

Omega 3 fatty acids in the elderly

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Abstract

Population ageing affects the entire world population. Also at world level one can observe a sharp increase in the proportion of older people. The challenge posed by population ageing translates into ensuring that the extra years of life will be as good as possible, free from high-cost dependency. Omega-3 fatty acids are now generally recognized as potential key nutrients to prevent the pathological conditions associated to the aging process. Ageing physiological process, its association with quality of life and the impact of omega-3 fatty acids intake and/or status is the focus of the present review. This report deals with the effects of omega-3 fatty acids on normal aging of older adults (≥ 65 years) mainly on the effects such as nutritional status itself, cognition, bone health, muscle tonus, and general health status. The preliminary broad search of the literature on the effects of omega-3 fatty acids on normal aging yielded 685 citations. Forty two full text papers were checked for inclusion and thirty six studies were finally included in this review. It may be concluded that paradoxically even though the elderly population is the largest one, the number of studies and the methodology employed clearly lacks of sufficient evidence to establish definite conclusions on the effects of omega-3 fatty acids on aging metabolism without pathological conditions and on quality of life.

Key words: Bone diseases: Bone fractures: Omega-3 fatty acids: Osteoblast: Osteoclast: Osteoporosis: Systematic review

Introduction

Over a period of 100 years, the proportion of people aged 60 and more will triple, from a mere 11% in 1950 to no less than 33% in 2050^(1–4). Nutrition is one of the major determinants of successful aging, defined as the ability to maintain three key elements: low risk of disease and disease-related disability, high mental and physical function, and active engagement of life^(5–6). Food is not only critical to one's physiological well-being but also contributes to one's social, cultural, and psychological quality of life⁽⁷⁾. In fact, quality of life is mentioned worldwide as an important issue in future research related to active and healthy “successful” ageing.

Physiological and functional changes that occur with aging can result in changes in nutrient needs^(8–9). Knowledge of nutrient requirements of older adults is growing yet is still inadequately documented^(10–11). Older adults have unique nutrient needs⁽¹²⁾. Both cross-sectional and longitudinal studies document that the quantity of food and energy intake usually decreases substantially across the spectrum of aging. Surprisingly, there is a lack of information about fatty acids, mainly long-chain polyunsaturated omega-3. Strategies to prevent and (or) reduce morbidity in the elderly are therefore required as worldwide the population ages. Increasing the intake of omega-3, particularly the long-chain *n*-3 PUFA may be one such strategy^(13–15).

Omega-3 fatty acids are now generally recognized as potentially beneficial for optimal function of the cardiovascular

system in adults^(16–17). As clear examples, because of the increasing risk of deteriorating health of the cardiovascular system and brain with age, is important to establish whether healthy aging is associated with changes in plasma ω 3 fatty acid content or response to fortification/supplementation⁽¹⁸⁾. It is becoming increasingly evident that long chain PUFA from the *n*-3 family appears to be neuroprotective and may also have unique properties in affecting neurobiology, both of critical interest during the aging process^(19–27). Intake of *n*-3 PUFA has also been associated with potential benefits in other age-related morbidities, including rheumatoid arthritis, depression and macular degeneration. In fact, surprisingly, in both plasma and red blood cells, several studies have reported that the content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) rises significantly from the second to the seventh decade of life^(28–33). Normally, higher plasma (and red cell) ω 3 fatty acid status in the elderly would seem to be due to higher fish/seafood intake but may also be due to aging-related changes in ω 3 metabolism. However, these findings are not universal, since other studies have found that the intake of polyunsaturated fatty acids decrease with age⁽³⁴⁾ and most older people eat less than the recommended amounts. In contrast to their proposed actions in childhood, where *n*-3 long-chain polyunsaturated fatty acids are required for healthy development of brain tissue, in older age are more like to act in a protective and health-maintaining manner. For example, *n*-3 are known to inhibit hepatic triglyceride synthesis and by modifying eicosanoid

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function, cause vascular relaxation, a diminished inflammatory process and decrease platelet aggregation⁽³⁵⁾.

Nevertheless, these studies all had important limitations, including a small number of subjects. In addition, although 65 years of age is frequently used as reference, there is no official or widely accepted definition of elderly, so the cut-off used in studies is often as low as 50 years of age. Furthermore, information about the health status, blood chemistry, cognitive function or physical activity of elderly research subjects is rarely given in sufficient detail to establish whether or not the data reported are for the healthy elderly. The main target of the present chapter of the systematic review is based on *moderately healthy elderly*, based on their active lifestyle, normal cognition and relatively good physical condition.

Ageing physiological process, its association with quality of life and the impact of omega-3 fatty acids intake and/or status is the focus of the present chapter. Undoubtedly, ageing is linked to several pathological conditions (osteoporosis, sarcopenia, neurodegenerative diseases, etc.) that are not targeted. The main question to be discussed in the present review is: How ω 3 fatty acids may affect the overall diet and quality of life in the elderly people subjects?

Methods

This report deals with the effects of omega-3 fatty acids on normal aging of older adults (≥ 65 years) and on their quality of life.

Study identification

We searched Medline (1966–2011), EMBASE (1980–2011) and LILACS (1982–2011). The terms used and the search strategies were the following:

Fatty Acids, Omega-3/all subheadings
 DHA
 EPA
 Aged
 Aged nutrition physiology
 Nutritional Status
 Diet records
 Dietary supplements
 Health
 Health Status Indicators
 Quality of life
 Cognition
 Cognition disorders
 Food, fortified
 Bone density
 Muscle tonus
 Deficiency (subheading)

The search strategies, which were applied in the three databases above mentioned, were as follows:

“Fatty Acids, Omega-3/all subheadings or “Docosahexaenoic acids (DHA)” or “Eicosapentaenoic acids (EPA)” or “DHA and EPA” and “Aged” or “Aged nutrition physiology” and “Nutritional status” or “Diet records” or “Dietary

supplements” or “Health” or “Health Status Indicators” or “Quality of life” or “Cognition” or “Cognition disorders” or “Food, fortified” or “Bone density” or “Muscle tonus” or “Deficiency” (subheading).

The search was not limited by language of publication or study design, in order to increase specificity. The titles and abstract obtained (a total amount of 685) were screened for relevant articles. The full texts of the relevant articles were checked for inclusion criteria ($n = 100$). Our purpose at this initial phase of screening was to identify articles that described studies about the effects of omega-3 fatty acids on normal healthy aging in human subjects and on their quality of life. Therefore, the full text of any articles for which it was not possible to determine relevance from the title and/or abstract was also retrieved for further review. At this point, only titles and/or abstracts that clearly did not meet these criteria for inclusion were rejected ($n = 643$). Two of the investigators (N. U. and M. A.) independently decided which studies met the inclusion criteria. Any differences were resolved by consensus, also by consulting a third reviewer (G. V.) in order to resolve any persisting difference. The flow diagram for screening process is depicted in (Fig. 1). The final number of studies included for the present systematic review was 36.

Study selection criteria

Studies were included if they met the following criteria; otherwise they were excluded:

1. The studies reported research on human subjects including at least a group ≥ 65 years.
2. All participants were healthy elderly people without diagnosis of a pathological condition.
3. The studies were related to the effects derived only from EPA or DHA or EPA plus DHA dietary intakes and/or status, without the presence of other confounding factors such as vitamin or mineral supplements, etc.
4. The studies reported dietary intakes of EPA or DHA or EPA plus DHA from natural food sources and/or fortified

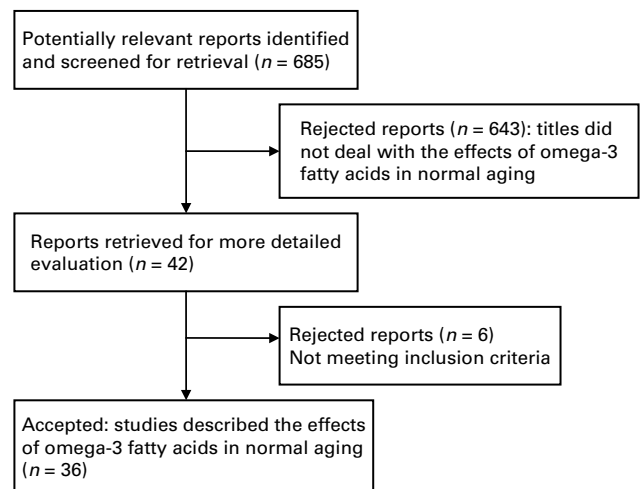


Fig. 1. Flow diagram for screening process.



Table 1. Characteristics of identified studies on the effects of omega-3 fatty acids on cognitive function in normal aging

Authors year	Study design	Population	Age (years/range)	Sex distribution % male	Total sample size	Study duration (months)	Outcome measure	Outcome
Kalmijn <i>et al.</i> , (1997) ⁽⁶⁰⁾	Cohort	Elderly from the Zutphen Elderly Study	69–89	100	476	36	MMSE	Inverse association between fish consumption and cognitive impairment (OR: 0.96 (0.57–1.62) and decline (OR: 0.78 (0.35–1.73).
Vakhapova <i>et al.</i> , (2010) ⁽⁶¹⁾	Randomized double-blind placebo-controlled study	Non-demented elderly with memory complaints	(73) 50–90	50.5	131	3.5	MMSE RAVLT score RCFT score	Phosphatidylserine-DHA (PS-DHA) (300 mg PS and 79 mg DHA + EPA 3:1) treatment improves verbal immediate memory. Those with higher baseline cognitive status were more likely to respond to treatment.
Johnson <i>et al.</i> , (2008) ⁽⁶²⁾	Double-blind intervention trial	Older women	60–80	0	49	4	Eight different cognitive test (verbal fluency, digit span forward and backward, shopping list task, word list memory test, memory in reality apartment test, NES2 pattern comparison test, stroop test, NES2 mood scales)	Supplementation with 800 mg/day of DHA improves verbal fluency.
Whalley <i>et al.</i> , (2004) ⁽⁶³⁾	Observational study	Cohort living independently in the community	64	51.1	350	–	MMSE RSPM RAVLT WAIS	Dietary fish oil intake and erythrocyte <i>n</i> -3 content are associated with better cognitive aging. At the age of 64 y food supplements users had higher digit symbol (mental speed) results than nonusers, after adjustment for childhood IQ.
Heude <i>et al.</i> , (2003) ⁽⁶⁴⁾	Cohort	Cohort from the Etude du Vieillissement Artériel (EVA)	63–74	47.9	246	4	MMSE	Content total <i>n</i> -3 fatty acids in erythrocyte membrane, which can reflect dietary fat intake, were inversely associated with cognitive decline (OR: 0.59; 95%CI: 0.38–0.93). After adjustment, this association was significant for DHA but not for EPA.
Vercambre <i>et al.</i> , (2009) ⁽³⁷⁾	Cohort	E3N French longitudinal cohort	62–68	0	4,809	156	IADL 7 DECO	Inverse association between fish consumption and cognitive decline (OR: 0.80 (0.64–0.99) but not significant for functional impairment (OR: 0.99 (0.81–1.21). The same for <i>n</i> -3 fatty acids intake: cognitive decline (OR: 0.79 (0.63–0.98); functional impairment (OR: 0.94 (0.77–1.15).

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Table 1. Continued

Authors year	Study design	Population	Age (years/range)	Sex distribution % male	Total sample size	Study duration (months)	Outcome measure	Outcome
Velho <i>et al.</i> , (2007) ⁽⁶⁵⁾	Prospective study	Free-living elderly from a Portuguese town near Lisbon (Oeiras)	Over 65	29.4	110	8.5 ± 3.5	MMSE	At follow-up 57% showed a mild improvement of their MMSE score. The consumption of <i>n</i> -3 fatty acids was significantly higher than subjects without improvement.
Dullemeijer <i>et al.</i> , (2007) ⁽³⁸⁾	Longitudinal study and cross-sectional study	Sample of FACIT trial (placebo group)	50–70	72	807 (cross-sectional study) 404 (longitudinal study)	36	5 cognitive test: Concept Shifting Test, Stroop Color-Word Test, Word Learning Test, Letter Digit Substitution Test, Verbal Fluency Test MMSE	Higher plasma proportions of <i>n</i> -3 fatty acids are associated with less decline in 3-y cognitive performance in sensorimotor speed and complex speed but not in memory, information-processing speed and word fluency.
Laurin <i>et al.</i> , (2003) ⁽⁴¹⁾	Longitudinal study and cross-sectional study	Population of the Canadian Study of Health and Aging	> 65	?	122	60	Zaudig's criteria	In the cross-sectional analysis, no significant difference in omega-3 PUFA concentration was observed between controls and cases of cognitive impairment. In the prospective analysis a higher EPA concentration was found in cognitively impaired cases compared to controls.
Dangour <i>et al.</i> , (2010) ⁽²⁴⁾	Randomized, double-blind, controlled trial (OPAL study)	Cognitively healthy adults from 20 general practices in England and Wales	75 (70–79)	55	748	24	CVLT	No evidence of a beneficial effect of fish oil supplementation (200 mg EPA plus 500 mg DHA) on cognitive function in older people. There was no change in cognitive function scores over 24 mo, and intention-to-treat analysis showed no significant differences between trial arms at 24 mo in the CVLT or any secondary cognitive outcome.
Yurko-Mauro <i>et al.</i> , (2010) ⁽⁶⁶⁾	Randomized, double-blind, placebo controlled trial	Subjects enrolled at 19 sites in the United States	Over 55	42	485	6	CANTAB PAL 6 CANTAB VRM CANTAB SOC CANTAB SWM	Supplementation with 900 mg/d DHA improved learning and memory function in ARCD and is a beneficial supplement that supports cognitive health with aging.

Table 1. Continued

Authors year	Study design	Population	Age (years/range)	Sex distribution % male	Total sample size	Study duration (months)	Outcome measure	Outcome
Van Gelder <i>et al.</i> , (2007) ⁽⁷⁷⁾	Cohort	Elderly from the Zutphen Elderly Study	70–89	100	210	60	MMSE	Fish consumers had significantly less 5 y subsequent cognitive decline than did non-consumers. An average difference of ≈ 400 mg/d in EPA + DHA intake was associated with a 1.1-point significant difference in cognitive decline.
González <i>et al.</i> , (2010) ⁽⁶⁷⁾	Cross-sectional	Institutionalized elderly population of Asturias (Spain)	75.3 ± 6.7	41.7	304	–	MMSE	Higher <i>n</i> -3 fatty acids intake are higher in the group of elderly with a better cognitive score (MMSE > 24).
Van de Rest <i>et al.</i> , (2008) ⁽³⁹⁾	Randomized, double-blind, placebo controlled trial	Healthy subjects aged > 65 years recruited of a database of volunteers with interest in participating in studies at Wageningen University.	70	55	302	6.5	MMSE 5 cognitive test: Trail Making Test, Stroop Color-Word Test, Word Learning Test, Wechsler Digit Span Task Test, Verbal Fluency Test	There were no significant differential changes in any of the cognitive domains for either low-dose fish oil supplementation compared with placebo.
Richter <i>et al.</i> , (2010) ⁽⁶⁸⁾	Single-center, open-label study	Volunteers aged > 60 years with subjective memory complaints from Haifa, Israel.	69.3	37.5	8	1.5	Cognitive Drug Research (CDR) that includes nine separate tasks and five composite factors calculated from the results on the single tasks.	PS-omega-3 (37.5 mg EPA + DHA) may have a favourable effect on memory recall (42% of increase) in subjects with subjective memory complaints, specifically on the ability to store, hold, and retrieve information of an episodic nature.
Lauretani <i>et al.</i> , (2007) ⁽⁶⁹⁾	Cohort	Population aging in Chianti area (Italy). InCHIANTI study.	68.2/Different groups (3 groups over 65y)	46.4	827	3	Studies of the right peroneal nerve (ENG-neuro MYTO device)	DHA predicted significantly less decline of nerve conduction velocity (NCV) in participants older than 85 years of age. Omega-3 fatty acids and DHA predicted significantly less decline in compound muscle action potential (CMAP) in participants between 65 and 84 years old.
Van de Rest <i>et al.</i> , (2009) ⁽⁴²⁾	Longitudinal study and cross-sectional study	Participants were from the Veterans Affairs Normative Aging Study	68	100	1025 (cross-sectional study) 313 (longitudinal study)	72	Battery of cognitive test (memory/language, speed, visuospatial/attention)	Cross-sectional analyses showed no association between fatty fish or (<i>n</i> -3) PUFA intake and cognitive performance. Longitudinal analyses also did not show any significant associations fatty fish or (<i>n</i> -3) PUFA intake and cognitive change.

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Table 1. Continued

Authors year	Study design	Population	Age (years/range)	Sex distribution % male	Total sample size	Study duration (months)	Outcome measure	Outcome
Roberts <i>et al.</i> , (2010) ⁽⁷⁰⁾	Cross-sectional	Population of the Rochester epidemiology Project, from Olmsted County, MN, USA.	70–89	55.5	1233	–	CDR + Nine test in four cognitive domains: memory, executive function, language and visuospatial skills.	The OD of mild cognitive impairment (MCI) decreased with increasing PUFA intake. The OD (95 % confidence interval) were 0.62 (0.42–0.91) for omega-3 fatty acids.
Matsumoto <i>et al.</i> (2009) ⁽⁷¹⁾	Cohort	Community-dwellers recruited in two separate towns in Shimane (Japan)	> 65	?	54	48	Hasegawa dementia rating scale (HDS)	Subjects who showed improvements or no change in their HDS results consumed more DHA than those whose HDS results worsened.
Ortega <i>et al.</i> , (1997) ⁽⁴⁰⁾	Cross-sectional	Noninstitutionalized elderly people from Madrid (Spain)	65–90	41.5	260	–	MMSE PMSQ	No significant difference in PUFA intake between unsatisfactory responders in test and satisfactory.
Requejo <i>et al.</i> , (2003) ⁽⁷²⁾	Cross-sectional	Independently living elderly people from Madrid (Spain)	65–90	?	168	–	MMSE	Subjects with an adequate cognitive capacity showed greater intake of fish.
Kesse-Guyot <i>et al.</i> , (2011) ⁽⁷³⁾	Cohort	Population of the SU.VI.MAX study		?	3294	156	Cognitive test and self-reported cognitive difficulties scale	Self-reported cognitive difficulties were less frequent among subjects with higher intakes of total <i>n</i> -3 long chain fatty acids (OR = 0.72, 0.56–0.92) and EPA (OR Q4 versus Q1 = 0.74, 0.58–0.95).
Conquer <i>et al.</i> , (2000) ⁽⁷⁴⁾	Cross-sectional		77–83	?	55	–	6 cognitive test	Lower <i>n</i> -3 PUFA concentrations in cognitively impaired group.
Kalmijn <i>et al.</i> , (2004) ⁽⁷⁵⁾	Cross-sectional		45–70	?	1613	–	Test in cognitive domains: memory, psychomotor speed, cognitive flexibility and overall cognition.	Marine <i>n</i> -3 PUFA were inversely related to the risk of impaired overall cognitive function and speed (OR = 0.81, 0.72–0.90). Results for fatty fish consumption were similarly inverse.
Morris <i>et al.</i> , (2005) ⁽⁷⁶⁾	Prospective cohort study	Community from Chicago. Chicago Health and Aging Project.	> 65	?	3718	72	4 standardized tests	Higher fish intake, but not <i>n</i> -3 PUFA intake, associated with slower cognitive decline.
Beydoun <i>et al.</i> , (2007) ⁽²⁰⁾	Prospective cohort study	Volunteers from Minneapolis. ARIC study.	50–65	49.3	2251	72	DWRT DSST/WAIS-R WFT	Higher <i>n</i> -3 PUFA concentrations associated with lower risk of decline in verbal fluency. RCI < – 1.645.

MMSE: Mini Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test; RCFT: Rey Complex Figure Test; RSPM: Raven's Standard Progressive Matrices; WAIS: Wechsler Adult Intelligence Scale-revised; IADL 7: Instrumental Activities of Daily Living; DECO: Détérioration Cognitive Observée (observed cognitive deterioration); CVLT: California Verbal Learning Test; CANTAB PAL 6: visuospatial learning and episodic memory test; CANTAB VRM: Verbal Recognition Memory; CANTAB SOC: Stockings of Cambridge; CANTAB SWM: Spatial Working Memory; PMSQ: Pfeiffer's Mental Status Questionnaire; DWRT: Delayed Word Recall Test; DSST/WAIS-R: Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale-revised; WFT: Word Fluency Test

foods and/or supplements. The supplements (if applied) could be taken with any dose or duration.

5. All categories of epidemiological studies were included.
6. The dietary assessment included a validated methodology, regardless of the tool.
7. The studies informing of the nutritional status included also the standardized method utilized.

To increase the generalization of the results, no restrictions were established on participants' baseline nutritional status or other study settings (community dwelling, participants on their own ...)

Types of outcomes

We focused on the effects of omega-3 fatty acids on the main aspects derived from the impairment in the quality of life that is unavoidably associated to normal and physiological aging, such as nutritional status itself, cognition, bone health, muscle tonus, and general health status.

Data Extraction and quality assessment

Data were collected from each article for authors and year of publication, study design, population, age, sex distribution, total sample size, duration, outcomes of interest (Table 1).

Information about the methodological quality of the studies was also abstracted. One author abstracted the data by using an internal data extraction form, and another one checked the accuracy. A 10-item quality appraisal form, based on the one used by Avenell & Handoll (2005)⁽³⁶⁾, was used to assess the methodological quality of each included study. The 10 items included the concealment of randomization, intention-to-treat-analysis, blinding of participants, treatment provider and assessor, comparability of groups at entry, identical care programmes, the specification of inclusion and exclusion criteria, definition of the intervention, the overall duration, appropriateness of the follow up, and withdraws.

Data Analysis/Statistics

Due to the heterogeneity among studies, very few studies met the inclusion criteria. Therefore, it was not possible to perform a meta-analysis. The overall effects of omega-3 fatty acids within the studies are described. The point estimates and statistical testing that were described in the original studies are summarized.

Results

The effects of omega-3 fatty acids on normal aging that we summarize as follows are those reported within the 36 studies that were finally included in the present review. According to the quality scale used, all the trials got a score range of 12–20 (20 was the possible maximum score). All the trials were conducted in “developed” countries, and academic institutes or national organizations supported all of them. None reported pharmaceutical company and/or food industry funding.

Effects of omega-3 fatty acid on cognitive function in normal aging

We have retrieved a total of 26 articles that evaluated the effects of omega-3 fatty acids on cognitive function in normal aging and healthy older people. Thirteen were longitudinal studies, ten were cross-sectional (three of them included longitudinal and cross-sectional analysis) and six were randomized, double-blind controlled trials. All of the studies used the Mini Mental State Examination (MMSE) to evaluate global cognitive function which include questions about orientation to time and place, registration, attention and calculation, recall, language, etc and/or other specific test (e.g. verbal fluency, speed, visuospatial skills, etc). Most of them considered cognitive impairment as a MMSE score <25 and cognitive decline was defined as a drop of more than two points in the MMSE over the period studied; however, cognitive decline is defined uniquely according to each study, and thus comparing outcomes across studies must be interpreted with caution. One analyzed specifically changes in the nerve conduction velocity and compound muscle action potential. The content of omega-3 fatty acid was evaluated through dietary information (intake of fish or DHA/EPA) with appropriate questionnaires or concentration in plasma and/or erythrocyte membrane. The characteristics of the studies that were analyzed are described in Table 1.

Nineteen of all articles showed a positive relationship between an adequate fish consumption or *n-3* fatty acids intake (diet or supplements) or total content in erythrocyte membrane and cognitive status or less cognitive decline during aging. These results are promising and encourage further research in order to establish a safe and effective treatment solution for cognitive impairment and subsequently disability in elderly population. Promoting higher intakes of *n-3* PUFA in the diet or specific supplements may have substantial benefits in reducing their risk of cognitive decline. However, authors concluded that further studies are warranted to confirm and evaluate these potential positive effects.

Two of the articles showed some improvements but other measures remained unchanged. Vercambre *et al.*⁽³⁷⁾ observed an inverse association between fish consumptions and *n-3* fatty acids intake and cognitive decline but not significant for functional impairment. Dullemeijer *et al.*⁽³⁸⁾ concluded that higher plasma proportions of *n-3* fatty acids are associated with less decline cognitive performance in sensorimotor speed and complex speed but not in memory, information-processing speed and word fluency.

Five of the studies showed no positive effects of *n-3* fatty acids in cognitive function. Two RCTs^(24,39) used high doses or EPA plus DHA and olive oil or oleic acid as placebo but did not find significant changes in any cognitive domains over 6 and 24 months, respectively. Both of them recommended that further longer trials should be conducted. Three cross-sectional studies^(40–42) showed no significant differences in *n-3* PUFA intake between controls and cases of cognitive decline/impairment, and two of them^(41,42) also did not show any significant associations between fatty fish

Table 2. Characteristics of identified studies on the effects of omega-3 fatty acids on immune function in normal aging

Authors year	Study design	Population	Age (years/range)	Sex distribution% male	Total sample size	Study duration (months)	Outcome measure	Outcome
Bechoua <i>et al.</i> (2003) ⁽⁴⁴⁾	Randomized double-blind	Healthy non-institutionalized elderly people	70–83	30	20	1.5	Lymphocyte proliferation Biochemical markers known to be altered with age (PDE, phosphodiesterase activity; GSH-Px, Glutathione peroxidase activity)	The intake of low doses of <i>n</i> -3 fatty acids (30 mg EPA + 150 mg DHA/d) decreased the lymphoproliferative responses of elderly people to mitogens. PDE and GSH-Px activities were also modified by this low EPA + DHA supplementation.
Thies <i>et al.</i> (2001) ⁽⁴³⁾	Randomized, placebo-controlled, double blind, parallel	White elderly people living in their own homes	56–74	52.1	46	3	Natural Killer (NK) cell activity	A moderate amount of EPA but no other <i>n</i> -3 polyunsaturated fatty acids can decrease NK cell activity (in a reversible way) in healthy elderly subjects.
Thies <i>et al.</i> (2001) ⁽⁴⁶⁾	Randomized, placebo-controlled, double blind, parallel	White elderly people living in their own homes	55–75	52.1	46	1.5	Lymphocyte proliferation Production of interleukins	A moderate level of EPA but no other <i>n</i> -3 polyunsaturated fatty acids can decrease lymphocyte proliferation but not the production of interleukin-2 or interferon- γ .
Rees <i>et al.</i> (2006) ⁽³¹⁾	Controlled, double blind	Healthy voluntary older men (vs younger subjects)	53–70	100	62	3	Plasma and mononuclear cells (MNC) phospholipids composition Phagocytic activity and respiratory burst	Older subjects incorporate EPA into plasma and MNC phospholipids more readily than do younger subjects. Older subjects are more sensitive to the immunologic effects of EPA, and the neutrophil respiratory burst is lower at higher EPA intakes.
Wardwell <i>et al.</i> (2008) ⁽⁴⁵⁾	Cross-sectional and longitudinal	Independently community living males and females from the Champaign (Illinois) neighbourhood.	65–80	39.3	89	Not reported	T cell proliferation	EPA from diet and supplements was associated with PHA-induced proliferative responses

or *n*-3 PUFA intake and cognitive change over 5 and 6 years, respectively.

More prospective studies, as well as interventions studies investigating the association between *n*-3 PUFA and domain-specific measures are needed to clarify the current conflicting results observed in the literature.

Effects of omega-3 fatty acids on immune function in normal aging

A total of five studies (four RCT and one cross sectional and longitudinal) examining the effect of omega-3 fatty acids on immune function (Table 2) were included. All four RCT studies assessed the effect of moderate dietary supplementation with omega-3 fatty acids (EPA or EPA + DHA) on immune biomarkers known to be altered in normal healthy aging. Even very low doses of *n*-3 fatty acids resulted in significantly decreased proliferative responses of lymphocytes in two of the studies^(43–44). In one of them⁽⁴⁴⁾, also, this was accompanied by a marked significant ($P < 0.05$) increase of their particulate PDE activity (+56–57%) and an increase ($P < 0.05$) in cyclic nucleotide intracellular levels. At the same time, the glutathione peroxidase activity was markedly depressed ($P < 0.01$). The cross sectional study, on the contrary⁽⁴⁵⁾, reported significant positive correlations ($P < 0.05$) between PHA-induced proliferation and intake of DHA and EPA. However, these authors state that intakes of DHA plus EPA were inadequate for the studied population when compared to recommended intakes. They also suggest that dietary EPA *in vivo* might interact differently compared to *in vitro* studies where EPA is added to cell cultures.

On the other hand, a moderate amount of extra supplementary EPA (720 mg) resulted in a decrease of NK cell activity in the same elderly population⁽⁴⁶⁾. This decline (48%) was fully reversed by 4 weeks after supplementation had ceased.

The effects of different amounts of EPA on innate immune outcomes in older males compared to young were also evaluated⁽³¹⁾. EPA was incorporated in a linear dose-response fashion into plasma and mononuclear cell (MNC) phospholipids; incorporation was greater in the older men. This increased incorporation was associated with decreased production of prostaglandin E₂ by MNCs. Also, EPA treatment caused a dose-dependent decrease in neutrophil respiratory burst only in the older men.

These five above mentioned studies therefore suggest that even very low doses of omega-3 fatty acids may be sufficient to affect the immune responses of elderly subjects.

Effects of omega-3 fatty acids on bone health and muscle tonus in normal non-pathological aging

In total, three studies were identified that described the effects of omega-3 fatty acids on bone health or muscle tonus with normal aging; one was a RCT and two were cohort studies. The characteristics of the studies that were analyzed are described in Table 3. The three of them described positive outcomes derived from both dietary and supplemental omega-3 fatty acid intakes on aging.

Table 3. Characteristics of identified studies on the effects of omega-3 fatty acids on bone health and muscle tonus in normal aging

Authors year	Study design	Population	Age (years/-range)	Sex distribution % male	Total sample size	Study duration (months)	Outcome measure	Outcome
Farina <i>et al.</i> , (2011) ⁽⁴⁷⁾	Cohort	Participants of Framingham Osteoporosis Study who had a femoral neck (FN) or trochanter BMD measured at exam 20 for cross-sectional analyses and FN or trochanter BMD measured at exam 22 for longitudinal analyses	(67–91)	40	854	48	BMD of the right proximal hip (FN and trochanter)	Fish consumption (≥ 3 servings/wk) may protect against bone loss
Robinson <i>et al.</i> , (2008) ⁽⁴⁸⁾	Cross-sectional and retrospective cohort	Participants of the Hertfordshire Cohort Study still alive and living in Hertfordshire	59–73	52.5	2,983	72	Maximum grip strength	Fatty fish consumption (> 1 portions/wk) can have an important influence on muscle function in older men and women
Smith <i>et al.</i> , (2010) ⁽⁴⁹⁾	Randomized controlled trial	Older healthy adults (Clinical Trials, Gov number NCT00794079)	69–73	62.5	16	2	Rate of muscle protein synthesis (FSR) Phosphorylation of key elements of the anabolic signalling pathway	Omega-3 fatty acids stimulate muscle protein synthesis in older adults and may be useful for the prevention and treatment of sarcopenia

A single cohort study⁽⁴⁷⁾ that evaluated the effects of omega-3 fatty acids on bone health in aging was identified. This study investigated the associations between dietary polyunsaturated fatty acid and fish intakes and hip bone mineral density (BMD) at baseline (1988–1989, $n = 854$) and changes 4 year later in individuals ($n = 623$) with a mean age of 75 years in the Framingham Osteoporosis. High intakes (> 3 servings/wk) of fish relative to lower intakes were associated with maintenance of femoral neck BMD (FN-BMD) in men (dark fish + tuna, dark fish, and tuna) and in women (dark fish) ($P < 0.05$), thus suggesting that fish consumption may protect against bone loss. This study was adjusted for confounders, used valid methods to measure outcomes, and described withdrawals and dropouts.

Two studies that assessed the effect of omega-3 fatty acids on muscle tonus in normal aging were identified. The cohort study⁽⁴⁸⁾ examined the relationships between diet (fatty fish consumption) and grip strength in older men and women living in their own homes. Of the dietary factors considered in relation to grip strength, the most important was fatty fish consumption. An increase in grip strength of 0.43 kg (95% confidence interval CI = 0.13–0.74) in men ($P = 0.005$) and 0.48 kg (95% CI = 0.24–0.72) in women ($P < 0.001$) was observed for each additional portion of fatty fish consumed per week. Only one RCT study evaluating the effect of omega-3 fatty acids in muscle tonus in normal aging was retrieved⁽⁴⁹⁾. The objective was to evaluate the effect of omega-3 fatty acid supplementation for 8 weeks on the rate of muscle protein synthesis in elderly population (69–73 years). Omega-3 fatty acid supplementation (1.86 g EPA and 1.50 g DHA) augmented the hyperaminoacidemia-hyperinsulinemia-induced increase in the rate of muscle protein synthesis (from $0.009 \pm 0.005\%/h$ above basal values to $0.031 \pm 0.003\%/h$ above basal values; $P < 0.01$), which was accompanied by greater increases in muscle mTOR^{Ser2448} ($P = 0.08$) and p70s6k^{Thr389} ($P < 0.01$) phosphorylation, two elements of intramuscular signal transduction proteins involved in the regulation of muscle protein synthesis. The authors of these two studies suggest that these important influences on muscle function in older men and women raise the possibility that omega-3 fatty acids may be useful for the prevention and treatment of sarcopenia.

Effects of omega-3 fatty acids on quality of life and mortality in normal aging

Two single studies (both of them RCT) assessed the influence of omega-3 fatty acids in the quality of life of normal aging (Table 4). Moreover, the baseline characteristics of the population of the two studies were the same, 302 independently living older individuals. The studies differed in the outcomes measured^(50,51). The first one investigated the effect of EPA and DHA (1800 mg/d EPA + DHA, 400 mg/d EPA or placebo, for 26 wk) on mental well-being. The second one evaluated the effect on physical health, psychological health, social relationships and satisfaction with environment through the World Health Organization Quality of Life questionnaire (WHOQOL).

Plasma concentrations of EPA + DHA increased by 238% in the high-dose and 51% in the low dose fish-oil group, compared with the placebo group, reflecting excellent compliance. However, treatment with neither 1800 mg nor 400 mg differentially affected any of the measures and geriatric scales of mental well being. Following the same pattern, median baseline total WHOQOL scores ranged from 107 to 110 in the three groups and were not significantly different from each other. Treatment with 1800 mg or 400 mg EPA-DHA did not affect total Quality of Life questionnaire (QOL) or any of its separate domains after 26 weeks of intervention. For the interpretation of these results, however, it is quite interesting to note that the placebo capsules contained mainly oleic acid.

Two studies estimating the effect of omega-3 fatty acid on mortality in healthy aging were retrieved (Table 4). Folsom and Demissie⁽⁵²⁾ investigated the diet of a group of 720 postmenopausal women with low cancer and coronary heart disease risk. There was an inverse age- and energy-adjusted association between total mortality and fish intake, with a relative risk of 0.82 (95% confidence interval: 0.74, 0.91) for the highest versus lowest quintile. Estimated marine omega-3 fatty acid intake was not associated with total or cause-specific mortality. A recent intervention study⁽⁵³⁾ showed results similar to those above mentioned. A group of elderly men ($n = 282$) received a total of 2.4 g *n-3* PUFA in two capsules twice daily (49% EPA and 35% DHA) for 36 months. The authors observed in this supplemented population a tendency toward reduction in all-cause mortality that, despite the low number of participants, reached almost statistical significance ($P = 0.063$).

Discussion

In the present review we examined the effect of omega-3 fatty acids on different aspects which modulates the quality of life and the abilities to manage for a better life in aging. We finally included thirty-six articles that analyzed parameters related to cognitive decline, bone health and muscle tonus, immune function and general quality of life and mortality.

Results of the present systematic review suggest that the omega-3 fatty acids may have substantial benefits in reducing the risk of cognitive decline in older people, although there were five studies with no positive effects. The variability in outcomes between human studies which are confounded by methodological differences (type of food frequency questionnaire, test to measure cognitive decline, design of the study, etc), make it difficult for conclusions to be made at this time.

Two RCTs of the five negative studies used as placebo olive oil or oleic acid. Recently, Rosales⁽⁵⁴⁾ has published a letter in which explained the possible weakness in these studies. For example, as indicated by the authors, the study population might already consume a sufficient amount of PUFA in their diets and thus not be sensitive to the dose of DHA/EPA provided, but they have also rejected that control group might result in maintaining cognitive function in later life, comparable to the effects of DHA/EPA, because they consumed an extra amount of oleic acid (olive oil) which could provided



Table 4. Characteristics of identified studies on the effects of omega-3 fatty acids on quality of life and mortality in normal aging

Authors year	Study design	Population	Age (years/-range)	Sex distribution % male	Total sample size	Study duration (months)	Outcome measure	Outcome
Van de Rest <i>et al.</i> (2008) ⁽⁵⁰⁾	Randomized, double-blind, placebo-controlled trial	Independently living older volunteers with interest in participating in studies of Wageningen University, Netherlands (clinicaltrials.gov NCT00124852)	66.5–73.8	55	302	6	CES-D, Center for Epidemiologic Studies Depression Scale) MADRS, Montgomery Asberg Rating Scale GDS-15, Geriatric Depression Scale HADS-A, Hospital Anxiety and Depression Scale	No effect of EPA + DHA supplementation on mental well-being in the general older population studied.
Van de Rest <i>et al.</i> (2009) ⁽⁵¹⁾	Randomized, double-blind, placebo-controlled trial	Independently living older volunteers	66.5–73.8	55	302	6	WHOQOL-BREF, short version of the World Health Organization quality of life questionnaire	Supplementation with high or low doses of fish oil containing EPA + DHA did not influence the quality of life of healthy older individuals
Folsom & Demissie (2004) ⁽⁵²⁾	Prospective cohort	Old women initially free of heart disease and cancer (from Iowa Women's Health Study)	55–69	0	720	168	Total mortality Cause-specific mortality: cardiovascular; coronary heart disease; stroke; cancer	There was an inverse association between total mortality and fish intake. Estimated marine omega-3 fatty acid intake was not associated with total mortality or cause-specific deaths. Total mortality also was not associated separately with eicosapentaenoic or docosahexaenoic acids.
Einvik <i>et al.</i> (2010) ⁽⁵³⁾	Intervention	A group of elderly men, from The Diet and Omega-3 Intervention Trial (DOIT), predominantly without earlier clinical manifestations of cardiovascular disease.	64–76	100	563	36	All-cause mortality Cause-specific mortality: cardiovascular/noncardiovascular. Cardiovascular events: fatal/non-fatal	A tendency toward reduction in all-cause mortality in the <i>n</i> -3 polyunsaturated fatty acids groups. No effects was observed on cardiovascular events.

Omega 3 fatty acids in the elderly

benefits, albeit by different mechanisms. Actually, prospective studies have shown that the Mediterranean diet is associated with slower cognitive decline and a reduced risk of progression⁽⁵⁵⁾. Oleic acid, the major component of olive oil, has recently shown to provide a satiety factor, oleylethanolamide, which enhances memory consolidation without crossing the blood-brain barrier⁽⁵⁶⁾. This is important in verbal learning, organization, and memory. Oleoythanolamide is a mediator in maintaining cognitive function that it is not related to vascular or other nonvascular biological mechanisms (ie, metabolic, oxidative, and inflammatory). Thus, this evidence suggest that these RCTs should consider the benefits of oleic acid as well as omega-3 PUFA in protecting against age-associated cognitive decline and maintaining cognitive function in later life.

More prospective studies, as well as intervention studies investigating the association between *n*-3 PUFA and domain-specific measures are needed to clarify the current conflicting results observed in the literature, although these results are promising and encourage promotion higher intakes of *n*-3 PUFA in the diet or specific supplements since it seems to have substantial benefits in reducing their risk of cognitive decline⁽¹³⁾. Earlier intervention is a key factor in potentially treating age-related memory disorders and the maintenance of healthy brain during aging.

The elderly are particularly susceptible to infections due to a decline in immune function with age⁽³¹⁾. The infections also tend to have more severe consequences. Aging results in declines in lymphocyte functioning and proliferation, reductions in antibody formation, and declines on hormones necessary for thymus gland functioning. Environmental factors leading to declines in immune function include certain drug use, and deficiencies in nutrients required for immune function⁽¹⁴⁾. These deficiencies can be due to a reduction in food intake, as well as a reduced absorption and metabolism of nutrients. Active infections can increase the requirements for certain nutrients, and concomitant diseases can increase the morbidity of infections. Normal aging is accompanied by diverse changes in the immune system. Altered function of both T- and B-cells can be shown by losses in proliferative ability and interleukin-2 and interferon synthesis. This discusses the changes in immune function in the elderly that may be mediated by the intake/status of *n*-3 fatty acids, and the potential clinical implications of these changes in their metabolism. Only five studies related to this issue were included. The most stimulating global observation is that even low doses of omega-3 fatty acids may be sufficient to affect the immune response in elderly people under moderate dietary supplementation^(43–45). However, an important pitfall of all these studies is that those have not been evaluation long-term effects but also the impact on immunological biomarkers after supplementation is ceased.

A total of three studies were identified that described the effects of omega-3 fatty acids on bone health or muscles tonus with normal aging. Although clear scientific evidence seems to be still insufficient, the three of them described positive outcomes from dietary and supplemental omega-3 fatty acids. The most relevant observation in relation to bone

health is the very recent cohort study by Farina *et al.*⁽⁴⁷⁾ in which a long-term (four years changes) effect of consuming fatty fish has been assessed: maintenance of femoral neck bone mineral density either in men or women were well kept. Unfortunately, this is the only powerful study that we considered able to be included in the systematic review. As for the muscle tonus, supplementation with omega-3 fatty acids seems to be very useful and promising to stimulate the complicated protein synthesis during healthy aging⁽⁵⁷⁾. In fact, these nutrients may be considered of critical importance to prevent sarcopenia. Finally, undoubtedly clinical trials are urgent to test the effectiveness of these interventions with omega 3 in reducing the loss of bone health and muscle mass and function associated to normal aging⁽⁴⁷⁾.

Public health efforts to promote health and functional independence are critical strategies in helping older adults stay healthy⁽⁵⁸⁾. Research has shown that poor health does not have to be an inevitable consequence of aging^(1,59). Older adults who practice healthy behaviors, take advantage of clinical preventive services, and continue to engage with family and friends are more likely to remain healthy, live independently, and incur fewer health-related costs⁽²⁾. An essential component to keeping older adults healthy is preventing chronic diseases and reducing associated complications. About 80% of older adults have one chronic condition, and 50% have at least two. Infectious diseases (such as influenza and pneumococcal disease) and injuries also take a disproportionate toll on older adults.

In the present systematic review, only two RCT studies reached the criteria for inclusion and discussion. The outcomes to be evaluated after supplementation with EPA and DHA were mental well-being, physical health, psychological health and social relationship with no differences observed regardless of high vs. moderate dose^(39,41–42,50,51).

As for mortality an inverse age-and energy-adjusted association between total mortality and fish intake was found. In general, a tendency toward reduction in all-cause mortality is observed after EPA and DHA supplementation although the positive effect seems to be within a better dietary and quality of life patterns⁽⁵³⁾.

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