in AD and MCI patients. Finally, high-dose B vitamin supplementation in AD and MCI patients improved cognitive outcomes but only in the subjects with a high baseline plasma n-3 PUFA, while folic acid supplementation had positive impact on specific cognitive domains.

Key words: Alzheimer's disease, Dementia, Medical food, Nutraceuticals, Macronutrients, Micronutrients

INTRODUCTION

By 2050, the number of people living with Alzheimer's disease (AD), an age-related neurodegenerative disorder, or other dementias in the United States is projected to nearly double from 48 million to 88 million¹. Therefore, considering the public health impact of AD and

the absence of available disease-modifying therapies for AD treatment², there is a great need in preventing the onset of the disease and slowing AD progression. In the last two decades, in addition to cardiovascular risk factors, several observational studies suggested a wide variety of potentially modifiable risk factors for late-life cognitive impairment and AD such as psychological

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conditions, education level, engagement in social and mentally stimulating activities, sensory changes, and lifestyle including diet, physical activity and voluptuary habits^{3,4}. In particular, several nutritional supplements have been studied for their potential role as neuroprotective interventions in AD and cognitive disorders in older age.⁵ This protective effect could be mediated by several pathobiological pathways involved in AD development such as amyloid- β (A β) deposition, neurofibrillary degeneration, synapse loss, inflammation, oxidative stress, mitochondrial dysfunction, loss of vascular integrity, and neuronal injury. In particular, late-life cognitive disorders were associated with synaptic abnormalities and dysfunction⁶, the last currently considered as one of the pathological hallmarks of AD⁷. Therefore, several observational studies and randomized clinical trials (RCTs) have proposed nutritional interventions as preventive or therapeutic approaches in order to slow the progression of cognitive impairment in older subjects or reducing AD risk and progression. In particular, several meta-analyses and systematic/scoping reviews investigated the efficacy of different nutritional supplementations in preventing late-life cognitive disorders in cognitively healthy older adults with encouraging findings⁸⁻¹². Some of these studies found that n-3 polyunsaturated fatty acids (PUFAs) were associated with improved global cognition and some specific cognitive domains, magnetic resonance imaging (MRI) findings, and/or cognitive-related biomarkers⁹⁻¹². B vitamins, and vitamin E supplementations did not affect cognition⁸ or had limited efficacy^{9,11,12}, while adherence to the Mediterranean diet was significantly associated with better cognitive performance and less cognitive decline^{10,12}. Moreover, for patients with mild cognitive impairment (MCI), AD, or dementia, there were fewer systematic reviews and meta-analyses investigating RCTs conducted on nutritional intervention¹³⁻¹⁶.

Furthermore, in the last years, according to the National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines for AD due to AD pathology¹⁷ and International Working Group (IWG)-1¹⁸ and IWG-2 criteria for AD¹⁹, it has been suggested a direct impact of nutrition on brain structure and activity changes⁴. Furthermore, there was an increased need to objectively quantify the effects of nutrients on cognitive-related outcomes not only in terms of cognitive scores or clinical scales, so opening the era of brain imaging biomarkers also for nutritional epidemiology²⁰. Finally, the use of objective measures of dietary habits, not only using daily semi-quantitative food frequency questionnaires, but also biochemical markers (e.g., serum concentration or red blood cells levels), also emerged to achieve more reliable findings. The present study sought to provide a comprehensive systematic review of the RCTs published in the past

three years (2014-2016) about nutritional intervention efficacy in slowing cognitive impairment progression and achieving cognitive-related outcomes in patients aged 60 years and older with late-life cognitive disorders, i.e., MCI, preclinical AD, prodromal AD, AD, unspecified dementia, and vascular dementia (VaD), using different levels of investigation (i.e., medical food/nutraceutical supplementation/multidomain approach and dietary food/macro- and micronutrient approaches).

NUTRITIONAL INTERVENTION THROUGH MEDICAL FOOD/NUTRACEUTICAL SUPPLEMENTATION AND MULTIDOMAIN APPROACH

MEDICAL FOODS/NUTRACEUTICALS

Table I shows selected RCTs published in the last three years that evaluated the efficacy of nutritional intervention through medical foods/nutraceutical supplementation and multidomain approach in the treatment of patients with late-life cognitive disorders aged over 60 years²¹⁻²⁷. Therefore, it is likely that the potency of single nutrients may be insufficient to achieve a clinically relevant benefit⁵. Based on the increasing body of evidence about the potential beneficial effect of specific nutrients properly combined, several RCTs investigated medical foods and nutraceutical supplementations characterized by a specific well studied combination of nutrients in different phases of cognitive dysfunction. Several medical foods and multinutrient interventions have been tested showing promising findings, not only in earlier phases of cognitive impairment⁵.

Fortasyn Connect[®]

The medical food Fortasyn Connect[®] contains a specific nutrient combination of docosahexaenoic acid (DHA) 1200 mg, eicosapentaenoic acid (EPA) 300 mg, uridine monophosphate 625 mg, choline 400 mg, folic acid 400 mcg, vitamin B6 1 mg, vitamin B12 3 mcg, vitamin C 80 mg, vitamin E 40 mg, selenium 60 mcg, and phospholipids 106 mg, designed to ameliorate synapse loss, synaptic dysfunction, and other pathological pathways affected in AD patients²⁸. In fact, several neuroprotective effects of Fortasyn Connect[®] have been reported in preclinical studies such as increases in markers of synaptogenesis²⁹, neurotransmitter synthesis and release²⁹, and cerebral blood flow³⁰, preservation in matter integrity³⁰, reduction in A β production and toxicity³¹, and restoration of neurogenesis³². In two previous RCTs, Souvenir I³³ and Souvenir II³⁴, Fortasyn Connect[®] improved memory performance in mild AD patients not taking AD medications. In particular, in

Souvenir I, Fortasyn Connect® significantly improved delayed verbal recall test of the Wechsler Memory Scale revised edition (WMS-r) in mild AD patients [Mini Mental State Examination (MMSE) score 20-26] after 12 weeks of intervention *versus* placebo without effects on the 13-item modified Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog)³³. In Souvenir II, significant improvements on the memory domain composite z-score based on a Neuropsychological Test Battery (NTB) during the 24 weeks were observed in mild AD patients (MMSE score \geq 20)³⁴. In addition, an exploratory analysis of results from a 24-week open-label extension (OLE) of Souvenir II suggested that memory function improved throughout 48 weeks in patients with mild AD taking Fortasyn Connect®³⁵. However, a third RCT, the S-Connect study, in patients with mild-to-moderate AD (MMSE score 14-24) receiving AD medications did not show any Fortasyn Connect® effects on cognition³⁶. In a recent effect size analysis conducted on Souvenir I, Souvenir II, S-Connect, and the OLE of Souvenir II, in patients with mild AD, effect sizes were 0.21 [95% confidence interval (CI): -0.06, 0.49] for the primary outcome in Souvenir II (NTB z-score) and 0.20 (95% CI: 0.10, 0.34) for the co-primary outcome of Souvenir I (WMS-r delayed recall). No effect was shown on cognition in patients with mild-to-moderate AD (S-Connect)³⁷. Recently, a biomarker panel of ten plasma lipids, including 8 phosphatidylcholine species, showed to predict conversion from cognitive normal aged adults to amnesic MCI or AD within 2-3 years with > 90% accuracy³⁸, with the reduced levels of these plasma phospholipids reflecting altered phospholipid metabolism in the brain and periphery. Using data from the Souvenir II³⁴, a 24-week intervention with Fortasyn Connect® in 96 drug-naïve patients with very mild to mild AD significantly increased 5 of the 7 measured biomarker phosphatidylcholine species (Tab. I)²¹, suggesting that this nutritional intervention could be useful in asymptomatic subjects with a plasma lipid biomarker profile prognostic of AD. Considering synaptic loss as an early pathological hallmark in AD related to memory impairment, macroscopic brain activity modifications measured with electro- and magnetoencephalography (EEG and MEG) might indicate synaptic changes in AD and has been proposed to identify nutritional intervention effects in clinical trials. In an interesting RCT was investigated the Fortasyn Connect® effects on synaptic integrity and function, assessed by advanced EEG analysis, considering brain activity-based networks as a derivative of underlying synaptic function (Tab. I)²². In this RCT, 179 drug-naïve mild AD patients were randomised to receive Fortasyn Connect® or placebo for 24 weeks. The network measures in the beta band were significantly different between groups. In fact, it

decreased in the control group, but remained relatively unchanged in the supplemented one, suggesting Fortasyn Connect® role in preventing the progressive network disruption in AD patients. However, these network measures were not related to memory performance (Tab. I)²². Using cumulative data from the Souvenir I (n = 212), Souvenir II (n = 259), S-Connect (n = 527), and the OLE of Souvenir II (n = 201), Rijpma et colleagues showed that circulating levels of micronutrients and fatty acids, including uridine, selenium, folate, vitamin B12, vitamin E, vitamin C, DHA and EPA, decreased in the AD population and can be increased by 12-48-week oral supplementation with Fortasyn Connect®²³. In the OLE study, similar levels were reached in former control product/initial active product users, whereas 24-week continued active product intake showed no suggestion of a further increase in nutrient levels (Tab. I)²³. Furthermore, in another RCT, comparing quantitative markers regarding spectral properties, functional connectivity, and graph theoretical aspects of MEG from the Souvenir II MEG sub-study in 55 drug-naïve mild AD patients, no significant intervention effects were found between the Fortasyn Connect® group and the placebo one (Tab. I)²⁴.

Other nutraceutical formulations

Two trials reported significant and promising findings on a nutraceutical multinutrient formulation [400 ug folic acid, 6 ug B12, 30 I.U. alpha-tocopherol, 400 mg S-adenosyl methionine (SAM), 600 mg N-acetyl cysteine, and 500 mg acetyl-L-carnitine] in AD and MCI patients (Tab I)^{25,26}. In the first RCT, including 106 AD patients randomized to the nutraceutical formulation or placebo for 3 or 6 months, followed by an additional nutraceutical formulation supplementation of 6 months, participants in the intervention group improved statistically *versus* baseline and placebo in cognitive performance evaluated by CLOX-1 (Clock Drawing Test sensitive to executive control) and age- and education-adjusted Dementia Rating Scale (DRS), and in the memory domain of the age-education-adjusted DRS (Tab. I)²⁵. In the second RCT, 34 MCI subjects were randomized for 6 months to the nutraceutical formulation or placebo and then, for another 6-month period, all individuals received nutraceutical formulation. Interestingly, the nutraceutical formulation cohort improved in the age- and education-adjusted DRS and maintained baseline performance in CLOX-1, while the placebo cohort did not improve in the age- and education-adjusted DRS and declined in CLOX-1, but during the open-label extension improved in the age- and education-adjusted DRS and ceased declining in CLOX-1 (Tab. I)²⁶.

MULTIDOMAIN APPROACH

According to the increasing interest on healthy lifestyle

Table I. Randomized clinical trials evaluating the efficacy of nutritional intervention through medical food/nutraceutical supplementation and multidomain approach in the treatment of patients with late-life cognitive disorders aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Medical food/nutraceutical supplementation					
Hartmann et al., 2014 ²¹	96 drug-naïve mild AD patients Mean age: not reported	Fortasyn Connect® Placebo	24 weeks	Plasma concentration of specific PC species	Five of the 7 measured PC species were significantly increased following the 24-week treatment with this multinutrient combination
de Waal et al., 2014 ²²	179 drug-naïve mild AD patients Mean age: 73.3 years	Fortasyn Connect® Placebo	24 weeks	NTB and EEG	Significant effects on network measures in the beta band without significant effects on cognitive outcomes
Rijpmma et al., 2015 ²³	1199 drug-naïve mild and mild-to moderate AD patients Mean age: 74.5 years	Fortasyn Connect® Placebo	12-24 weeks	Plasma levels of B vitamins, choline, vitamin E, selenium, uridine and homocysteine and proportions of DHA, EPA and total n-3 PUFAs in plasma and erythrocytes	12-24-week active product intake increased plasma and/or erythrocyte micronutrients: uridine, choline, selenium, folate, vitamins B6, B12 and E, and levels of DHA and EPA
van Straaten et al., 2016 ²⁴	55 drug-naïve patients with mild AD Mean age: 69.0 years	Fortasyn Connect® Placebo	24 weeks	EEG and MEG	No statistically significant intervention effects
Remington et al., 2015a ²⁵	106 AD patients Mean age: 77.8 years	Nutraceutical formulation (400 ug folic acid, 6 ug B ₁₂ , 30 I.U. alpha-tocopherol, 400 mg S-adenosyl methionine (200 mg active ion), 600 mg N-acetyl cysteine, and 500 mg acetyl-L-carnitine) Placebo	12 months (3 or 6 months with a 6-month open-label extension study)	CLOX-1, DRS, NPI, and ADCS-ADL	At 3 months, there was cognitive improvement for the intervention group in CLOX-1 and the DRS total score and memory domain score
Remington et al., 2015b ²⁶	34 MCI patients Mean age: 62.0 years	Nutraceutical formulation (400 ug folic acid, 6 ug B ₁₂ , 30 I.U. alpha-tocopherol, 400 mg S-adenosyl methionine (200 mg active ion), 600 mg N-acetyl cysteine, and 500 mg acetyl-L-carnitine) Placebo	12 months (6 months with a 6-month open-label extension study)	CLOX-1 and DRS	The nutraceutical formulation cohort improved in the DRS and maintained baseline performance in CLOX-1. The placebo cohort did not improve in DRS and declined in CLOX-1, but during the open-label extension study improved in DRS and ceased declining in CLOX-1



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Multidomain approach					
Köbe et al., 2016 ²⁷	22 MCI patients Mean age: 70 years	Multidomain intervention with n-3 PUFA, aerobic exercise and cognitive stimulation Control group	6 months	AVLT, TMT-A-B, SCWT, forward and backward digit spans, verbal fluency (semantic and phonemic) Erythrocyte membrane fatty acid compositions, anthropometric measures, serum vascular, metabolic and inflammatory parameters, and structural MRI	Gray matter volume decreased in the frontal, parietal and cingulate cortex of patients in the control group, while 39 gray matter volume in these areas was preserved or even increased after the multidomain intervention. No significant differences in cognitive performance or other vascular, metabolic and inflammatory parameters were observed between groups

AD: Alzheimer's disease; PC: phosphatidylcholine; EEG: electroencephalography; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; PUFAs: polyunsaturated fatty acids; MEG: magnetoencephalography; MRS: magnetic resonance spectroscopy; PME: phosphomonoester; PDE: phosphodiester; tCho: choline-containing compounds; MRI: magnetic resonance imaging; CLOX-1: clock drawing task sensitive to executive control; DRS: Dementia Rating Scale; NPI: Neuropsychiatric Inventory; ADCS-ADL: Alzheimer's Disease Cooperative Study – Activities of Daily Living; AVLT: Auditory Verbal Learning Test; TMT-A-B: Trail Making Test part A and B; SCWT: Stroop Color-Word Test

including good dietary habits and physical activity as an effective multidomain therapeutic approach for cognitive impairment, several studies investigated the efficacy of physical exercise programs combined with nutrient supplementations. Epidemiological studies demonstrated that links exist between nutrition, physical activity, and cognitive and social stimulation that help to improve brain health ⁵. The findings of several RCTs have suggested that some single-domain interventions, i.e., antihypertensives, nutritional supplements, cognitive training, and physical activity, had protective effects on cognitive decline ³⁹, but these results have seldom been replicated in larger samples. As prevention has been advocated as an effective way to reduce the burden of AD ⁴⁰, multidomain interventions seem therefore appropriate to target the multiple factors involved in cognition and ageing. In the last years, some European multidomain intervention trials with nutritional guidance, physical exercise, cognitive training and social activities, and management of vascular/metabolic risk factors conducted in subjects at risk of cognitive decline [Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability

(FINGER) ⁴¹ and the Prevention of Dementia by Intensive Vascular care (preDIVA) trial ⁴²] or with subjective memory complaints [Multi-domain Alzheimer Preventive Trial (MAPT) ⁴³] showed some promising findings with beneficial effects on cognition in an at-risk older general population ⁴¹ and some benefits on dementia incidence in at-risk subgroups (i.e., preDIVA participants with untreated hypertension at baseline who adhered to the intervention) ⁴². However, we had only limited data on patients with established cognitive dysfunction. In a recent RCT, the effect of combined n-3 PUFA supplementation, aerobic exercise and cognitive stimulation *versus* n-3 PUFA supplementation and non-aerobic exercise was evaluated on cognitive function and gray matter volume at MRI in patients with MCI (Tab. I) ²⁷. This trial demonstrated that n-3 PUFA intake combined with aerobic exercise and cognitive stimulation over six months led to reduced atrophy in AD-related brain regions of MCI patients, compared to n-3 PUFA intake plus the control condition of stretching and toning. No significant group differences emerged for cognitive parameters over time (Tab. I) ²⁷.

NUTRITIONAL INTERVENTION THROUGH FOOD AND MACRONUTRIENT SUPPLEMENTATION

Foods

Table II shows selected RCTs published in the last four years evaluating the efficacy of nutritional intervention using a food or macronutrient approach in the treatment of patients with late-life cognitive disorders aged over 60 years⁴⁴⁻⁵².

Nuts

Considering the known links among late-life cognitive decline, AD, and oxidative stress^{53,54}, Brazil nuts, the best food source of an important antioxidant trace element, i.e., selenium⁵⁵, have been recently investigated as a possible source of supplementation for late-life cognitive disorders. However, only a few studies have investigated whether selenium supplementation can benefit cognitive performance, and in most of them, selenium was part of a multinutrient supplementation^{33,34,56}. Furthermore, none of these RCTs have used foods rich in selenium as a source of supplementation. Recently, in a small RCT on 31 MCI patients randomly assigned to ingestion of Brazil nuts or placebo for 6 months, verbal fluency, and constructional praxis were the cognitive domains significantly improved in the supplemented group (Tab. II)⁴⁴.

MACRONUTRIENTS

Lipids

In AD brains, it has been reported a reduction in choline acetyltransferase, a biosynthetic enzyme of acetylcholine responsible for converting choline into acetylcholine⁵⁷. Therefore, the first dietary lipids proposed as potential therapeutic agents in AD were lecithin, the major dietary source of choline, and alpha lipoic acid, both able to increase acetylcholine production⁵⁸. However, the first studies documented how use of lecithin, after the first exciting results, has not really helped to improve the cognitive deficits of treated patients in a significant manner⁵⁹. Furthermore, a decline of phospholipids in neuronal membranes, particularly phosphatidylserine (PS), has been associated with memory impairment and deficits in mental cognitive abilities^{60,61}, leading to the proposal that administration of endogenously occurring phospholipids may prevent or reverse age-related neurochemical deficits. Recently, early pilot studies performed with a brain-health food supplement containing a proprietary blend of 100 mg PS and 80 mg phosphatidic acid (PA) produced from soy lecithin have been proposed⁴⁵. Among these studies, a 2-month RCT assessed the effect of three PS/PA capsules/day (300 mg PS plus 240 mg PA/day) or placebo on daily

functioning, mental health, emotional state, and self-reported general condition in patients with AD (Tab. II)⁴⁵. In AD patients, daily functioning (i.e., 7 activities of daily living) under PS/PA (n = 53) remained unchanged, but declined from 5.62 to 4.90 under placebo (n = 39), with significant group difference. The PS/PA group had 3.8% deterioration and 90.6% stability in daily functioning, compared to 17.9% and 79.5% under placebo. The PS/PA patients reported positive trend with a 49% improved general condition, compared to 26.3% under placebo (Tab. II)⁴⁵.

Fatty acids

Many epidemiological studies have demonstrated that dietary fatty acids may play a key role in several pathological conditions. Long-chain (LC) PUFAs, such as DHA, EPA, and arachidonic acid (ARA) are among the most studied macronutrients in late-life cognitive disorders and neurodegeneration⁶². In particular, an increasing body of epidemiological evidence suggested that elevated saturated fatty acids could have negative effects on MCI, while a clear reduction of risk for cognitive decline has been found in population samples with elevated fish consumption, high intake of monounsaturated fatty acids (MUFAs) and LC PUFAs, particularly n-3 PUFAs⁶³. Despite the strong evidence in cognitive decline prevention coming from observational studies, findings coming from RCTs in cognitively healthy older adults were controversial considering the great heterogeneity of samples and outcome measures as well as neuropsychological tools or MRI findings¹². In a RCT, 39 AD patients were randomized for 12 months to placebo, n-3 PUFA supplementation (fish oil concentrate containing a daily dose of 675 mg DHA and 975 mg EPA), or the same n-3 PUFA supplementation plus alpha lipoic acid (600 mg/day). No difference in ADAS-cog between placebo and n-3 PUFA supplementation or between placebo and n-3 PUFA supplementation plus alpha lipoic acid was reported. For MMSE, there was no difference between placebo and n-3 PUFA supplementation, but a significant difference between placebo and n-3 PUFA supplementation plus alpha lipoic acid was found (Tab. II)⁴⁶. In the OmegaAD study, systemic oxidative stress and inflammatory biomarkers were evaluated following oral supplementation of dietary n-3 PUFA (1.7 g DHA and 0.6 g EPA) or placebo for 6 months. In this RCT, F2-isoprostane in urine increased in the placebo group after 6 months, but there was no clear difference in treatment effect between supplemented and non-supplemented patients on the urinary levels of F2-isoprostanes and 15-keto-dihydro-PGF_{2α}. At baseline, the levels of 15-keto-dihydro-PGF_{2α}, a major metabolite of PGF_{2α} and biomarker of inflammatory response, showed negative correlative relationships with

Table II. Randomized clinical trials evaluating the efficacy of nutritional intervention using a food/macronutrient approach in the treatment of patients with late-life cognitive disorders aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Food supplementation					
Cardoso et al., 2016 ⁴⁴	31 older subjects with MCI Mean age: 77.7 years	Daily Brazil nut intake (estimated 288.75 µg of selenium) Placebo	6 months	CERAD neuropsychological test battery total score, CERAD subtests (verbal fluency, BNT, constructional praxis, word list learning test, and word list recall) Blood selenium concentrations, erythrocyte glutathione peroxidase activity, oxygen radical absorbance capacity, and malondialdehyde	In the supplemented group there were significant improvement of some cognitive domains, i.e., verbal fluency and constructional praxis
Macronutrient approach					
Lipids					
Moré et al., 2014 ⁴⁵	96 patients with AD Aged 50-90 years	100 mg phosphatidylserine plus 80 mg phosphatidic acid in lecithin three times daily Placebo (starch)	2 months	7-ADL, MMSE, and RDT	Significant positive effect of this supplementation on daily functioning, positive trends on emotional state and on self-reported general condition. No adverse effects were reported
Fatty acids					
Shinto et al., 2014 ⁴⁶	39 AD patients Mean age: 75.9 years	n-3 PUFAs n-3 PUFAs + alpha-lipoic acid Placebo	12 months	ADAS-cog, MMSE, ADL, and IADL	No difference in ADAS-cog between placebo and n-3 PUFA supplementation or between placebo and n-3 PUFA supplementation plus alpha lipoic acid was reported. For MMSE, there was no difference between placebo and n-3 PUFA supplementation, but a significant difference between placebo and n-3 PUFA supplementation plus alpha lipoic acid was found



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Fatty acids					
Freund-Levi et al., 2014a ⁴⁷	40 moderate AD patients Mean age: 70.5 years	n-3 PUFA (1.7 g DHA and 0.6 g EPA) Placebo	6 months	Urinary levels of F2-isoprostane, 8-iso-PGF _{2α} , and 15-keto-dihydro-PGF _{2α}	F2-isoprostane in urine increased in the placebo group after 6 months, but there was no clear difference in treatment effect between supplemented and non-supplemented patients on the urinary levels of F2-isoprostanes and 15-keto-dihydro-PGF _{2α}
Freund-Levi et al., 2014b ⁴⁸	33 mild-to-moderate AD patients Age: over 65 years	n-3 PUFA (1.7 g DHA and 0.6 g EPA) Placebo	6 months	CSF PUFA levels, plasma PUFA levels, and CSF biomarkers of AD and inflammation	The n-3 PUFA supplemented group displayed significant increases in CSF and plasma EPA, DHA and total n-3 PUFA levels, whereas no changes were found in the placebo group. Changes in DHA levels in CSF were inversely correlated with CSF levels of total and phosphorylated tau, and directly correlated with soluble interleukin-1 receptor type II
O'Callaghan et al., 2014 ⁴⁹	33 MCI patients Age: over 65 years	EPA-rich fish oil (1.67 g EPA plus 0.16 g DHA/day), DHA-rich fish oil (1.55 g DHA plus 0.40 g EPA/day) LA (safflower oil, LA 2.2 g/day)	6 months	Telomere length	Telomere shortening was greatest in the LA group than in the DHA and EPA groups. Increased erythrocyte DHA levels were associated with reduced telomere shortening in the DHA group
Eriksdotter et al., 2015 ⁵⁰	165 AD patients Mean age: 72.5 years	n-3 PUFA (1.7 g DHA and 0.6 g EPA) Placebo Subsequently, all patients received the n-3 PUFA formulation for the next 6 months	12 months	ADAS-cog, MMSE, and plasma PUFA levels	A significant positive association between the changes of plasma DHA levels and changes of total scores of ADAS-cog. No significant correlation between changes of n-3 PUFA levels and changes of MMSE scores nor any of its sub-items



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Fatty acids					
Phillips et al., 2015 ⁵¹	76 participants with CIND or AD Mean age: 71.1 years	n-3 PUFAs (600 mg EPA and 625 mg DHA per day) Placebo (olive oil)	4 months	MMSE, HVLT-R, MMSES7, MMSEWB, BASDEC, other neuropsychological measures of executive functioning, language, verbal reasoning, visual memory, and BADLS	No significant effects on cognitive, depressive, and functional outcomes
Yassine et al., 2016 ⁵²	70 AD patients Mean age: not reported	Algae-derived DHA oil (2 g/day of DHA) Placebo (corn/soy oil)	18 months	Plasma and CSF DHA levels, CSF A β ₁₋₄₂ , tau, and phosphorylated tau. APOE genotype	After 18 months of DHA supplementation, APOE ϵ 4 allele and lower CSF A β ₁₋₄₂ levels were associated with less transport of DHA to CSF. These findings may suggest that brain amyloid pathology may limit the delivery of DHA to the brain in AD

MCI: mild cognitive impairment; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; ADAS-Cog: Alzheimer's disease Assessment scale, Cognitive subscale; VLT: Verbal Learning Test-Revised; MMSE: Mini Mental State Examination; FCSRT: Free and Cued Selective Reminding Test; PS: phosphatidylserine; PA: phosphatidic acid; AD: Alzheimer's disease; ADL: activities of daily living; RDT: Tel-Aviv University Rosen Target Detection test; PUFAs: polyunsaturated fatty acids; IADL: instrumental activities of daily living; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; CSF: cerebrospinal fluid; LA: linoleic acid; CIND: cognitive impairment no dementia; HVLT-R: Hopkins Verbal Learning Test-Revised; MMSES7: mini mental state examination Serial Sevens; MMSEWB: mini-mental state examination World Backwards; BASDEC: Brief Assessment Schedule Depression Cards; BADLS: Bristol's Activities of Daily Living Scale; A β : amyloid B; APOE: apolipoprotein E

n-3 PUFAs, and a positive correlation to the n-6 PUFA linoleic acid (LA), while 8-iso-PGF_{2 α} , a consistent *in vivo* biomarker of oxidative stress, correlated negatively to the n-6 PUFA ARA (Tab. II)⁴⁷. Findings from the same RCT, the OmegaAD study, on 33 moderate AD patients suggested that at 6 months the n-3 PUFA supplemented group (1.7 g DHA and 0.6 g EPA) showed significant increases in cerebrospinal fluid (CSF) and plasma EPA, DHA and total n-3 PUFA levels, whereas no changes were observed in the placebo group. Changes in CSF and plasma levels of EPA and n-3 PUFA docosapentaenoic acid were strongly correlated, in contrast to those of DHA. Changes in DHA levels in CSF were inversely correlated with CSF levels of total and phosphorylated tau, and directly correlated with soluble interleukin-1 receptor type II (Tab. II)⁴⁸. In 33 MCI patients aged over 65 years, randomized to receive a supplement rich in the long-chain n-3 PUFAs EPA (1.67 g EPA plus 0.16 g DHA/day) or DHA (1.55 g DHA plus 0.40 g EPA/day) versus n-6 PUFA LA (2.2 g/day) for 6 months, telomere shortening, a marker of accelerated aging also linked to cognitive ability and MCI⁶⁴, was greater in the LA group than in the DHA and EPA groups. Increased erythrocyte DHA levels were associated with reduced

telomere shortening in the DHA group. These findings suggested that telomeric shortening may be attenuated by n-3 PUFA supplementation (Tab. II)⁴⁹. Other findings from the OmegaAD study on 165 AD patients showed a significant positive association between the changes of plasma DHA levels and changes of total ADAS-cog scores suggesting a potential protective role of increasing plasma n-3 PUFA levels in preservation of cognitive functioning. However, changes of plasma n-3 PUFA levels and changes MMSE scores and its sub-items were not significantly related (Tab. II)⁵⁰. On the other hand, no significant findings on cognitive, depressive, and functional domains have been reported in another RCT including 76 participants [57 with cognitive impairment no dementia (CIND) and 19 with AD] randomized to receive either n-3 PUFAs (600 mg EPA and 625 mg DHA per day) or placebo for 4 months (Tab. II)⁵¹. Finally, in the Alzheimer's Disease Cooperative Study (ADCS)-sponsored DHA clinical trial, at baseline, there were no significant differences between CSF or plasma DHA levels by CSF A β ₁₋₄₂ tertiles or apolipoprotein E (APOE) ϵ 4 status in AD patients supplemented with 2 g/day of DHA or AD patients assuming placebo (Tab. II)⁵². After 18 months of DHA supplementation, participants

at the lowest $A\beta_{1-42}$ tertile had significantly lower CSF DHA levels and lower CSF-to-plasma DHA ratios compared to the other tertiles. Baseline CSF $A\beta_{1-42}$ levels were significantly lower in APOE $\epsilon 4$ carriers than in APOE $\epsilon 4$ noncarriers. Participants carrying the $\epsilon 4$ allele demonstrated a less pronounced increase in CSF DHA level compared with noncarriers, with a possible interaction effect between treatment and APOE genotype. These findings suggested that APOE $\epsilon 4$ allele and lower CSF $A\beta_{1-42}$ levels were associated with less transport of DHA to CSF (Tab. II) ⁵².

NUTRITIONAL INTERVENTION THROUGH MICRONUTRIENT CHANGES

ANTIOXIDANTS VITAMINS AND TRACE ELEMENTS

Table III shows selected RCTs published in the last four years evaluating the efficacy of nutritional intervention through supplementation of dietary micronutrients in the treatment of patients with late-life cognitive disorders aged over 60 years ⁶⁵⁻⁷³. Given the suggested relationship between cognitive impairment and oxidative stress ^{53 54}, and consequently cell death, membranes peroxidation, and $A\beta$ deposition, several antioxidant vitamins or minerals and trace elements with antioxidant properties have been proposed for the treatment of AD, MCI, and other late-life cognitive disorders ⁵⁶. However, findings coming from RCTs were contrasting ¹⁶. In a RCT including 561 AD patients assigned to receive 2000 IU/day of vitamin E (alpha tocopherol), 20 mg/d of memantine, the combination, or placebo, no significant findings have been reported on cognitive outcomes (MMSE, ADAS-cog). However, ADCS-Activities of Daily Living Inventory scores declined significantly less in the vitamin E group compared with the placebo one, suggesting a beneficial effect in slowing functional decline in AD patients (Tab. III) ⁶⁵. Furthermore, in another trial including 256 MCI subjects assigned to receive either 300 mg of vitamin E plus 400 mg vitamin C per day or placebo for one year, no significant differences in MMSE score were reported, despite significant improvement in most of the oxidative stress biomarkers measured (Tab. III) ⁶⁶. Among trace elements with antioxidant properties, selenium was part of multinutrient supplementations in AD ^{33 34 56}. In a 24-week Phase IIa RCT, 40 mild-to-moderate AD patients (MMSE 14-26) with a mean age of 70.5 years were randomized to a supranutritional sodium selenate group (VEL015 10 mg three times per day), chosen for its selenium content and high solubility, or control (VEL015 320 μ g three times per day) or placebo groups. Exploratory biomarkers included cognitive tests, neuroimaging (diffusion

MRI and FDG-PET), and CSF (p-tau, t-tau, and $A\beta_{1-42}$). No significant differences between the supranutritional and control groups were observed for cognition, CSF, and FDG-PET biomarkers. Only one secondary biomarker, diffusion MRI measures, showed group differences, with less deterioration in the supranutritional group (Tab. III) ⁶⁷.

HOMOCYSTEINE-RELATED VITAMINS

A possible modifiable risk factor of dementia is an elevated plasma homocysteine (Hcy) level. In fact, Hcy may be toxic for neurons and vascular endothelial cells ⁷⁴, and cross-sectional and prospective studies have shown associations between elevated Hcy levels and cognitive decline and dementia ⁷⁵. Hcy levels can be lowered by supplementation with folic acid (vitamin B9) and vitamin B12 ⁷⁶. Although observational studies have shown a strong association between poor vitamin B6, B12, and folate levels and increased risk of dementia, suggesting a preventive and protective role of these micronutrients, evidence from RCTs appeared to be unclear ¹². Findings from the Homocysteine and B Vitamins in Cognitive Impairment (VITACOG) trial on 168 MCI patients, randomly assigned either to placebo (n = 83) or to daily high-dose B vitamin supplementation (folic acid, 0.8 mg; vitamin B6, 20 mg; vitamin B12, 0.5 mg) (n = 85) suggested that after 2 years of supplementation there was a significant interaction between B vitamin treatment and plasma combined n-3 PUFA (EPA and DHA) on brain atrophy rates at MRI (Tab. III) ⁶⁸. In MCI subjects with high plasma concentrations of n-3 PUFA (EPA+DHA 0.590 mmol/L), B vitamin supplementation slowed the mean brain atrophy rate by 40% compared with subjects in the placebo group. In contrast, in MCI subjects with low n-3 PUFA concentrations (0.390 mmol/L), there was no beneficial effect of B vitamins on brain atrophy (Tab. III) ⁶⁸. Other findings from the VITACOG trial including 266 MCI subjects randomized to B vitamins (folic acid, vitamins B6 and B12) or placebo for 2 years, final scores for verbal delayed recall (episodic memory), global cognition, and CDR-SB scores were better in the B vitamin-treated group according to increasing baseline plasma concentrations of n-3 PUFAs, whereas in the placebo group scores were similar across these concentrations. These findings suggested that at low n-3 PUFA concentrations, B vitamin treatment had no effect on cognitive decline in MCI. However, at n-3 PUFA plasma levels in the upper normal range, B vitamins might slow cognitive decline. In particular, DHA in this study was more effective than EPA in enhancing the cognitive effects of B vitamins (Tab. III) ⁶⁹. In another RCT including 159 MCI subjects randomized to a daily intervention of 400 μ g folic acid *versus* placebo for 6 months, folic

Table III. Randomized clinical trials evaluating the efficacy of nutritional intervention using a micronutrient approach in the treatment of patients with late-life cognitive disorders aged over 60 years (2014-2016).

Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Antioxidant vitamins and trace elements					
Dysken et al., 2014 ⁶⁵	561 AD patients Mean age: 78.8 years	2000 IU/d of vitamin E (alpha tocopherol) 20 mg/d of memantine 2000 IU of vitamin E (alpha tocopherol) + 20 mg/d of memantine Placebo	5 years (mean follow up: 2.3 years)	ADCS-ADL Inventory, ADAS-cog, MMSE, NPI, CAS, and Dependence Scale	No significant effects on cognitive outcomes
Naeini et al., 2014 ⁶⁶	256 subjects with MCI Mean age: 66.4 years	300 mg of vitamin E plus 400 mg of vitamin C/day Placebo	1 year	MMSE Serum oxidative stress markers Three-day dietary record forms	Despite significant improvement in most of the oxidative stress biomarkers, no significant effects on cognitive outcomes
Malpas et al., 2015 ⁶⁷	40 mild-to-moderate AD patients Mean age: 70.5 years	Supranutritional sodium selenate group (VEL015 10 mg three times per day) Control group (VEL015 320 µg three times per day) Placebo	24 weeks	MMSE, ADAS-Cog, COWAT, CFT, and 3 tests from the CogState computerized battery: OCL, IDN, and DET Diffusion MRI and FDG- PET CSF biomarkers	Only one secondary biomarker, diffusion MRI measures, showed group differences, with less deterioration in the supranutritional group
Homocysteine-related vitamins					
Jernerén et al., 2015 ⁶⁸	168 subjects with MCI Mean age: 76.6 years	Daily high- dose B vitamin supplementation (folic acid, 0.8 mg; vitamin B6, 20 mg; vitamin B12, 0.5 mg) Placebo	2 years	Structural MRI Plasma n-3 PUFA	A significant interaction effect between high-dose B vitamin treatment and n-3 PUFA concentrations on rate of atrophy of the whole brain was found. The beneficial effect of high-dose B vitamin supplementation was augmented by a high baseline status of plasma n-3 PUFA
Oulhaj et al., 2016 ⁶⁹	266 subjects with MCI Mean age: 76.8 years	Daily high- dose B vitamin supplementation (folic acid, 0.8 mg; vitamin B6, 20 mg; vitamin B12, 0.5 mg) Placebo	2 years	HVLT-DR, TICS-M, and CDR Plasma n-3 PUFA APOE genotype	When n-3 PUFA concentrations were low, B vitamin treatment had no effect on cognitive decline in MCI, but when n-3 PUFA levels were in the upper normal range, B vitamins interacted to slow cognitive decline



Reference	Study sample	Intervention(s)	Duration	Cognitive-related outcomes and nutritional assessment	Principal results
Homocysteine-related vitamins					
Ma et al., 2016 ⁷⁰	159 subjects with MCI Mean age: 74.7 years	Folic acid (400 µg/day) Placebo	6 months	WAIS-RC and MMSE Serum Hcy, SAM, SAH, folic acid, and vitamin B12	Folic acid group had statistically significant increase in global cognitive function (WAIS-RC) and some WAIS-RC sub-tests investigating short-term verbal memory and visuoconstructional ability
Chen et al., 2016 ⁷¹	121 patients with AD Mean age: 67.9 years	Donepezil /10 mg / day) plus folic acid (1.25 mg/day) Donepezil /10 mg /day)	6 months	MMSE Serum folate, Aβ, IL-6, TNFα, plasma Hcy, SAM, SAH, and the mRNA levels of PS, IL-6, and TNF-α in leukocytes	The mean MMSE was slightly increased in the intervention group compared to that in the control group. Post-treatment plasma SAM and SAM/SAH levels were significantly higher, while Aβ ₁₋₄₀ , PS1-mRNA, and TNFα-mRNA levels were lower in the intervention group than in the control group. The Aβ ₁₋₄₂ /Aβ ₁₋₄₀ ratio was also higher in the intervention group
Flavonoids and carotenoids					
Gleason et al., 2015 ⁷²	65 AD patients Mean age: 79 years	Soy isoflavones (100 mg/day) Placebo	6 months	List Learning, Paragraph Recall, BVRT, CFR, phonemic fluency, animal fluency, Digit Symbol, Digit Span, SCWT, Mazes, TMT-A-B, CFC, and GPB APOE genotype and plasma isoflavone levels	No cognitive benefits over placebo after 6 months of supplementation, and global cognition declined at similar rates in both treatment and control groups
Nolan et al., 2016 ⁷³	31 AD patients and 31 age-similar control subjects Mean age: 78 years	Carotenoids (10 mg meso-zeaxanthin, 10 mg lutein, 2 mg zeaxanthin) Placebo (sunflower oil)	6 months	MMSE, phonemic fluency, animal fluency, and three tasks from the CANTAB	No significant effects on all cognitive outcomes

AD: Alzheimer's disease; ADCS-ADL: Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADAS: Alzheimer's Disease Assessment Scale; MMSE: Mini Mental State Examination; NPI: Neuropsychiatric Inventory; CAS: Caregiver Activity Survey; MCI: mild cognitive impairment; COWAT: Controlled Oral Word Association Test; CFT: Category Fluency Test; OCL: one-card learning memory task; IDN: identification reaction time task; DET: detection reaction time task; MRI: magnetic resonance imaging; FDG-PET: fluorodeoxyglucose positron emission tomography; CSF: cerebrospinal fluid; PUFA: polyunsaturated fatty acids; HVLT-DR: Hopkins verbal learning test with delayed recall; TICS-M: telephone inventory for cognitive status-modified; CDR: Clinical Dementia Rating; APOE: apolipoprotein E; WAIS-RC: Chinese version of the Wechsler Adult Intelligence Scale-Revised; Hcy: homocysteine; SAM: S-adenosylmethionine; SAH: S-adenosyl homocysteine; Aβ: amyloid β; PS: presenilin; IL-6: interleukin-6; TNF-α: tumor necrosis factor α; BVRT: Benton Visual Retention test; CFR: Complex Figure Recall; SCWT: Stroop Color Word test; TMT-A-B: trail making test part A and B; CFC: Complex Figure Copy; GPB: Grooved Peg Board; CANTAB: Cambridge Neuropsychological Test Automated Battery

acid supplementation was associated with a significant increase in global cognitive function (Chinese version of the Wechsler Adult Intelligence Scale-Revised, WAIS-R) and some WAIS-RC sub-tests investigating short-term verbal memory and visuoconstructional ability, probably related to reduced Hcy levels also observed in this trial after six months, and even after 3 months of supplementation (Tab. III) ⁷⁰. Finally, in another RCT, 121 AD being treated with donepezil were randomly assigned into two groups with (intervention group) or without (control group) supplemental treatment with folic acid (1.25 mg/d) for 6 months. The mean MMSE was slightly increased in the intervention group compared to that in the control group. Folic acid supplementation improved also markers of inflammation suggesting that folic acid may be beneficial in patients with AD in concert with donepezil and that inflammation may play an important role in the interaction between folic acid and AD (Tab. III) ⁷¹.

FLAVONOIDS

Flavonoids [flavanols (catechin, epicatechin, epigallocatechin, and epigallocatechingallate-EGCG), flavonols (quercetin and kaempferol), flavones (luteolin and apigenin), isoflavones (daidzein and genistein), flavanones (esperetin and naringenin), and anthocyanidins (pelargonidin, cyanidine, and malvidin) have also been proposed to prevent or treat cognitive impairment or dementia ⁷⁷⁻⁷⁸. The polyphenol subgroups of flavanols, anthocyanins and flavanones have been shown to be the most beneficial in terms of neuroprotection ⁷⁹. Recent RCTs showed significant improvements in some cognitive domains after flavonoid interventions ⁸⁰. However, the great heterogeneity in sample, flavonoid dose, follow-up and cognitive tests used led to inconsistent findings ⁸⁰. In a RCT, 65 AD patients over the age of 60 were treated with 100 mg/day soy isoflavone, or matching placebo capsules for six months. Although no significant differences in treatment effects emerged on cognitive outcomes between treatment groups or genders, among individuals who were effectively able to metabolize the soy isoflavone daidzein to equol, data suggested an association between plasma levels of equol and performance on verbal fluency and speeded manual dexterity (Tab. III) ⁷².

CAROTENOIDS

Carotenoids lutein and zeaxanthin are found in certain fruits and vegetables (i.e., spinach, broccoli, peppers, melon) ⁸¹, while meso-zeaxanthin has been identified in fish ⁸² and is also believed to be generated from lutein at the retina ⁸³. High carotenoid intake has been found to result in a reduced risk of AD ⁸⁴. Nonetheless, recent interventional studies administering lutein and zeaxanthin

have shown improvement in different domains of cognition in patients free of AD ⁸⁵⁻⁸⁶. Indeed, a RCT in 31 patients with AD and 31 age-similar control subjects who were supplemented with carotenoids (10 mg meso-zeaxanthin, 10 mg lutein, 2 mg zeaxanthin) or placebo (sunflower oil) found no benefit in measures of cognitive function performed in the trial. However, the active supplement improved visual function (contrast sensitivity) in AD and control groups (Tab. III) ⁷³.

DISCUSSION

The association between diet and cognitive function or dementia has been largely investigated in observational studies ⁴, while there was a lack of evidence from RCTs dealing with the treatment of AD and other late-life cognitive disorders through dietary interventions. Indeed, in the last four years, several meta-analyses and systematic/scoping reviews investigated the efficacy of different nutritional supplementations in preventing late-life cognitive disorders in cognitively healthy older adults ⁸⁻¹². However, there were fewer similar studies on patients with dementia, AD, or MCI ¹³⁻¹⁶. In the present article, we systematically reviewed RCTs published in the last four years exploring nutritional intervention efficacy in slowing cognitive impairment progression and achieving cognitive-related outcomes in patients aged 60 years and older with late-life cognitive disorders, using different levels of investigation (i.e., medical food/nutraceutical supplementation/multidomain approach and dietary food/macro- and micronutrient approaches). In the present systematic review, we included studies focusing on dementia, AD, prodromal AD, MCI, and different models of late-life cognitive impairment/decline, but we did not find studies focusing in particular on nutritional intervention for VaD. From the reviewed RCTs, there was emerging evidence that nutritional intervention through medical food/nutraceutical supplementation (Fortasyn Connect®) and multidomain approach improved MRI findings and cognitive-related biomarkers (plasma lipid biomarker profile prognostic of AD, EEG findings, and circulating levels of supplemented micro- and macronutrients), but without clear effect on cognition in mild AD and MCI and with one substantially negative MEG study. However, another nutraceutical formulation showed positive effects on specific cognitive domains in AD and MCI patients (Tab. I). Moreover, for food supplementation, there was some evidence of a positive effect of antioxidant-rich foods (nuts) in improving specific cognitive domains and cognitive-related outcomes in MCI and mild-to-moderate dementia, but only in small samples (Tab. II). For lipid supplementation, there were only

limited effects of phospholipids in MCI and mild AD, while there was convincing evidence for fatty acid supplementation, mainly n-3 PUFAs, in improving specific cognitive domains and/or cognitive-related biomarkers in MCI and AD (Tab. II). Furthermore, among selected RCTs that evaluated the efficacy of nutritional intervention through supplementation of dietary micronutrients, there was evidence for antioxidant vitamin and trace element supplementations of an impact in improving only cognitive-related outcomes and biomarkers, without effect on cognitive function in AD and MCI patients (Tab. III). For Hcy-related vitamin supplementation, there was evidence of an impact of high-dose B vitamin supplementation in AD and MCI patients in improving cognitive outcomes but only in the subjects with a high baseline status of plasma n-3 PUFA, and of folic acid supplementation in improving specific cognitive domains. Finally, there was no evidence of significant improvement in cognitive outcomes after flavonoid and carotenoid supplementations (Tab. III).

In the last four years, some meta-analyses and systematic reviews investigated the efficacy of different nutritional supplementations for the treatment of AD and other late-life cognitive disorders^{13-16 78}. For patients with MCI, AD, or dementia, other recent systematic reviews and meta-analyses investigating less recent RCTs suggested some efficacy of medical foods/nutraceuticals in specific cognitive domains at early stage of AD¹⁵ or in patients with dementia, AD, and MCI with also neuropsychological symptoms⁷⁸. An increasing body of evidence suggested that Fortasyn Connect® could have clinically detectable effects in early AD patients³⁷. In fact, considering that synapses formation is compromised by the neurodegeneration characterizing the later stages of AD, the potential beneficial effect on neuroprotection and synaptogenesis of Fortasyn Connect® may be limited in later AD stages compared with earlier ones³⁷. Furthermore, other systematic reviews found no convincing evidence for the efficacy of n-3 PUFA supplements in the treatment of mild to moderate AD, at least on cognitive outcomes¹⁴, or vitamin E supplementations in people with MCI to prevent progression to dementia, or improve cognitive function in people with MCI or dementia due to AD¹⁶. Finally, another systematic review and meta-analysis found weak evidence of benefits with vitamins B supplementation for the domain of memory in patients with MCI, with no significant cognitive benefits in AD patients¹³. Therefore, while there were encouraging findings with specific dietary supplementations in the earlier phases of AD or MCI, results from RCTs were contrasting for moderate AD patients probably based also on a great heterogeneity in sample size.

In the last years, considering the known less efficacy of single nutrients *versus* combined ones in improving cognitive function and the bidirectional interaction between cognitive and physical dimensions in older age⁸⁷, several studies proposed medical foods or a multidimensional approaches, including supplements and physical activity, with some promising results in subjects with and without cognitive impairment^{27 41-43}, particularly in at-risk subgroups. Considering evidence showing a greater efficacy of nutritional intervention in earlier stage of AD, it is necessary to increase disease biomarkers use in order to allow diagnosis in the earlier phase of cognitive dysfunction, i.e., subjective memory decline⁸⁸, so identifying subjects at risk of developing AD and dementia.

However, some limitations should be reported for the present systematic review article. An important limitation was linked to the great heterogeneity of included RCTs not only in terms of study samples and trial durations, but also in relation to the outcome measures and nutrients intake quantification. This heterogeneity made really difficult to give clear answers about the efficacy of dietary intervention in older adults without cognitive dysfunction. However, there are several interesting concepts coming from the reviewed RCTs to underline. The first one was the emerging use of innovative measures of dietary habits, not only daily semi-quantitative food frequency questionnaires but also biomarker dosages such as blood exams or urinary excretion. This resulted into an objective quantification of nutrient supplementation but also of nutritional status of patients at baseline. Furthermore, as shown in the present systematic review, recent RCTs underlined the importance to consider emerging cognitive-related outcomes in order to achieve more clinically focused and reliable findings. Therefore, in addition to clinical scales and neuropsychological tests, serum, CSF, neuroimaging, and other cognitive-related biomarkers have been proposed. The result was an objective quantification of dietary habits and nutritional state of patients at baseline and of the nutrition-related impact on cognitive impairment and AD pathobiology to achieve more clinically focused and reliable findings. In conclusion, medical food/nutraceutical supplementation (Fortasyn Connect® and another similar combinatorial formulation), nutritional interventions with antioxidant-rich foods (nuts), and macronutrient (n-3 PUFAs) and micronutrient (antioxidant and Hcy-related vitamins) supplementations could be really effective in achieving cognitive-related outcomes in MCI and AD patients. However, to obtain more statistically significant and reliable results, RCTs would be conducted in larger selected samples characterized by well defined cognitive function status, nutritional and dietary habits at baseline, with longer follow-up, and would include further objective measures of

cognitive-related outcomes as blood or CSF biomarkers and neuroimaging findings.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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