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Vitamin D, homocysteine and n − 3PUFA status according to physical and cognitive functions in older adults with subjective memory complaint: Results from cross-sectional study of the MAPT trial

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ABSTRACT

Objective: The aim of this study was to investigate the nutritional markers (Vitamin D, homocysteine, n − 3PUFA) status of older subjects aged 70 years and older with subjective memory complaint, according to their physical and cognitive function.

Main outcome measures: This study is a secondary analysis of the MAPT study. Subjects were classified into four groups: 1) Physical limitation with cognitive impairment (PLCI), 2) cognitive impairment (CI), 3) physical limitation (PL) and 4) no physical or cognitive deficits (NPCD). Baseline nutritional characteristics of the four groups according to Vitamin D (n = 732), Omega-3 polyunsaturated fatty acid (n − 3PUFA) (n = 1537) and plasma total homocysteine (tHcy) (n = 729) status were investigated. Analysis was performed taking continuous and dichotomized value for Vitamin D insufficiency ([25(OH)D] < 30 ng/ml, high homocysteine level (tHcy ≥ 15 μmol/L) and low n − 3PUFA (DHA + EPA ≤ 4.82%) nutritional markers for clinical relevance.

Results: PLCI group showed the lowest mean level of Vitamin D and highest level tHcy compared to the other groups. In multivariate analysis, taking continuous nutritional markers, only high Vitamin D was associated with reduced likelihood of PLCI (OR 0.97, 95% CI (0.95 to 0.99) P = 0.011). While taking the dichotomized values the group with low levels of n − 3PUFA showed higher likelihood of PL only (OR 1.55, 95% CI (1.12 to 2.15), P = 0.009). Furthermore, our sensitivity analysis for Vitamin D with cut-off [25(OH)D] < 20 ng/ml,(i.e., Vitamin D deficiency), showed more likelihood of PL (OR 1.62, 95% CI (1.01 to 2.60) P = 0.046), CI (OR 1.90, 95% CI (1.16 to 3.10) P = 0.010), and highest likelihood of PLCI (OR 1.99, 95% CI (1.21 to 3.28) P = 0.006).

Conclusion: In older adults with subjective memory complaints, Vitamin D deficiency status may present higher likelihood of functional deficits, including coexisting or separate physical and cognitive decline. While older adults with low level of n − 3PUFA were more likely to demonstrate physical decline only.

1. Introduction

Older individuals are known to have reduced functional status such as physical and cognitive functions (Clegg et al., 2013; Deary et al., 2009), making them vulnerable to endogenous and exogenous stressors, leading to myriad of age related negative outcomes (Clegg et al., 2013). Functional limitations in older adult might be of varying nature and degree, for e.g., reduced grip strength or gait speed are commonly presented form of physical decline (Fried et al., 2001). Whereas, subjective memory decline might be the most common presentation of early cognitive deterioration in aged individuals (Reid and Maclullich, 2006), which may further progress to more severe cognitive decline such as mild cognitive impairment (MCI) (associated with physical limitation and other age related adverse events (Yu et al., 2018; Brigola et al., 2015)), or even to dementia (Reid and Maclullich, 2006; Roberts et al., 2009; Mitchell et al., 2014; Jessen et al., 2010). Findings from various studies have shown that the co-existence of physical limitation with cognitive decline is a very common condition in older adults (Boyle et al., 2010; Robertson et al., 2013). Moreover, evidence from past studies suggest that subjects who are physically frail might show

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higher level of cognitive decline compared to the physically functional older subjects (Avila-Funes et al., 2009; Robertson et al., 2014; Wu et al., 2015). It is well-established that nutritional deficits in older adults can influence or impact their level of physical and cognitive functioning (Cruz-Jentoft et al., 2017; Vandewoude et al., 2016). Among the various nutritional markers associated with aging, Vitamin D, Omega-3 polyunsaturated fatty acids (n − 3PUFA and plasma total homocysteine (tHcy) (also linked with low level of vitamin B, oxidative stress and inflammation) have been extensively studied in the past (Dyall, 2015; Fougère et al., 2017a; Fougère et al., 2017b; Hooper et al., 2018; Jeromson et al., 2015; Hooshmand et al., 2012; Kuo et al., 2007; Smith and Refsum, 2016; Veeranki and Tyagi, 2013; Wong et al., 2013a; Darwish et al., 2015; Landel et al., 2016; Brouwer-Brolsma et al., 2013; Wong et al., 2013b). Evidence show insufficiency of Vitamin D (Darwish et al., 2015; Landel et al., 2016; Brouwer-Brolsma et al., 2013; Wong et al., 2013b; Houston et al., 2007; Zhou et al., 2016), low level of n − 3PUFA, in particular docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (Dyall, 2015; Hooper et al., 2018; Jeromson et al., 2015; Sydenham et al., 2012), and high tHcy (Smith and Refsum, 2016; Wong et al., 2013a; Dufouil et al., 2003; Reutens and Sachdev, 2002; Vidoni et al., 2018) not only to influence physical and musculoskeletal function (such as sarcopenia), but also cognitive functioning in older subjects.

At present, nutritional intervention represents an effective strategy to modify age related functional limitation (Guyonnet et al., 2015; Dionyssiotis et al., 2017), therefore should be investigated for the potential modifiable nutritional deficits in various geriatric conditions, in particular Vitamin D, tHcy and n − 3PUFA. However, the majority of the past studies have focused the relationship of nutrition either with physical limitation or cognitive decline separately. Furthermore, the association of nutritional deficits with physical limitation has been largely represented by the frail older population. However, community dwelling older adults may not be severely frail (Collard et al., 2012). In a general community setting older subjects frequently present some degree of physical limitation accompanied with possible precursors of cognitive impairment such as subjective memory complaints (Boyle et al., 2010; Robertson et al., 2013; Cohen et al., 2016). Besides, these populations might be at higher risk of further functional deterioration (Feng et al., 2017; Panza et al., 2015). In addition, nutritional deficits in older population with co-existing physical and cognitive limitations might be different compared to older subjects with either of the limitations. This should be further investigated in terms of nutritional deficits that are known to influence both physical and cognitive functions in older adults. Furthermore, results from such studies could facilitate clinicians and researchers to design and implement effective intervention strategies to overcome age related adverse events and maintain functionality in old age.

Therefore, in this study we investigated the nutritional status (according to Vitamin D, tHcy and n − 3PUFA) of subjects 70 years or over with subjective memory complaints according to their physical and cognitive functional status. This study is a cross-sectional secondary analysis of baseline data from the Multi-domain Alzheimer Disease Preventive Trial (MAPT). We hypothesized that older subjects with coexisting physical limitation and cognitive impairment could have worse levels of these nutritional parameters compared to subjects with no physical or cognitive deficits.

2. Methods

2.1. MAPT (Multi-domain Alzheimer Disease Preventive Trial) study

Details of the MAPT study have been described before (Vellas et al., 2014). In brief, MAPT is a four arm randomized controlled trial that investigated the efficacy of isolated supplementation with n − 3 PUFA, an isolated multi-domain intervention (consisting of nutritional counseling, physical exercise advice, cognitive stimulation), or a combination of the two interventions, versus placebo on cognitive function of older adults aged 70 or above. Written consent was obtained from all participants. The MAPT study is registered on a public-access clinical trial database (www.clinicaltrials.gov, Number: NCT01513252). The trial protocol was approved by the French Ethical Committee located in Toulouse (CPP SOOM II) and was authorized by the French Ministry of Health.

2.1.1. Study population

A total of 1680 subjects were randomized and followed for three years in the MAPT study. In brief, inclusion criteria of the MAPT population were any of the following: (1) subjective memory complaint, (2) limitation in one instrumental activity of daily living (IADL) (Lawton and Brody, 1969), (3) slow gait speed (i.e., ≤0.8 m/s or 5 s to walk 4 m). However, in the present study subject numbers differed according to the data availability of biomarker investigated.

Exclusion criteria included: (1) subjects with dementia and mini mental state examination (MMSE) (Folstein et al., 1975) score < 24, (2) limitation in basic activities of daily living (ADL) (i.e. ADL score of < 6) (Katz et al., 1963), (3) with severe depression assessed by Geriatric depression scale (GDS) (Yesavage et al., 1983), (4) intake of n − 3 PUFA supplementation within six months.

2.1.2. Classification of study population

The participants were classified into four groups on the basis of physical limitation and cognitive impairment. Physical limitation was assessed using the Fried's frailty phenotype criteria (Fried et al., 2001) that include: unintentional weight loss in the past year, low grip strength, slow gait speed, self-reported exhaustion and decreased physical activity. Subjects with limitation in any one of the five criteria were taken to be physically limited. Cognitive impairment was assessed by the clinical dementia rating (CDR) scale (Hughes et al., 1982), with CDR = 0.5 defining impairment. From this, we identified the following four groups:

Group 1) “Physical limitation with cognitive impairment” (PLCI): ≥1 Fried's criteria and CDR = 0.5.
Group 2) “Cognitive impairment” (CI): CDR = 0.5 without physical limitations i.e. Fried's criteria = 0.
Group 3) “Physical limitation” (PL): ≥1 Fried's criteria without cognitive impairment i.e. CDR = 0.
Group 4) No physical or cognitive deficits (NPCD).

2.1.3. Nutritional biomarker assessment methodology

Blood samples were taken during enrollment and Vitamin D, total plasma homocysteine and erythrocyte membrane fatty acid concentration were measured.

2.1.3.1. Vitamin D assessment methodology. Total plasma 25-hydroxyvitamin (D3 and D2 forms) was measured using a commercially available electro-chemiluminescence competitive binding assay (Cobas, Roche). In brief, the sample was denatured to release bound 25-hydroxyvitamin ([25(OH)D]) from vitamin D binding protein (VDBP). The sample was then incubated with recombinant ruthenium labelled VDBP to enable complex formation. Biotinylated Vitamin D (25-OH) was subsequently added and the entire complex became bound to a solid phase (through the interaction of biotin and streptavidin coated micro-particles). Unbound substance was removed then applying voltage to the electrode that induced a chemiluminescent emission, which then was quantified and concentrations of [25(OH)D] in ng/ml were derived against a standard curve.

2.1.3.2. Total plasma homocysteine assessment methodology. tHcy was measured using a commercially available enzymatic cycling assay (Cobas, Roche). In brief, oxidised homocysteine was first reduced and then reacted with *S*-adenosylmethionine to form methionine and *S*-