J Nutr Health Aging. 2019;23(9):805-812

RED BLOOD CELL OMEGA-3 FATTY ACID COMPOSITION AND PSYCHOTROPIC DRUG USE IN OLDER ADULTS: RESULTS FROM THE MAPT STUDY

A. GALLINI[*,1,2,3], A. YRONDI[*,2,4], C. CANTET[1,2,5], M. PONCET[3], B. VELLAS[1,2,5], L. SCHMITT[2,4], S. ANDRIEU[1,2,3] FOR THE DSA/MAPT STUDY GROUP[**]

1. UMR 1027, Inserm, Toulouse, France; 2. Université Paul Sabatier Toulouse III, Toulouse, France; 3. CHU Toulouse, Service d'Epidémiologie, Toulouse, France; 4. CHU Toulouse, Service de Psychiatrie, Toulouse, France; 5. CHU Toulouse, Gérontopôle, Toulouse; * these authors contributed equally to this work ** Members are listed at the end of the manuscript. Corresponding author: Adeline Gallini, PharmD, PhD, Epidemiology Department 37 allées Jules Guesde, 31062 Toulouse Cedex, Tel : +33 5 61 14 56 81, Fax : + 33 5 62 26 42 40, Email : adeline.gallini@univ-tlse3.fr

Abstract: Low docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) concentration has been associated with the development of some psychiatric disorders. *Objectives:* to assess the association between red blood cell (RBC) DHA-EPA concentration and psychotropic drug use in older adults and between the 1-year change in RBC DHA-EPA and psychotropic drug use at 12 months. *Design:* secondary analysis of multicenter, randomized controlled trial testing multidomain intervention and/or n-3 PUFA supplement on cognitive function (MAPT study). *Setting:* France, 2008-2014. *Participants:* 1680 participants ≥70 years, community-dwelling were included. *Measurements:* Psychotropic drug use was self-reported during medical interviews and assessments. RBC n-3 PUFA concentration was defined by % of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) among total fatty acids. Logistic regressions models controlling for age, sex, education, depression risk and intervention group were used. *Results:* 1594 participants had baseline DHA-EPA concentration available (mean age=75.5±4.5 years, 65% females). At baseline, participants with DHA-EPA ≤4.82% (lowest quartile) reported higher prevalence of use of overall psychotropic drugs (34.0% vs 24.4%; aOR=1.33, 95%CI=[1.03-1.72]), anxiolytic/hypnotic drugs (25.0% vs 18.2%; aOR=1.42, 95%CI=[1.07-1.89]), and antidepressants (18.3% vs 13.5%; aOR=1.25, 95%CI=[0.93-1.72]) than participants with higher DHA-EPA. Participants who experienced an increase in DHA-EPA from baseline were less likely to use a psychotropic drug at 12 months than participants with no change or a decrease (aOR=0.72, 95%CI=[0.55-0.96]). *Conclusion:* Low RBC DHA-EPA concentration was independently associated with psychotropic drug use. Future studies are needed to assess whether low RBC DHA-EPA is a risk marker for psychotropic drug use in older adults and to better understand underlying pathophysiological mechanisms. Registration number: ClinicalTrials.gov database (NCT00672685).

Key words: Psychotropic drug use, omega-3 fatty acids, elderly, prevention.

Background

Omega-3 polyunsaturated fatty acids (n-3 PUFAs), including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are key regulators of neurotransmission, neurogenesis and neuroinflammation and are therefore involved in brain development and functioning throughout lifespan (1, 2). Low levels of DHA-EPA have been found in series of patients suffering from various mental disorders including schizophrenia and mood disorders (3–5). In older adults, the attention has mostly been directed towards the role of DHA-EPA in cognitive function (6) or Alzheimer's disease (7) and little is known about the role of DHA-EPA in mental disorders and consequently psychotropic drug use in this population.

The use of psychotropic drugs in older populations is common, raising public health challenges. About 19% of subjects aged 65 years or older reported using at least 1 psychotropic drug over the last 12 months in 2000 in 6 Western European countries (ESEMeD/MHEDEA project) (8). And psychotropic drug use does not always overlap with an indication (9). In the ESEMeD/MHEDEA project, 10% of subjects without any mental disorder (according to the Diagnostic and Statistical Manual of Mental Disorders IV) were using psychotropic drugs (8). In a US cohort of older adults who recently started a psychotropic medication, clinical assessment retrieved a near-absence of symptoms of depression or anxiety in most subjects (10).

We make the hypothesis that low red blood cell (RBC) DHA-EPA concentration is independently associated with psychotropic drug use in older adults. These prescriptions are, in most cases, secondary to subjective complaints that do not fall within the scope of a psychiatric pathology (9), and therefore we believe that studying psychotropic drug use per se is relevant in this population.

Therefore, we aimed to assess the association between RBC DHA-EPA concentration and psychotropic drug use in older adults and to assess the relationship between the change in RBC DHA-EPA concentration and psychotropic drug use at 12 months.

Received March 29, 2019
Accepted for publication April 15, 2019
Published online September 12, 2019, http://dx.doi.org/10.1007/s12603-019-1252-4

Materials and Methods

Mapt study

This analysis was based on participants from the Multidomain Alzheimer Preventive Trial (MAPT) who were recruited between 2008 and 2011 throughout France. MAPT is a 36-month, multicenter, randomized controlled trial comparing the effect of 3 intervention groups (multidomain intervention and/or DHA-EPA supplement) and a placebo group on cognitive function. The study protocol was approved by French Ethical Committee, was authorized by competent authorities and registered in ClinicalTrials.gov database (NCT00672685). Full methods are described elsewhere (11). Briefly, participants were 70 years or older, community-dwelling and had to meet one of the three following criteria: (i) spontaneous memory complaint expressed to their physician, (ii) limitation in one instrumental activity of daily living (IADL) (12), or (iii) slow walking speed (i.e. ≤ 0.8 m/s). Subjects with a Mini Mental State Examination (MMSE) (13) score lower than 24, diagnosed with dementia, those with any difficulty in basic activities of daily living (ADL) (14) or those with any disease (e.g. severe depression, generalized anxiety) that could compromise the subject's participation were not included. Subjects using n-3 PUFA supplements at baseline were not included. Written informed consent was obtained from all participants.

Participants were randomized into 4 groups (ratio 1:1:1:1): (i) combined intervention (multidomain intervention plus nDHA-EPA supplement), (ii) multidomain intervention plus placebo, (iii) DHA-EPA supplement alone, or (iv) placebo alone. The multidomain intervention consisted of group sessions focusing on cognitive stimulation, physical activity and nutrition, and a preventive consultation. Participants were asked to take 2 capsules a day, containing either the DHA-EPA supplement or the placebo of similar appearance and taste. The DHA-EPA supplement contained natural fish oil providing a total daily dose of 800mg DHA and a maximum of 225mg EPA, which exceeded doses that can be obtained through diet alone. Details about procedures can be found elsewhere (11).

At baseline, and the 6- 12-, 24-, and 36-month visits, physical and neuropsychological examination of subjects was performed.

The primary outcome was a composite score of cognitive tests and results of the main analysis have been published elsewhere (15).

Psychotropic drugs

The use of any drug (prescribed or over-the-counter drug) was self-reported by the participant at each visit. In case of uncertain reports, a proxy was contacted. For each drug, we determined if the participant was exposed at a certain visit (e.g. baseline, 12-month visit) if the drug was ongoing at the date of the visit.

Drugs were coded using the World Health Organization's Anatomical, Therapeutic and Chemical (ATC) classification (16). We defined psychotropic drugs as antipsychotics and lithium (N05A), anxiolytic/hypnotic drugs (N05B, N05C) and antidepressants (N06A, N06CA). We also separately investigated the use of anxiolytic/hypnotic drugs and antidepressants.

%DHA+EPA

Red blood cell (RBC) fatty acid composition was examined at baseline and 12-month visit. RBC fatty acid analysis has low biological variability and measures long-term intake of DHA and EPA (17).

After extraction of lipids from red blood cells, %DHA-EPA of total fatty acids was determined using gas chromatography (11). Since there was no consensual cut-off to define low DHA-EPA concentration, we used the lowest quartile of DHA-EPA distribution to define participants with low baseline DHA-EPA (i.e. ≤ 4.82% in our analysis population).

According to the change in DHA-EPA concentration between baseline and 12 months, we defined 2 groups of participants: participants with no change or a decrease in DHA-EPA and participants with an increase in DHA-EPA. To our knowledge, there is no consensual cut-off value that could be used to determine a significant change in DHA-EPA.

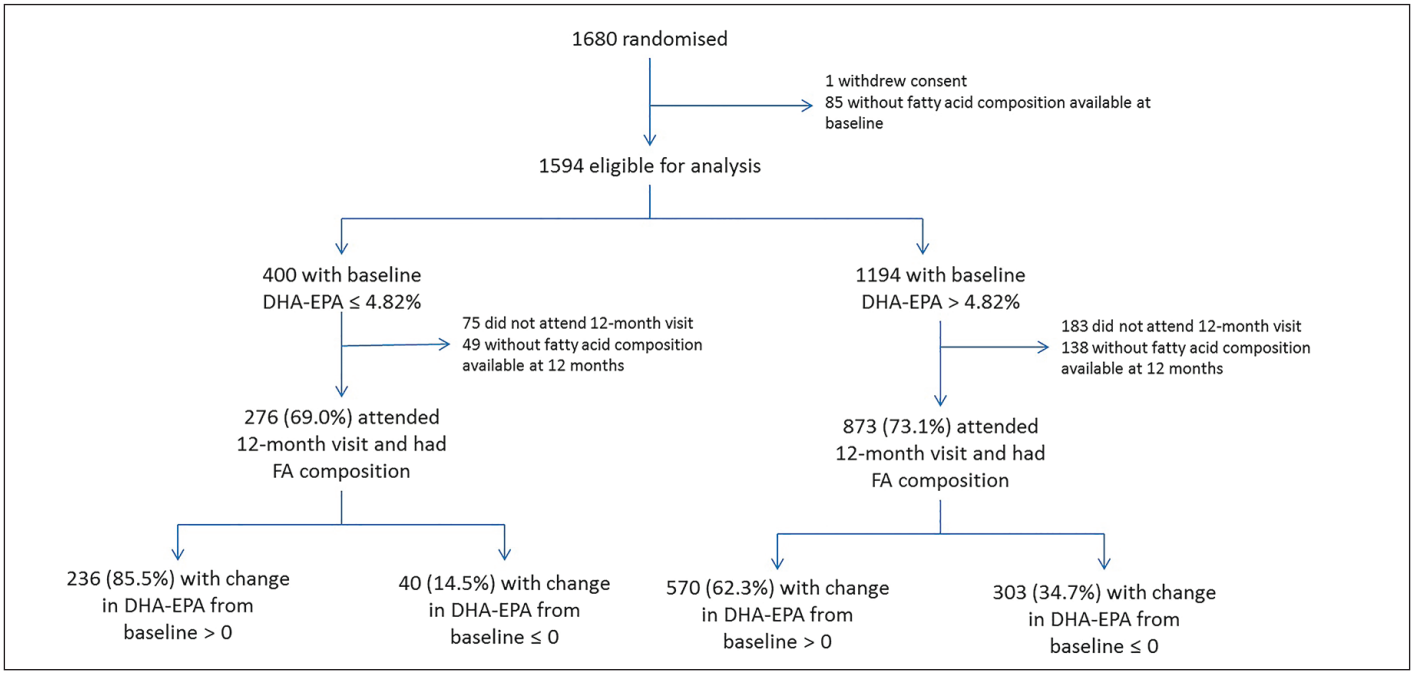
Other variables

Among variables measured in the MAPT Study, we used the following covariates that were measured at baseline. They consisted of sociodemographics (age, sex, education level), examination of physical and cognitive function (gait speed measured over 4 meters, frailty status as measured by Fried's criteria (18,19), independence for instrumental activities of daily living, and mini-mental state examination) and evaluation of depressive symptomatology using the Geriatric Depression Scale (GDS) (20).

Statistical analyses

The present analysis was restricted to participants with available RBC fatty acid analysis at baseline. We compared the characteristics of participants with low or high RBC DHA-EPA concentration at baseline using chi2 tests or Fisher exact tests where appropriate. The association between low DHA-EPA and psychotropic drug use was investigated using multivariable logistic regression controlling for age, sex, education and GDS. Covariates were chosen a priori based on literature review of potential confounding factors. Interactions were tested. For analyses of the association between change in RBC DHA-EPA concentration and psychotropic drug use, multivariate logistic regression models were used controlling for age, sex, education, GDS and intervention arm. Sensitivity analyses included a larger adjustment on frailty status, and were conducted to separately study the association between low DHA and psychotropic drug use and between low EPA and psychotropic drug use. All statistical analyses were performed

Figure 1
Flow chart of participants in the MAPT study according to red blood cell DHA-EPA quartile (N=1680)



Abbreviations: DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; FA: fatty acids.

using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

1680 participants were included in the MAPT study. In this analysis, only participants with available red blood cell fatty acid composition at baseline were included (N=1594, 94.9%) (Figure 1). There were no significant differences on major characteristics between participants with or without FA composition available, but for gait speed where participants without FA composition were more likely to walk slowly than participants with FA composition (21% had gait speed ≤ 0.8m/s vs 11%) (Supplementary Table 1).

At baseline, mean age was 75.5 years ± 4.5 (SD), 65% were females and mean MMSE was 28.0 ± 1.7. Mean DHA-EPA concentration was 5.9% ± 1.5 (Table 1). We defined participants with low RBC DHA-EPA concentration as participants within the lowest quartile of the DHA-EPA distribution: i.e. 400 participants with DHA-EPA concentration ≤ 4.82% (mean: 4.0% ±0.6) vs 1194 participants with DHA-EPA concentration >4.82% (mean 6.2% ±1.2). At baseline, participants with low DHA-EPA concentration were more likely to have lower educational attainment (31.5% had no education or only primary education vs 19.2%, p<0.001), poorer cognitive performance (mean MMSE score: 27.9 ±1.7 vs 28.2 ±1.6, p=0.002), more likely to be considered pre-frail or frail according to Fried's criteria (51.2% had at least 1 frailty criteria vs 44.7%, p=0.027) and more often had a GDS score ≥ 5 (30.7% vs 24.4%, p=0.013) than participants with higher DHA-EPA concentration.

Overall, 28.5% reported the use of at least 1 psychotropic drug, 19.9% ≥ 1 anxiolytic/hypnotic drug (93% of those were using ≥ 1 benzodiazepine drug) and 14.7% ≥ 1 antidepressant at baseline. Very few participants used antipsychotics (N=12) or lithium (N=2). Participants with low DHA-EPA concentration consistently reported higher prevalence of use of psychotropic drugs than participants with higher DHA-EPA concentration: 34.0% vs 24.4% for overall psychotropic drugs (p=0.005), 25.0% vs 18.2% for anxiolytic/hypnotic drugs (p=0.003), 18.3% vs 13.5% for antidepressants (p=0.020) (Table 1). Corresponding crude odds-ratios (OR) are presented in Table 2. Controlling for age, sex, education and risk of depression (GDS ≥ 5), the association between low DHA-EPA concentration and higher use of psychotropic drugs remained significant for overall psychotropic drugs (adjusted OR aOR=1.33, 95%CI=[1.03-1.72]), for anxiolytic/hypnotic drugs (aOR=1.42, 95%CI=[1.07-1.89]), but not for antidepressants (aOR=1.25, 95%CI=[0.90-1.72]) (Table 2). Parameters associated with covariates in adjusted models are presented in Supplementary Table 2.

At 12 months, 15.8% and 14.0% of participants with low and high baseline DHA-EPA concentration had dropped off, respectively (p=0.320) (Figure 1). Overall, 1336 participants attended the 12 month-visit and 29.9% were exposed to at least 1 psychotropic drug at 12 months. Red blood cell FA composition was available for 1149 participants at 12 months (86.0% of the participants who attended the 12-month visit)

Table 1
Baseline characteristics of participants according to red blood cell DHA-EPA quartile (MAPT, N=1594)

				DHA-EPA quartile				
		Total N=1594		Lowest quartile ≤ 4.82% N=400		3 highest quartiles > 4.82% N=1194		p*
Baseline characteristics		**N or mean**	**% or SD**	**N or mean**	**% or SD**	**N or mean**	**% or SD**	
DHA+EPA % (mean, SD)		5.88	1.53	4.02	0.63	6.50	1.21	--
Age (N,%)								0.034
	<75 years	785	49.2	175	43.7	610	51.1	
	75-79 years	519	32.6	141	35.3	378	31.7	
	80 years or older	290	18.2	84	21.0	206	17.2	
Female (N,%)		1037	65.1	253	63.2	784	65.7	0.381
Education level (N,%)								<0.001
	No diploma or primary school certificate	347	22.7	123	31.5	224	19.2	
	Secondary education	522	33.5	129	33.1	393	33.6	
	High-school diploma or higher	689	44.2	138	35.4	551	47.2	
BMI kg/m² (mean, SD)		26.12	4.06	26.41	3.77	26.02	4.15	0.099
Walking speed ≤ 0.8 ms/s (N,%)		181	11.5	56	14.1	125	10.6	0.053
≥ 1 limitation in IADL /5 (N,%)		84	5.5	25	6.4	59	5.1	0.342
MMSE (mean, SD)		28.07	1.59	27.86	1.69	28.15	1.55	0.002
Score CDR = 0.5 (N,%)		669	42.0	174	43.6	495	41.5	0.451
≥ 1 Fried's frailty criteria (N,%)		707	46.3	197	51.2	510	44.7	0.027
GDS ≥ 5 (N,%)		412	26.0	122	30.7	290	24.4	0.013
Intervention arm								0.307
	PUFA supplementation + multidomain intervention	399	25.0	104	26.0	295	24.7	
	PUFA supplementation alone	401	25.2	111	27.8	290	24.3	
	Multidomain intervention	394	24.7	87	21.8	307	25.7	
	Control	400	25.1	98	24.5	302	25.3	
≥ 1 psychotropic drug (N,%)		455	28.5	136	34.0	455	28.5	0.005
≥ 1 anxiolytic-hypnotic drug (N,%)		317	19.9	100	25.0	317	19.9	0.003
≥ 1 antidepressant drug (N,%)		234	14.7	73	18.3	234	14.7	0.020

Abbreviations: BMI: body mass index, CDR: clinical dementia rating, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, GDS : geriatric depression scale, IADL : instrumental activities of daily living, MMSE : mini-mental state examination, SD : standard deviation; * Chi square tests or exact Fisher tests for categorical variables according to frequencies; t-tests or Mann-Whitney-Wilcoxon tests for continuous variables according to their distribution.

(Figure 1). On average, DHA-EPA concentration increased by 1.70% ± 2.56 between baseline and 12 months. This increase was more pronounced in the group of participants with low baseline DHA-EPA concentration, where 55% of subjects were randomized in PUFA supplementation groups vs 48% of subjects with higher baseline DHA-EPA concentration (+3.05% ± 2.50 vs +1.28% ± 2.42, p<0.001) (Figure 2). Taking into account PUFA supplementation randomization group, participants with low baseline DHA-EPA still experienced a superior increase in DHA-EPA concentration between baseline and 12 months compared to participants with higher baseline DHA-EPA concentration (inter-group difference=+1.54%, SE=0.14, p<0.001). Overall, 806 participants (70.1%; 85.5% of participants with low baseline DHA-EPA and 62.3% with high baseline DHA-EPA concentration) experienced an increase in DHA-EPA concentration between baseline and 12 months (mean change: +2.92% ± 1.99) and 343 participants (29.9%) experienced no change or a decrease in DHA-EPA concentration (-1.16% ± 0.94, 25% experienced a decrease of less than 0.5%) (Figure 1).

Table 3 presents the association between 12-month change in DHA-EPA concentration and the probability of being exposed to a psychotropic drug at 12 months. Participants who experienced an increase in DHA-EPA concentration were less likely to use a psychotropic drug at 12 months (aOR=0.72, 95%CI=[0.55-0.96]) than participants with no change or a decrease in DHA-EPA concentration controlling for age, sex, education, baseline GDS and multidomain intervention. Similar association was found with antidepressant use (aOR=0.66, 95%CI=[0.47-0.94]) and there was a non-significant trend towards the same association for the use of anxiolytic/hypnotic drugs (aOR=0.79, 95%CI=[0.58-1.09]). Supplementary Table 3 presents aORs for covariates.

When taking into account both the change in DHA-

Table 2
Association between low DHA-EPA concentration and use of psychotropic drugs at baseline in MAPT study (N=1549)

	Crude analysis			Multivariate analysis*		
Use of at least 1	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
Psychotropic drug	1.41	1.11-1.80	0.005	1.33	1.03-1.72	0.031
Anxiolytic/hypnotic drug	1.50	1.15-1.97	0.003	1.42	1.07-1.89	0.015
Antidepressant	1.43	1.06-1.94	0.020	1.25	0.90-1.72	0.184

* Logistic regression controlling for age (3 classes), sex, education (3 classes) and GDS (<≥ 5); OR: odds-ratio, 95%CI: 95%-confidence interval for the estimated odds-ratio, p: p-value from logistic regressions

Table 3
Association between change in DHA-EPA concentration between baseline and 12 months and the use of psychotropic drugs at 12 months in MAPT study (N=1149)

	Change in DHA-EPA		Crude analysis			Multivariate analysis*		
Use of at least 1	**No change or Decrease N=343**	**Increase N=806**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
Psychotropic drug	120 (35.0%)	224 (27.8%)	0.72	0.55-0.94	0.015	0.72	0.55-0.96	0.025
Anxiolytic/hypnotic drug	80 (23.3%)	152 (18.9%)	0.76	0.56-1.04	0.085	0.79	0.58-1.09	0.147
Antidepressant	67 (19.5%)	112 (13.9%)	0.67	0.48-0.93	0.016	0.66	0.47-0.94	0.019

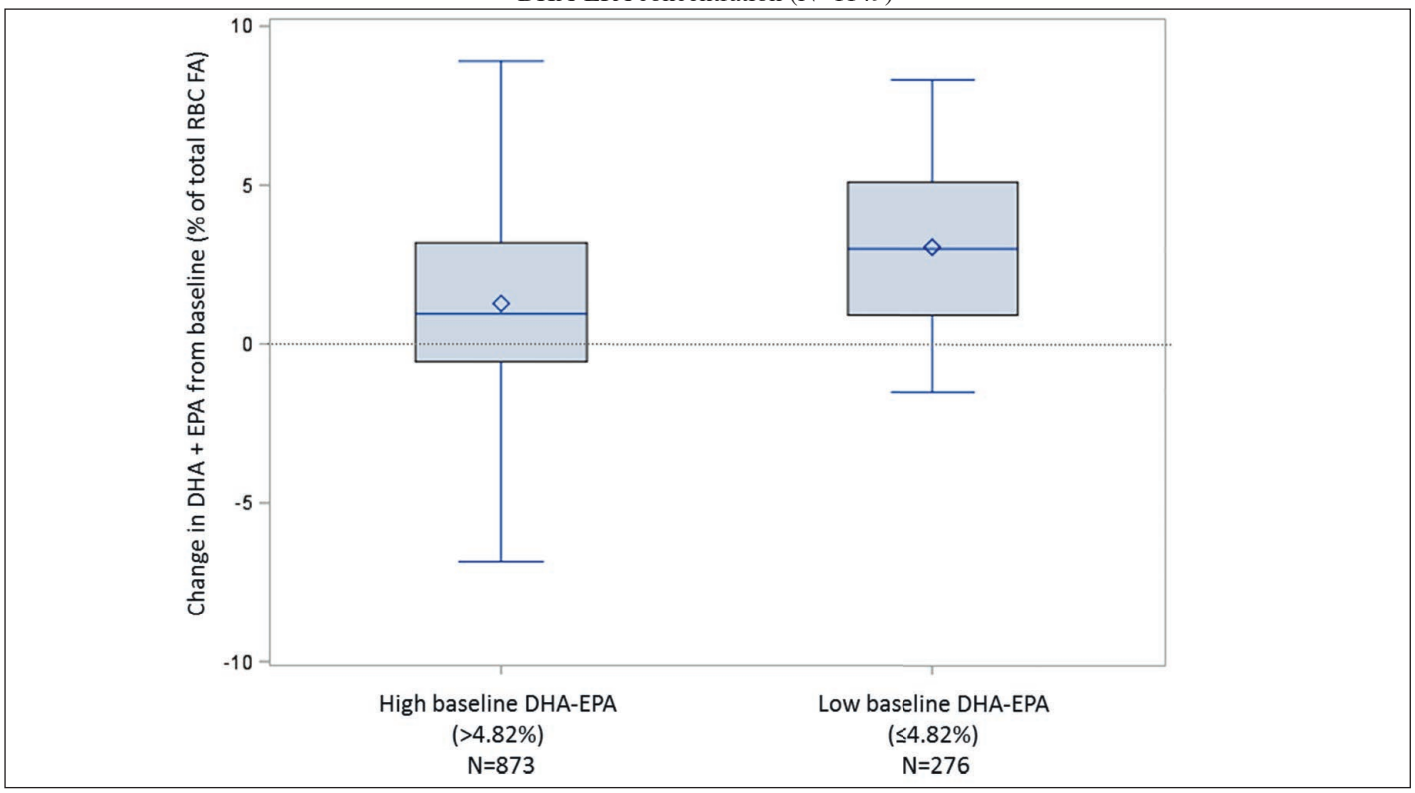
* Logistic regression controlling for age (3 classes), sex, education (3 classes), baseline GDS (<≥ 5) and multidomain intervention [N=1126]; OR: odds-ratio for the association with an increase in DHA-EPA concentration (reference = decrease or no change), 95%CI: 95%-confidence interval for the estimated odds-ratio, p: p-value from logistic regressions

Table 4
Factors associated with the use of overall psychotropic drugs, anxiolytic-hypnotic drugs or antidepressants at 12 months in MAPT study taking into account baseline DHA-EPA quartile and evolution (N=1126)

	Psychotropic Drugs			Anxiolytic-Hypnotic Drugs			Antidepressants		
Characteristics	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**	**OR**	**95%CI**	**p**
Change in DHA-EPA from baseline function of baseline DHA-EPA quartile*			0.056			0.148			0.125
High baseline DHA-EPA and change >0	1			1			1		
High baseline DHA-EPA and change ≤0	1.54	1.13-2.12		1.45	1.01-2.07		1.48	1.00-2.18	
Low baseline DHA-EPA and change >0	1.30	0.92-1.85		1.43	0.97-2.11		1.01	0.64-1.58	
Low baseline DHA-EPA and change ≤0	1.21	0.58-2.50		1.23	0.54-2.81		1.80	0.80-4.04	
Age			0.140			0.059			0.723
<75 years old	1			1			1		
75-80 years old	1.22	0.90-1.65		1.28	0.91-1.80		0.92	0.63-1.35	
80 years old or more	1.41	0.99-2.02		1.60	1.08-2.39		1.12	0.71-1.75	
Female	1.65	1.23-2.20	0.001	1.56	1.12-2.18	0.008	1.49	1.03-2.16	0.033
Education			0.665			0.251			0.582
No diploma or primary school certificate	0.89	0.62-1.28		0.70	0.46-1.07		1.26	0.81-1.95	
Secondary education	1.06	0. 8-1.43		0.91	0.65-1.29		1.14	0.78-1.67	
High school diploma or university level	1			1			1		
Baseline GDS >=5	2.95	2.20-3.95	<0.001	2.73	1.99-3.76	<0.001	2.89	2.05-4.09	<0.001
Multidomain intervention	1.15	0.88-1.51	0.291	1.00	0.74-1.35	0.998	1.29	0.92-1.80	0.136

OR: odds-ratio, 95%CI: 95%-confidence interval for the estimated odds-ratio, p: p-value from logistic regression; DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, GDS: Geriatric Depression Scale; *high baseline DHA-EPA: >4.82%; low baseline DHA-EPA: ≤4.82%

Figure 2
Distribution of the change in red blood cell DHA-EPA concentration (%) between baseline and 12 months according to baseline DHA-EPA concentration (N=1149)



Positive values indicate higher DHA-EPA concentration at 12 months than at baseline. Diamond ◊ indicates mean value. Abbreviations: DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; RBC FA: red blood cell fatty acids.

EPA concentration and baseline DHA-EPA concentration, the probability of using a psychotropic drug at 12 months was lowest for participants with high baseline DHA-EPA concentration and who experienced an increase in DHA-EPA concentration over the 12 months (Table 4). In participants with high baseline DHA-EPA concentration, the odds of using psychotropic drugs, anxiolytic/hypnotic drugs and antidepressants were significantly higher in participants who experienced no change or a decrease in DHA-EPA from baseline compared to participants who experienced an increase (aOR=1.54, 95%CI=[1.13-2.12]; aOR=1.45, 95%CI=[1.01-2.07], aOR=1.48, 95%CI=[1.00-2.18], respectively). Compared with participants with high baseline DHA-EPA concentration and who experienced an increase, participants with low baseline DHA-EPA concentration, whether they experienced an increase or not in DHA-EPA concentration, were consistently at higher risk of using any psychotropic drug at 12 months, but this was not statistically significant (Table 4).

Results were stable in sensitivity analyses with further control for frailty status and when considering only either DHA or EPA concentration (not shown).

Discussion

Our study has three main findings. First, older adults with low RBC DHA-EPA concentration were exposed to a 33% increase in the prevalence of psychotropic use at baseline than counterparts with high DHA-EPA concentration, controlling for known risk factors of psychotropic drug use such as female sex, age, education level or presence of depressive symptoms (21–23). Second, over 12 months, participants who experienced an increase in DHA-EPA concentration from baseline, mainly through supplementation, had a 27% lower chance to use a psychotropic drug at 12 months than participants with no change or a decrease. Third, at 12 months, among participants with low baseline DHA-EPA concentration, there was no significant difference in the chance of using psychotropic drugs between participants who had experienced or not an increase in DHA-EPA concentration.

Low baseline DHA-EPA concentration tended to be associated with older age, depressive symptoms and poorer physical and cognitive function; therefore suggesting that low RBC DHA-EPA concentration could represent a risk marker of various pejorative health outcomes in the old age, as well as psychotropic drug use. Furthermore, low RBC DHA-EPA concentration represented a risk marker for psychotropic

drug use in older adults independently of sex, age, education, depressive symptoms (and frailty status [not shown]). To our knowledge, no study has specifically studied the relationship between RBC DHA-EPA concentration and psychotropic drug use in older adults. Nonetheless, our results are in line with epidemiological studies that have found a relationship between PUFAs and mental illnesses (3–5,24) but not with findings from the Nurses Health study where the intake of long-chain n-3 PUFA as measured by food frequency questionnaires was not associated with depression risk (25). Our results are also in line with biological evidence proposing a causal mechanism between low n-3 PUFAs and mental illnesses development (1). Furthermore, one study conducted in the general older population has evidenced the role of antidepressants on the relationship between plasmatic EPA, but not DHA, concentration and severity of depressive symptomatology (26), highlighting the relevance of the approach we followed distinguishing between the drug and the disease in the older population.

Future studies are needed to assess whether low RBC DHA-EPA concentration could be a risk factor (i.e. assess the plausibility of a causal relationship) for psychotropic drug use in older adults, and in particular for inappropriate psychotropic drug use. Reducing inappropriate psychotropic drug use in older adults is a public health challenge. Therefore, identifying a modifiable risk factor of such use could have implications in clinical practice. For instance, older adults identified with low RBC DHA-EPA could be carefully screened for anxiety, depressive or sleep disorders. In this study, we did not have access to the appropriateness of psychotropic drug use. However as evidenced in the literature, prevalence of misuse is high in the older population and is awaited to also be high in this study that did not include patients suffering from major psychiatric conditions.

Furthermore, studies would be needed to assess whether n-3 PUFA supplementation could be relevant to tackle this modifiable factor. In the case that acting on n-3 PUFA levels represents a relevant target; ad hoc prevention trials would be needed. However, trials that tested the efficacy of n-3 PUFAs in the treatment of mental disorders, such as depression, have yielded inconsistent results (27–29). Weaknesses have been identified in such trials; and inadequate dosing and duration should be avoided in future trials. Our preliminary data suggest that, if relevant, supplementation would need to come early and for longer durations than 12 months. The Beyond Ageing Project Phase 2 trial is currently ongoing and tests the effect of a 12-month regimen of omega-3 fatty acids and/or sertraline to prevent depression in 450 older participants at risk for depression (30).

Our study presents several strengths. Among them, the included population was well characterized, the data were prospectively collected during standardized assessments and we were able to control for main confounders. Also, DHA-EPA concentration was assessed in RBCs reflecting accurate long-term n-3 PUFA intake compared to plasmatic concentration or food-frequency questionnaires. However, our study has some limitations. First, the randomized controlled trial MAPT was not designed to assess the relationship between RBC DHA-EPA concentration and psychotropic drug use and therefore, we report here exploratory secondary analyses based on the included cohort. Second, we restricted the follow-up to one year since RBC FA analysis was only available at baseline and 12-month visit. About 16% of the included participants had dropped off from the study over the first year and there were missing data on RBC FA analysis at the 12-month visit. In particular, there were more dropouts among those with low baseline DHA-EPA. One year also seemed to be too short to evidence a potential benefice of n-3 PUFA supplementation, if any, since deficits may have been constituted over the lifespan (2). Also, we lacked statistical power to specifically study the effect of change in DHA-EPA in participants with low baseline DHA-EPA. Third, we were not able to assess the appropriateness of psychotropic drug use since we lacked detailed psychiatric assessments, apart from the GDS, and included subjects were likely to represent a rather heterogeneous population regarding psychiatric comorbidities. However, subjects suffering from major psychiatric conditions (eg. major depressive disorder, generalized anxiety, schizophrenia…) were not eligible in this study. Last, we were not able to study the effect of RBC DHA-EPA concentration on the evolution of psychotropic drug use because of too few changes occurring during the year (27 participants had discontinued using psychotropic drugs and 54 had started using one). Likewise, we were not able to study the evolution of drug doses which could have been an interesting outcome.

Conclusion

To our knowledge, this is the first study showing an association between low red blood cell levels of n-3PUFAs and the use of psychotropic drugs in an elderly population independently of other known risk factors. Future studies are needed to assess whether low RBC n-3 PUFA is a risk factor for psychotropic drug use, and in particular misuse, in older adults.

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

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

Francine Fontaine from the University of Montreal. Co-Investigators in associated centres: Jean-François Dartigues, Isabelle Marcet, Fleur Delva, Alexandra Foubert, Sandrine Cerda (Bordeaux); Marie-Noëlle-Cuffi, Corinne Costes (Castres); Olivier Rouaud, Patrick Manckoundia, Valérie Quipourt, Sophie Marilier, Evelyne Franon (Dijon); Lawrence Bories, Marie-Laure Pader, Marie-France Basset, Bruno Lapoujade, Valérie Faure, Michael Li Yung Tong, Christine Malick-Loiseau, Evelyne Cazaban-Campistron (Foix); Françoise Desclaux, Colette Blatge (Lavaur); Thierry Dantoine, Cécile Laubarie-Mouret, Isabelle Saulnier, Jean-Pierre Clément, Marie-Agnès Picat, Laurence Bernard-Bourzeix, Stéphanie Willebois, Iléana Désormais, Noëlle Cardinaud (Limoges); Marc Bonnefoy, Pierre Livet, Pascale Rebaudet, Claire Gédéon, Catherine Burdet, Flavien Terracol (Lyon), Alain Pesce, Stéphanie Roth, Sylvie Chaillou, Sandrine Louchart (Monaco); Kristelle Sudres, Nicolas Lebrun, Nadège Barro-Belaygues (Montauban); Jacques Touchon, Karim Bennys, Audrey Gabelle, Aurélia Romano, Lynda Touati, Cécilia Marelli, Cécile Pays (Montpellier); Philippe Robert, Franck Le Duff, Claire Gervais, Sébastien Gonfrier (Nice); Yves Gasnier and Serge Bordes, Danièle Begorre, Christian Carpuat, Khaled Khales, Jean-François Lefebvre, Samira Misbah El Idrissi, Pierre Skolil, Jean-Pierre Salles (Tarbes). MRI group: Carole Dufouil (Bordeaux), Stéphane Lehéricy, Marie Chupin, Jean-François Mangin, Ali Bouhayia (Paris); Michèle Allard (Bordeaux); Frédéric Ricolfi (Dijon); Dominique Dubois (Foix); Marie Paule Bonceour Martel (Limoges); François Cotton (Lyon); Alain Bonafé (Montpellier); Stéphane Chanalet (Nice); Françoise Hugon (Tarbes); Fabrice Bonneville, Christophe Cognard, François Chollet (Toulouse). PET scans group: Pierre Payoux, Thierry Voisin, Julien Delrieu, Sophie Peiffer, Anne Hitzel, (Toulouse); Michèle Allard (Bordeaux); Michel Zanca (Montpellier); Jacques Monteil (Limoges); Jacques Darcourt (Nice). Medico-economics group: Laurent Molinier, Hélène Derumeaux, Nadège Costa (Toulouse). Biological sample collection: Christian Vincent, Bertrand Perret, Claire Vinel (Toulouse). Safety management : Pascale Olivier-Abbal. DSA Group : Sandrine Andrieu, Christelle Cantet, Nicola Coley.

Conflicts of Interests: The MAPT study was supported by grants from the French Ministry of Health (PHRC 2008, 2009), Pierre Fabre Research Institute (manufacturer of the omega-3 supplement), Exhonit Therapeutics SA, and Avid Radiopharmaceuticals Inc.

Ethical Standards: The present experiments comply with the current laws of the country in which they were performed.

References

1. Guixà-González, R.; Javanainen, M.; Gómez-Soler, M.; Cordobilla, B.; Domingo, J. C.; Sanz, F.; Pastor, M.; Ciruela, F.; Martinez-Seara, H.; Selent, J. Membrane Omega-3 Fatty Acids Modulate the Oligomerisation Kinetics of Adenosine A2A and Dopamine D2 Receptors. Sci. Rep., 2016;6, 19839. doi :10.1038/srep19839.
2. Pusceddu, M. M.; Kelly, P.; Stanton, C.; Cryan, J. F.; Dinan, T. G. N-3 Polyunsaturated Fatty Acids through the Lifespan: Implication for Psychopathology. Int. J. Neuropsychopharmacol. 2016;19 (12). doi : 10.1093/ijnp/pyw078.
3. McNamara, R. K.; Welge, J. A. Meta-Analysis of Erythrocyte Polyunsaturated Fatty Acid Biostatus in Bipolar Disorder. Bipolar Disord. 2016;18 (3), 300–306. doi : 10.1111/bdi.12386.
4. Tiemeier, H.; van Tuijl, H. R.; Hofman, A.; Kiliaan, A. J.; Breteler, M. M. B. Plasma Fatty Acid Composition and Depression Are Associated in the Elderly: The Rotterdam Study. Am. J. Clin. Nutr. 2003;78 (1), 40–46. doi : 10.1093/ajcn/78.1.40.
5. Liu, J. J.; Galfalvy, H. C.; Cooper, T. B.; Oquendo, M. A.; Grunebaum, M. F.; Mann, J. J.; Sublette, M. E. Omega-3 Polyunsaturated Fatty Acid (PUFA) Status in Major Depressive Disorder with Comorbid Anxiety Disorders. J. Clin. Psychiatry, 74 2013;(7), 732–738. doi : 10.4088/JCP.12m07970.
6. Dangour, A. D.; Allen, E.; Elbourne, D.; Fasey, N.; Fletcher, A. E.; Hardy, P.; Holder, G. E.; Knight, R.; Letley, L.; Richards, M.; et al. Effect of 2-y n-3 Long-Chain Polyunsaturated Fatty Acid Supplementation on Cognitive Function in Older People: A Randomized, Double-Blind, Controlled Trial. Am. J. Clin. Nutr. 2010;91 (6), 1725–1732. doi : 10.3945/ajcn.2009.29121.
7. Dangour, A. D.; Whitehouse, P. J.; Rafferty, K.; Mitchell, S. A.; Smith, L.; Hawkesworth, S.; Vellas, B. B-Vitamins and Fatty Acids in the Prevention and Treatment of Alzheimer's Disease and Dementia: A Systematic Review. J. Alzheimers Dis. JAD, 2010;22 (1), 205–224. doi : 10.3233/JAD-2010-090940.
8. Alonso, J.; Angermeyer, M. C.; Bernert, S.; Bruffaerts, R.; Brugha, T. S.; Bryson, H.; de Girolamo, G.; Graaf, R.; Demyttenaere, K.; Gasquet, I.; et al. Psychotropic Drug Utilization in Europe: Results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) Project. Acta Psychiatr. Scand. Suppl. 2004;No. 420, 55–64. doi : 10.1111/j.1600-0047.2004.00331.x.
9. Ohayon, M. M.; Lader, M. H. Use of Psychotropic Medication in the General Population of France, Germany, Italy, and the United Kingdom. J. Clin. Psychiatry 2002;63 (9), 817–825.
10. Maust, D. T.; Chen, S. H.; Benson, A.; Mavandadi, S.; Streim, J. E.; DiFilippo, S.; Snedden, T. M.; Oslin, D. W. Older Adults Recently Started on Psychotropic Medication: Where Are the Symptoms? Int. J. Geriatr. Psychiatry, 2015;30 (6), 580–586. doi : 10.1002/gps.4187.
11. Vellas, B.; Carrie, I.; Gillette-Guyonnet, S.; Touchon, J.; Dantoine, T.; Dartigues, J. F.; Cuffi, M. N.; Bordes, S.; Gasnier, Y.; Robert, P.; et al. MAPT study: a multidomain approach for preventing alzheimer's disease: design and baseline data. J. Prev. Alzheimers Dis. 2014;1 (1), 13–22.
12. Lawton, M. P.; Brody, E. M. Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living. The Gerontologist, 1969;9 (3), 179–186.
13. Folstein, M. F.; Folstein, S. E.; McHugh, P. R. "Mini-Mental State". A Practical Method for Grading the Cognitive State of Patients for the Clinician. J. Psychiatr. Res. 1975;12 (3), 189–198.
14. Katz, S.; Ford, A. B.; Moskowitz, R. W.; Jackson, B. A.; Jaffe, M. W. Studies of Illness in the Aged. The Index of ADL: A Standardized Measure of Biological and Psychosocial Function. JAMA J. Am. Med. Assoc., 1963;185, 914–919.
15. Andrieu, S.; Guyonnet, S.; Coley, N.; Cantet, C.; Bonnefoy, M.; Bordes, S.; Bories, L.; Cufi, M.-N.; Dantoine, T.; Dartigues, J.-F.; et al. Effect of Long-Term Omega 3 Polyunsaturated Fatty Acid Supplementation with or without Multidomain Intervention on Cognitive Function in Elderly Adults with Memory Complaints (MAPT): A Randomised, Placebo-Controlled Trial. Lancet Neurol. 2017;16 (5), 377–389. doi : 10.1016/S1474-4422(17)30040-6.
16. World Health Organisation Collaborating Centre for Drug Statistics Methodology. ATC / DDD Index.
17. Harris, W. S.; Thomas, R. M. Biological Variability of Blood Omega-3 Biomarkers. Clin. Biochem. 2010;43 (3), 338–340. doi : 10.1016/j.clinbiochem.2009.08.016.
18. Fried, L. P.; Tangen, C. M.; Walston, J.; Newman, A. B.; Hirsch, C.; Gottdiener, J.; Seeman, T.; Tracy, R.; Kop, W. J.; Burke, G.; et al. Frailty in Older Adults: Evidence for a Phenotype. J. Gerontol. A. Biol. Sci. Med. Sci. 2001;56 (3), M146-156.
19. Fried, L. P.; Ferrucci, L.; Darer, J.; Williamson, J. D.; Anderson, G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. J. Gerontol. A. Biol. Sci. Med. Sci. 2004;59 (3), 255–263.
20. Yesavage, J. A.; Brink, T. L.; Rose, T. L.; Lum, O.; Huang, V.; Adey, M.; Leirer, V. O. Development and Validation of a Geriatric Depression Screening Scale: A Preliminary Report. J. Psychiatr. Res. 1982;17 (1), 37–49.
21. Johnell, K.; Fastbom, J.; Rosén, M.; Leimanis, A. Inappropriate Drug Use in the Elderly: A Nationwide Register-Based Study. Ann. Pharmacother. 2007;41 (7), 1243–1248. doi : 10.1345/aph.1K154.
22. Johnell, K.; Fastbom, J. The Use of Benzodiazpines and Related Drugs amongst Older People in Sweden: Associated Factors and Concomitant Use of Other Psychotropics. Int. J. Geriatr. Psychiatry, 2009;24 (7), 731–738. doi : 10.1002/gps.2189.
23. Haider, S. I.; Johnell, K.; Weitoft, G. R.; Thorslund, M.; Fastbom, J. The Influence of Educational Level on Polypharmacy and Inappropriate Drug Use: A Register-Based Study of More than 600,000 Older People. J. Am. Geriatr. Soc. 2009;57 (1), 62–69. doi : 10.1111/j.1532-5415.2008.02040.x.
24. Parker, G.; Gibson, N. A.; Brotchie, H.; Heruc, G.; Rees, A.-M.; Hadzi-Pavlovic, D. Omega-3 Fatty Acids and Mood Disorders. Am. J. Psychiatry, 2006;163 (6), 969–978. doi : 10.1176/ajp.2006.163.6.969.
25. Lucas, M.; Mirzaei, F.; O'Reilly, E. J.; Pan, A.; Willett, W. C.; Kawachi, I.; Koenen, K.; Ascherio. A. Dietary Intake of N-3 and n-6 Fatty Acids and the Risk of Clinical Depression in Women: A 10-y Prospective Follow-up Study. Am. J. Clin. Nutr, 2011;93 (6), 1337–1343. doi : 10.3945/ajcn.111.011817.
26. Féart, C.; Peuchant, E.; Letenneur, L.; Samieri, C.; Montagnier, D.; Fourrier-Reglat, A.; Barberger-Gateau, P. Plasma. Eicosapentaenoic Acid Is Inversely Associated with Severity of Depressive Symptomatology in the Elderly: Data from the Bordeaux Sample of the Three-City Study. Am. J. Clin. Nutr. 2008;87 (5), 1156–1162. doi : 10.1093/ajcn/87.5.1156.
27. Montgomery, P.; Richardson, A. J. Omega-3 Fatty Acids for Bipolar Disorder. Cochrane Database Syst. Rev. 2008;No. 2, CD005169. doi : 10.1002/14651858.CD005169.pub2.
28. Mello, A. H.; Gassenferth, A.; Souza, L. R.; Fortunato, J. J.; Rezin, G. T. ω-3 and Major Depression: A Review. Acta Neuropsychiatr. 2014;26 (3), 178–185. doi : 10.1017/neu.2013.52.
29. Appleton, K. M.; Sallis, H. M.; Perry, R.; Ness, A. R.; Churchill, R. Omega-3 Fatty Acids for Depression in Adults. Cochrane Database Syst. Rev. 2015;No. 11, CD004692. doi : 10.1002/14651858.CD004692.pub4.
30. Cockayne, N. L.; Duffy, S. L.; Bonomally, R.; English, A.; Amminger, P. G.; Mackinnon, A.; Christensen, H. M.; Naismith, S. L.; Hickie, I. B. The Beyond Ageing Project Phase 2--a Double-Blind, Selective Prevention, Randomised, Placebo-Controlled Trial of Omega-3 Fatty Acids and Sertraline in an Older Age Cohort at Risk for Depression: Study Protocol for a Randomized Controlled Trial. Trials, 2015;16, 247. doi : 10.1186/s13063-015-0762-6.