FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2014/2015

Maria João Marques de Sousa

Prevention of Alzheimer's disease: the role of the Mediterranean diet

março, 2015

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UNIVERSIDADE DO PORTO

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Mestrado Integrado em Medicina

Área: Neurologia

Tipologia: Monografia

Trabalho efetuado sob a Orientação de:

Joana Cruz Guimarães Ferreira Almeida

Trabalho organizado de acordo com as normas da revista:

Revista de Nutrição

março, 2015

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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

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NOME

Maria João Marques de Sousa

CARTÃO DE CIDADÃO OU PASSAPORTE (se estrangeiro)	E-MAIL	TELEFONE OU TELEMÓVEL
13918196	mjmsousa@gmail.com	932410734

NÚMERO DE ESTUDANTE	DATA DE CONCLUSÃO
200900224	2015

DESIGNAÇÃO DA ÁREA DO PROJECTO

Neurologia

TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

Prevention of Alzheimer's disease: the role of the Mediterranean diet

ORIENTADOR

Joana Cruz Guimarães Ferreira Almeida

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"I find myself learning the 'art of losing' everyday. Losing my bearings, losing objects, losing sleep, but mostly, losing memories. All my life I have accumulated memories. They have become, in a way, my most precious possessions. (…) Everything I have accumulated in life, everything I have worked so hard for, now all that is being ripped away. As you can imagine, or as you know, this is hell. But it gets worse. Who can take us seriously when we are so far from who we once were? Our strange behavior and fumbled sentences change others' perception of us and our perception of ourselves. We become ridiculous. Incapable. Comic. But this is not who we are. This is our disease. And like any disease, it has a cause. It has a progression. And could have a cure. My greatest wish is that my children, our children, the next generation, do not have to face what I'm facing."

Still Alice. Directed by Richard Glatzer and Wash Westmoreland. Sony Pictures Classics, 2014.

A todos os doentes do mundo que, dia após dia, aprendem a "arte de perder".

Prevention of Alzheimer's disease: the role of the Mediterranean diet

Prevenção da doença de Alzheimer: o papel da dieta Mediterrânica

Maria João Sousa[1]
Joana Guimarães[2]

[1]Faculty of Medicine, University of Porto, Portugal
mjmsousa@gmail.com
[2]Neurology and Neurosurgery Unit of Clinical Neurosciences and Mental Health Department, Faculty of Medicine, University of Porto, Portugal
joanaalmeida@med.up.pt

Corresponding author at:
Serviço de Neurologia, Hospital de São João
Alameda Professor Hernâni Monteiro, 4200-319 Porto, Portugal
Tel.: + 351 225512100
Fax: + 351 225025766
E-mail address: mjmsousa@gmail.com

Short title: Mediterranean diet and dementia / *Dieta Mediterrânica e demência*

Abstract

Alzheimer's disease is the most frequent type of dementia. It has been increasing exponentially and is now considered a 21st century epidemic, contributing substantially to the morbidity and mortality among the elderly population. Thus, this disease is a growing major public health concern with a profuse socioeconomic impact. In addition, the existing pharmacological agents only offer modest symptomatic relief and cannot address the progressive neurodegeneration nor cure the disease. Therefore, finding effective preventive and therapeutic measures, that could delay the onset or reverse the course of the disease, is crucial. Several studies have shown that lifestyle factors may play a central role in reducing the risk of developing Alzheimer's disease or, at least, in delaying its clinical symptoms. Among these disease-modifying factors, healthy nutrition has drawn much attention, given that it might strongly influence the risk of cognitive decline, dementia and Alzheimer's disease. Such a healthy dietary pattern is the Mediterranean diet, which has been widely associated with increased longevity and lower risk of several chronic diseases. It may also play a protective role against age-related changes in cognitive function, predementia syndromes and dementia. These beneficial effects are thought to result from the combined effect of several nutritional components, such as wine, olive oil, fish, fruits and vegetables. Therefore, the Mediterranean diet might constitute an effective preventive strategy for Alzheimer's disease, with low costs and few side effects. Importantly, these promising preventive measures may translate into strong epidemiological health outcomes, which might lead to a significant progress on public health.

Resumo

A doença de Alzheimer é o tipo mais frequente de demência. O número de doentes tem aumentado exponencialmente, sendo atualmente considerada uma epidemia do século XXI e contribuindo significativamente para a morbilidade e mortalidade da população idosa. Assim, é um importante problema de saúde pública, com um impacto socioeconómico crescente. Os fármacos usados atualmente apenas contribuem para o alívio sintomático e não atuam ao nível do processo neurodegenerativo nem curam a doença. Deste modo, desenvolver medidas preventivas e terapêuticas, que sejam eficazes a atrasar ou a reverter o curso da doença, é de extrema importância. Vários estudos têm demonstrado que fatores relacionados com o estilo de vida desempenham um papel central em reduzir o risco de doença de Alzheimer ou, pelo menos, em atrasar o aparecimento dos sintomas. Um destes fatores é a nutrição, que influencia significativamente o risco de declínio cognitivo, demência e doença de Alzheimer. Um padrão dietético promissor é a dieta Mediterrânica, que tem sido

associada a um aumento da longevidade e redução do risco de várias doenças crónicas. Desempenha igualmente um papel protetor nas alterações da função cognitiva relacionadas com a idade, síndromes pré-demenciais e demência, provavelmente através do efeito combinado de vários componentes nutricionais, tais como vinho, azeite, peixe, frutas e vegetais. Assim, a dieta Mediterrânica poderá representar uma estratégia preventiva eficaz para a doença de Alzheimer, com baixos custos e escassos efeitos colaterais. Estas medidas preventivas promissoras poderão traduzir-se em resultados epidemiológicos importantes, o que poderá culminar num progresso significativo na saúde pública.

Keywords
Alzheimer's disease; prevention; diet; Mediterranean diet

Abbreviations

Aβ: β-amyloid
AD: Alzheimer's disease
ADI: Alzheimer's Disease International
ApoE: apolipoprotein-E
APP: amyloid-precursor-protein
CRP: C-reactive protein
DHA: docosahexaenoic acid
FA: fatty acid
HDL: high-density lipoprotein
HEI-2005: Healthy Eating Index-2005
hsCRP: high-sensitivity CRP
IL-6: interleukin-6
MCI: mild cognitive impairment
MeDi: Mediterranean diet
MUFA: monounsaturated fatty acids
PS1: presenilin-1
PS2: presenilin-2
PUFA: polyunsaturated fatty acids
ROS: reactive oxygen species
UNESCO: United Nations Educational Scientific and Cultural Organisation
WHICAP: Washington Heights-Inwood Columbia Aging Project
WHO: World Health Organisation

Introduction

Since its first description in the beginning of the XX century, Alzheimer's disease (AD) has gone from a rarely reported disorder to one of the most frequent causes of disability in the elderly. Accordingly, cognitive decline and particularly AD are major contributors to morbidity and mortality worldwide and constitute a significant burden to patients, caregivers and society. Numerous studies performed in the last decades have given essential insights on the nature of AD and, importantly, on the magnitude of the problem. However, research on AD is still an endless challenge, particularly in the area of prevention [1].

Ever since the times of the Ancient Greece that it is recognized that lifestyle modifications, such as diet and exercise, can actually prevent or even treat several diseases, a concept that is well reflected on the well-known Hippocratic saying "Let food be thy medicine and medicine be thy food" [2].

Recently, many efforts have been made in describing the association between diet and cognitive function, given that several studies have reported that the risk of developing cognitive decline, dementia and AD is strongly influenced by nutrient intake and dietary practices [3]. In fact, among all the lifestyle factors proposed as the first-line of protection against the onset and progression of cognitive dysfunction, diet constitutes a promising preventive or even therapeutic approach, as research has shown that certain nutrients and dietary patterns directly interfere with pathological mechanisms in AD [4, 5]. Such a dietary pattern is the Mediterranean diet (MeDi). Studies have shown that it is related to increased longevity and lower risk of several chronic diseases, including AD [6].

Methods

An online search was conducted on Pubmed using the query *(Alzheimer disease [MeSH Terms] AND diet)*. Titles and/or abstracts were analyzed, with full text available, limited to the period between 2004 and 2014. From the 165 articles obtained, 53 were selected and analysed. After excluding some of these articles and after a complementary search on "Related citations" and on the references of the selected articles, a final number of 41 references was obtained.

Alzheimer's disease: the dimension of the problem

AD is a neurodegenerative disorder firstly described by Alois Alzheimer in 1907 [7, 8]. Since then, it has been increasing exponentially and is now considered a 21st century epidemic, affecting approximately 26 million people worldwide and one quarter of the people aged above 85 [8-11].

AD is the most frequent type of dementia, accounting for more than 75% of the more than 35 million cases around the world. In developed countries, it is estimated that 1 in 10 individuals over the age of 65 and more than 1 in 3 individuals over 85 suffer from a form of dementia [12].

According to the World Health Organisation (WHO), AD contributes substantially to the morbidity and mortality among the elderly population [13]. It is clinically characterized by progressive cognitive decline, impairment of the daily life activities and several neuropsychological deformities [7]. Initially, AD mostly affects short-term memory (memory for recent events) and language skills, but, as it evolves, it progressively affects cognition, function, behavior and mood [14, 15]. In fact, it is the second more common cause of disability, right after depression [16]. Therefore, it is a devastating disease for patients, as it even takes away their sense of self, and also for families, which are strongly affected emotional, physical and financially by the rapidly increasing caregiver burden [14, 15, 17].

It is estimated that the prevalence of AD will double every 20 years, foreseeing a total of approximately 115 million people affected by the year of 2050 [12]. This expected considerable rise may be explained by the growth of the population above the age of 65, as well as by the lengthening of the average life expectancy [8, 16]. This change towards an aging population is extremely relevant, given that the incidence of all forms of dementia almost doubles every five years of age [18]. Being already one of the major contributors for the health system expenses in many developed countries, this rising incidence will, not surprisingly, be accompanied by significant increases in the direct and indirect costs to society [16, 18]. Accordingly, the Alzheimer's Disease International (ADI) predicts that the costs will increase approximately 85% by the year of 2030 [14].

Overall, AD constitutes a growing major public health concern with a profuse socioeconomic impact [19].

Key points of Alzheimer's disease physiopathology

The AD brain presents with two major pathological hallmarks that ultimately lead to neurodegeneration: senile plaques and neurofibrillary tangles [16].

Senile plaques, also known as neuritic or amyloid plaques, consist of deposits of extracellular β-amyloid (Aβ) peptide and degenerating neurons and it is thought that they play an essential role in the inflammatory phenomena [16, 20].

Intraneuronal neurofibrillary tangles mainly consist of bundles of filaments which contain the microtubule-associated protein tau [7, 16]. A hyperphosphorylated tau induced by stress is found in the hippocampus and cerebral hemispheres of AD

patients. Since learning and short-term memory are attributed to the hippocampus, the development of tangles in this region is related to the cognitive impairment that occurs in the initial stages of the disease. In the last stages of AD, especially in pyramidal neurons and their synapses of the neocortical and cerebral cortex, there is formation of tangles and a large neuronal loss [16].

The AD brain is also submitted to increased oxidative stress and inflammation, which also play a significant role in the neurodegeneration process [16].

Oxidative damage is believed to play an important role in AD pathology and consists of free radical attack that occurs as oxidized proteins, peroxidized lipids and damaged mitochondria and DNA [10, 16]. Thus, the human organism is provided with a mechanism to deal with or prevent the onset of oxidative stress: endogenous antioxidants [10]. However, the brain is especially susceptible to oxidative stress due to its lower levels of antioxidants, which make it not as capable at eliminating free radicals. This limitation creates an anti/prooxidant imbalance scenario, amplifying the oxidative stress status [16].

Chronic inflammation can also be observed around amyloid plaques, which leads to further reactive oxygen species (ROS) production and, consequently, to an amplification of the damaging effects of oxidative stress [16]. C-reactive protein (CRP) is an inflammatory marker that has been identified in senile plaques and neurofibrillary tangles and that is upregulated in AD brains [21]. Increased levels of proinflammatory cytokines is also an important feature of the AD brains [16].

Alzheimer's disease risk and protective factors

Although the etiological factors of AD are still partially unknown, several studies have provided growing evidence of the role of a number of risk and protective factors in the development of the disease [12]. Similarly to other chronic diseases, the development of AD undoubtedly involves a complex interaction of factors, including lifestyle ones, that may start or exacerbate the neurodegenerative process [22, 23].

Older age is the most well-established nonmodifiable risk factor, with the number of affected people doubling every four years after the age of 65 [13, 24]. Also an important nonmodifiable risk factor is genetics: the apolipoprotein-E (ApoE) genotype and mutations in amyloid-precursor-protein (APP), presenilin-1 (PS1) and presenilin-2 (PS2) genes [20].

Modifiable risk factors have also been extensively studied and include low education, history of depression, head trauma, cerebrovascular disorders, cardiovascular risk factors (hypertension, hypercholesterolemia, heart disease, diabetes, smoking, excessive alcohol consumption, obesity and physical inactivity) and

diet [20, 24]. In fact, these factors exert more influence on the prevalence of AD than genetics [21]. Proof of this is that a higher prevalence of AD is observed in elderly immigrants living in the USA, when compared to individuals living in their homelands [25].

These disease-modifying factors have been object of many research in recent years, given that interventions that alter the course of them constitute potential preventive measures [19, 25]. Therefore, when motivated and supported by health professionals, individuals can influence their late-life cognitive performance and risk of brain disorders through lifestyle options [10, 15, 26]. Among these, nutrition has drawn much attention, as an increasing amount of evidence suggests that it may constitute a key factor in the development of AD [10, 21].

The importance of Alzheimer's disease prevention

Given the predicted dramatic rise in the number of AD patients worldwide, finding effective preventive and therapeutic measures, that could delay the onset or reverse the course of the disease, is a crucial matter [8, 18].

Currently, the existing two classes of pharmacological agents for symptomatic treatment of AD (acetylcholinesterase inhibitors and a glutamate receptor antagonist) only offer modest symptomatic relief and cannot address the progressive neurodegeneration nor cure the disease [14, 24]. In fact, research has shown that these agents can slow the progression of some symptoms for only 6 to 12 months and 50% of the patients might show no response [15].

Thus, in the absence of curative strategies to date, prevention of AD through management of risk factors is essential [11, 18]. In fact, it is estimated that delaying the clinical stage of AD by 1 and 5 years could decrease its prevalence by 25% and 50%, respectively, after 5 years of implementation of preventive measures [11]. While improving clinical outcomes, an efficient preventive strategy would also reduce financial costs and, consequently, lighten the burden of AD on health care systems [13].

The most well-established risk factors of AD, age and the ApoE genotype, are not possible targets for prevention [4]. Hence, two of the most promising primary preventive measures would address vascular factors (such as controlling hyper and hypotension, obesity and diabetes) and lifestyle factors, such as maintaining an active social network, participating in physical and intellectual stimulating activities and choosing a healthy nutrition pattern [12, 16].

An increasing amount of evidence suggests that lifestyle factors, particularly diet, may play an essential role in managing the illness [8]. Intervention in these areas may reduce the risk of developing AD or, at least, delay its clinical symptoms [12]. In

fact, since AD normally develops late in life, for a number of individuals delaying the clinical symptoms could be just as positive as a cure. Accordingly, in recent years there has been an increasing consumer demand for foods that have beneficial effects in several diseases, including AD – in 2002, 8% and 50% of the consumers confessed that they had bought foods aiming to prevent a certain health condition and to manage or treat conditions, respectively [8].

Early intervention in the preclinical and prodromal stages of the disease, before the development of clinical symptoms, is of utmost importance [5]. Intervention in these stages would allow a delay on the development of mild cognitive impairment (MCI), a transitional and potentially reversible stage between normal aging and dementia or AD, or even reverse MCI to normal cognitive function, therefore avoiding or delaying its progression to dementia [4, 27]. Between 6 and 25% of patients with MCI convert to AD every year, making MCI an appealing stage for preventive interventions [7, 27]. In fact, given the absence of an effective pharmacological treatment for MCI, these patients frequently ask physicians if there are any preventive measures they can adopt to avoid the progression to AD, which is characterized by a global cognitive deterioration severe enough to interfere significantly with their daily life, unlike MCI [1, 7].

The role of diet on Alzheimer's disease

In recent years, several studies have shown the benefits of a healthy nutrition on several chronic diseases, such as cardiovascular diseases, several types of cancers, Parkinson's disease and diabetes [11, 28]. Hence, since it constitutes one of the most important modifiable environmental factors, there has been a growing interest on the potential beneficial effect of diet also on AD [19, 29]. As an example, some dietary components, such as antioxidants and fish, have been reported to reduce the risk of developing AD, contrasting with other components, such as saturated fatty acids and excessive consumption of alcohol [19].

However, foods are not consumed individually, but as part of a whole daily diet; in fact, the concept of "dietary pattern" has gained much attention lately regarding several diseases (such as cirrhosis and several types of cancer), given that it takes into consideration the interactions between the components of a diet, consequently better reflecting its complexity [19, 28-30]. Furthermore, current studies about the role of individual foods on the risk of AD have presented inconsistent results, partly because people eat meals combining different nutrients or food items that probably have additive and/or synergistic effects [6, 23]. Therefore, defining diet by dietary patterns has the ability to capture its multidimensionality and may certainly be more enlightening

to understand the effect of nutrition on AD and also on other chronic diseases [28, 30].

The Mediterranean diet pattern

In 2013, the traditional MeDi was recognised as an Intangible Cultural Heritage of Humanity of Croatia, Cyprus, Italy, Greece, Morocco, Portugal and Spain by the United Nations Educational Scientific and Cultural Organisation (UNESCO) [23].

The MeDi is difficult to define due to some differences in eating and drinking habits between the Mediterranean countries [13]. Nevertheless, the most well-known version was presented in the 1990s by Dr Walter Willet of Harvard University's School of Public Health and a scientific consensus has been achieved [13, 14]. Thus, the traditional MeDi consists of high intake of plant-based foods (fruit as the typical daily dessert, vegetables, legumes, breads, other types of cereals and nuts); olive oil as the main source of monounsaturated fatty acids (MUFA; used in cooking and salad dressing) but low intake of saturated fat; moderately high intake of fish, depending on the proximity of the sea, as a source of omega-3 polyunsaturated fatty acids (PUFA); low to moderate intake of dairy products (mostly cheese and yogurt); low to moderate intake of poultry; regular low to moderate intake of wine (normally during meals); low intake of red meat and a maximum of four eggs weekly [4, 6, 14, 25, 31]. The total fat and the amount of saturated fat is between 25 and 35% and 8% or less of the daily caloric allowance, respectively [14]. Hence, the hallmark of the traditional MeDi is the high intake of olive oil (leading to a high ratio MUFA/PUFA) [32]. In fact, the term "Mediterranean diet" is used to refer to the dietary pattern from Mediterranean regions that produce olive oil, its main source of fat, and whose origin is on the Greeks and Romans, who practiced their agriculture on the Mediterranean climate (warm and humid) [13, 21].

Evidence of the benefits of the Mediterranean diet on cognitive status and Alzheimer's disease

The benefits of the MeDi pattern were described for the first time by Keys et al. in the Seven Countries Study in the 1950s and 60s. They realised that countries from the South Europe (Greece, Italy and Yugoslavia) presented one of the highest life expectancies worldwide and the rates of coronary heart disease, several types of cancer and other chronic diseases were among the lowest. Thus, the authors hypothesised that this optimal health status could be linked to their traditional diet [4, 23].

Since then, an increasing line of evidence has emerged for the protective effects of the MeDi in a number of chronic diseases, as well as in the overall mortality,

being now considered one of the healthiest dietary patterns worldwide [23, 33]. Accordingly, a study showed that adherence to the MeDi is associated with an important improvement in health status, significantly reducing the overall mortality (9%), mortality from cardiovascular diseases (9%), incidence and mortality from cancer (6%) and incidence of Parkinson's disease and AD (13%). These results appear to be clinically significant for public health, especially for including the MeDi pattern on a primary prevention strategy of major age-related chronic diseases [14].

Several years after the Seven Countries Study, and assuming the concept of "what is good for the heart is good for the brain", the Washington Heights-Inwood Columbia Aging Project (WHICAP) was the first study to report a beneficial effect of the MeDi on AD [4, 14]. Scarmeas et al. concluded that single foods were not significantly associated with risk for AD, unlike the MeDi pattern: higher adherence to the MeDi was significantly associated with a reduced risk of developing AD [14, 34]. The individuals with a medium and high adherence to the MeDi had a 15 to 21% and a 39 to 40% reduction in AD risk, respectively, and for each additional unit on the MeDi adherence score there was a 9 to 10% reduction in the risk of developing AD [34, 35]. These results remained unchanged after adjustment for several common potential confounders (age, sex, ethnicity, ApoE genotype, education, caloric intake, BMI, smoking and comorbidity index) and the gradual risk reduction for higher adherences suggested a dose-response trend [35].

The Three-City Study, developed in France, showed that a higher adherence to the MeDi was significantly associated with better global cognitive function and episodic memory over time [14].

In 2013, Samieri et al. suggested that long-term adherence to the MeDi was related to average global cognitive function and verbal memory, a strong early predictor of AD in the elderly, and found that higher adherence delayed cognitive aging by approximately 1 year [36].

Adherence to the MeDi also reduces the risk of developing MCI and of conversion of MCI to AD, suggesting that an early intervention may even reduce the risk of developing the prodromal stage of AD [25, 27]. A study from the Mayo Clinic (USA) described a reduced risk of MCI with higher intake of vegetables and a higher unsaturated/saturated fatty acids ratio [14]. Another study concluded that for every one-unit rise in the authors' MeDi adherence score there was an 8% reduction in the risk of developing MCI [3].

Furthermore, higher adherence to the MeDi is not only associated with a reduced risk of developing AD but also with lower mortality in AD [28]. A study showed that individuals with medium and high adherence to the MeDi lived 1.33 and 3.91 years

longer, respectively, when compared to those with a low adherence [37].

Nevertheless, Féart et al. suggested that there might be a window of opportunity for this beneficial effect in slowing the cognitive decline and delaying the onset of dementia – during the 5 years preceding the clinical diagnosis of dementia, the pathophysiological processes are probably too advanced to be reversed by diet. Therefore, the MeDi would only be effective 5 years or more before the clinical diagnosis of dementia, when the AD pathology and neuronal loss are still limited [13, 32].

Although the majority of studies have been developed in Mediterranean populations, recent research has shown beneficial effects also in non-Mediterranean countries [38]. In fact, the WHICAP, mentioned above, was developed in a multiethnic population of New York [35]. In a study developed in 2012, Gardener et al. presented similar findings on an elderly Australian cohort. Interestingly, given that Australia is a geographically isolated country with a multiethnic population, these similar results are in agreement with the idea that the protective effects of the MeDi are transferable to different populations [39]. Similarly, other studies developed in India and in the North of Europe reached the same conclusions [35].

Table 1 summarizes the main aims and findings of the selected studies relating the MeDi to AD.

Table 1. Summary of the selected studies relating the association between the MeDi and risk of AD

Author/year	Number of patients	Objective	Main conclusions
Scarmeas et al., 2006 [35]	2258	To evaluate the association between the MeDi and risk of AD.	Higher adherence to the MeDi was associated with a reduction in risk of AD.
Scarmeas et al., 2006 [30]	1984	To evaluate the association between the MeDi and AD in different AD populations and possible vascular mechanisms.	Higher adherence to the MeDi was associated with a reduction in risk of AD. Introduction of vascular variables did not interfere in the magnitude of the association, suggesting that it might be explained by oxidative or inflammatory mechanisms

			rather than vascular ones.
Scarmeas et al., 2007 [37]	192	To investigate the association between the MeDi and mortality in AD patients.	Patients with medium and high adherence to the MeDi had lower risk of mortality when compared to those with a low adherence.
Scarmeas et al., 2009 [27]	1875	To evaluate the association between the MeDi and MCI.	Higher adherence to the MeDi was associated with lower risk of developing MCI and lower risk of conversion of MCI to AD.
Féart et al., 2009 [32]	1410	To examine the association between the MeDi and cognitive performance changes and risk of dementia in an elderly French cohort.	Higher adherence to the MeDi was associated with slower cognitive decline evaluated with the Mini-Mental State Examination (MMSE), but not consistently with other cognitive tests. However, it was not associated with risk for incident dementia.
Gu et al., 2010 [40]	1219	To evaluate the association between adherence to the MeDi and AD risk and possible inflammatory and metabolic mechanisms.	Higher adherence to the MeDi was associated with lower risk of developing AD. Introduction of inflammatory and metabolic markers into the statistical model did not change the magnitude of the association.
Tangney et al., 2011 [41]	3790	To investigate whether adherence to the MeDi or to the Healthy Eating Index-2005 (HEI-2005) was associated with cognitive changes in older adults.	Higher adherence to the MeDi was associated with slower rates of cognitive decline, even after adjustment for several variables. No such association was observed with the HEI-2005.

Gardener et al., 2012 [39]	970	To examine the association between adherence to the MeDi and risk of AD and MCI in an elderly Australian cohort.	A significant difference in adherence to the MeDi was observed between healthy controls and AD patients and between healthy controls and MCI patients. MeDi was also associated with changes on the MMSE score over 18 months.
Samieri et al., 2013 [36]	16058	To evaluate the association between long-term adherence to the MeDi and subsequent cognitive function and decline in a cohort of older women.	Long-term adherence to the MeDi was associated with better cognition but not with cognitive change.

HR = Hazard Ratio; CI = Confidence Interval; OR = Odds Ratio

Biological plausibility

It is likely that the beneficial role of the MeDi against age-related changes in cognitive function, predementia syndromes and dementia occurs through multiple pathways, namely vascular and non-vascular ones [11]. Accordingly, the MeDi is known to reduce the risk of cardiovascular diseases and cardiovascular mortality; thus, some research has shown that higher adherence to the MeDi results in a decreased number of infarcts and reduced white matter hyperintensity volume on MRI. Therefore, vascular mechanisms could actually be responsible for the protective role of the MeDi on AD [5]. Assuming that the MeDi exerts a beneficial effect on cardiovascular disorders and that cardiovascular risk factors are relevant in AD, Scarmeas et al. investigated whether the association between MeDi and AD was attenuated when vascular risk factors (history of stroke, diabetes, hypertension, heart disease and lipid levels) were simultaneously introduced in the statistical model. Surprisingly, the degree of the association was not modified, suggesting that it was not mediated by vascular comorbidities [4]. Instead, non-vascular mechanisms, such as inflammation, metabolic disorders and oxidative stress, might contribute to the association [23]. For example, in the ATTICA Study, developed in 2004, individuals with the highest adherence to the

MeDi had 20% and 17% lower CRP and interleukin-6 (IL-6) serum levels, respectively, and significant reductions in a number of other inflammatory and coagulation markers [35]. In 2010, Gu et al. performed another study on which they used high-sensitivity CRP (hsCRP) as a marker of systemic inflammation and fasting insulin and adiponectin as markers of metabolic profile. A reduced risk of AD was observed in individuals with higher adherence to the MeDi, but introducing hsCRP, fasting insulin or adiponectin into the statistical model did not affect the degree of the association. These results suggest that higher adherence to the MeDi might reduce the risk of AD through non-inflammatory or non-metabolic mechanisms or, alternatively, that these biomarkers do not entirely capture these pathways [40].

The contribution of oxidative stress and also other important mechanisms will be discussed in detail throughout the next section.

Components of the Mediterranean diet and their mechanisms of action on Alzheimer's disease

Recent research suggests that the protective effects of the MeDi against cognitive decline in the elderly population are probably due to the combined effect of a number of foods and nutrients already individually proposed to play a protective role in cognitive impairment or dementia [32]. Some of these foods are described individually in more detail below.

Wine

The role of moderate consumption of alcohol, especially wine, in neuroprotection has been widely recognized [41].

Moderate intake of wine, particularly during meals, is one of the hallmarks of the MeDi [25]. An increasing amount of evidence suggests that moderate drinkers (1 glass per day for women and 2 glasses per day for men) have a lower risk of AD and better cognitive performance, when compared to non-drinkers [8, 25]. A study developed in Bordeaux (France) showed that mild consumption of wine (1-2 glasses/day) was associated with protection from AD, while moderate consumption (3-4 glasses/day) conferred additional protection from incident dementia [13].

It is noteworthy that the protective effect of daily wine intake remains unchanged at older ages: a study concluded that individuals aged 65 years and above had a lower risk of developing AD when consuming up to 3 servings of wine over 4 years. However, this protective effect was not observed with intake of beer or liquor [13].

The mechanisms through which moderate consumption of wine protects against AD are still somehow unclear [19]. It might be partly attributed to changes induced by

alcohol, such as increases in high density lipoprotein (HDL) cholesterol and reductions in fibrinogen and other thrombotic factors, which help preserve brain vessels and prevent subclinical strokes, leading to a better cognitive function [25].

Another possible mechanism is the presence of natural antioxidants in wine, called polyphenols. Polyphenols are the most abundant antioxidants in our diet and are present in high quantities in red wine and olive oil [13, 19]. Numerous studies have described several health benefits of plant polyphenols: prevention of cardiovascular diseases, cancer chemoprevention, antimicrobial and anti-inflammatory activity and treatment of neurodegenerative diseases of the amyloid type [13].

Red wine contains at least 19 types of polyphenols; among these, resveratrol is the one present in highest levels (1.5-7 mg/mL) [13]. Resveratrol also occurs in abundance in grapes, but it is not present on beer or other spirits. Thus, a large part of the beneficial effect of wine on neurodegeneration can be attributed to resveratrol [10].

Polyphenols provide protective effects in AD through several mechanisms, such as free radicals' inactivation; inhibition of the inflammatory reaction and lipid membrane destabilization by Aβ aggregates; modulation of the activity of multiple enzymes and effects on intracellular signalling pathways and gene expression [13, 19]. In particular, resveratrol acts as a mitochondria-targeted antioxidant, maintaining normal mitochondria function and cell viability and reducing oxidative stress; promotes proteosome clearance of Aβ; produces nonamyloidogenic Aβ cleavage products that induce important neuroprotection genes; markedly reduces the levels of secreted and intracellular Aβ-peptides, protecting neurons from Aβ-induced neurotoxicity; reduces plaque formation and also activates a NAD+ dependent deacetylase, sirtuin I [8, 13, 19, 41].

Nevertheless, physicians should be cautious when advising patients about alcohol consumption, given that its excessive intake causes serious neurologic and other organs damage [17]. It seems reasonable to recommend moderation (less than 3 servings per day) to those who already drink, but non-drinkers should not be advised to initiate consumption, due to the risk of abuse and addiction, as well as other undesirable outcomes, such as falls in elderly individuals [20].

Fish and seafood

Several epidemiological studies have suggested that fish intake is associated with a reduced risk of dementia and AD. In fact, in 2003, Morris et al. concluded that consumption of fish at least twice a week was associated with a 60% risk reduction of developing AD [19]. Other studies also showed that regular fish intake slows cognitive decline and improves global cognitive function [5]. In the Rotterdam study, Kalmijn et

al. reported that intake of fish was not only associated with a reduction in AD risk but also in all-cause dementia. Intake of seafood, also a prominent component of the MeDi, is also associated with reduced risk of cognitive decline and dementia [13].

The benefits of fish are thought to be due to its high omega-3 PUFA content [19]. Fatty acids (FAs) are crucial components for the central nervous system, given that they are neuroprotective, perform an important role on the development of the brain and maintain the structural integrity of neuronal membranes [21, 25]. In fact, dietary FAs, especially PUFA, might determine the fluidity of synaptosomal membranes and therefore regulate neuronal transmission [21].

However, it is noteworthy that, unlike unsaturated fats, saturated fats affect memory function, possibly increasing the risk of AD – in animal studies, mice and rats fed with higher portions of saturated fats exhibited worse learning and memory. By contrast, as mentioned above, fish is rich in unsaturated fats, such as omega-3 PUFA; docosahexaenoic acid (DHA) is an important type of omega-3 PUFA and its major dietary sources are fish oils and fatty fishes [5]. The brain exhibits high levels of DHA, suggesting that it plays a significant neurophysiological role; proof of this is that deficiency of DHA during brain maturation results in negative outcomes on neural plasticity, insulin signalling and brain function in adulthood [13]. In addition, the brain levels of DHA tend to drop with aging, particularly in AD patients, and post-mortem analysis of AD brains reported low levels of omega-3 PUFA in the parahippocampal cortex, features that might contribute to the cognitive impairment [13, 25]. Accordingly, studies performed in animals have shown that dietary enhancement with DHA improves cognitive performance and slows AD pathology. These beneficial effects may be transposed to humans [25].

Thus, research has described several mechanisms that explain the benefits of fish intake as a major source of omega-3 PUFA. In a study developed in Chicago, the specific intake of omega-3 PUFA was associated with a decreased risk of AD. These fats have beneficial effects on the brain and vascular system, decreasing cerebrovascular and cardiovascular risk factors. Thus, they possibly limit AD pathology by reducing amyloid formation, minimizing aggregation into plaques and increasing its clearance [25]. Omega-3 PUFA also have anti-inflammatory properties, suggesting a role on inflammatory pathways [23]. Ultimately, they possibly have the ability to cause free radical scavenging, increase resistance to free radical attack and reduce lipid peroxidation by enhancing the activity of endogenous antioxidant enzymes [16].

Olive oil

Multiple studies have shown that a diet rich in olive oil is associated with healthier

aging and increased longevity [13].

As mentioned above, olive oil is also rich in antioxidant components, such as polyphenols and tocopherols [21]. In a 2010 study, a MeDi enriched in olive oil was found to reduce the expression of genes related to oxidative stress and inflammatory processes and lower the plasma levels of lipid oxidation and systemic inflammation markers [23]. Extra virgin olive oil contains turosol and caffeic acid, which have been shown to cause significant reductions on IL-6 production. It has also been shown that olive oil has the ability to raise the levels of antioxidant enzymes, such as paraoxonase and plasma carotenoids [30]. Additionally, polyphenols from olives have been reported to inhibit tau fibrillization. Accordingly, a study developed in 2009 showed that moderate or intensive use of olive oil resulted in reduced cognitive deficits regarding verbal fluency and visual memory [13].

Fruits and vegetables

Regular consumption of a medium or large proportion of fruits in the diet is associated with a decreased risk of AD and dementia. Higher vegetables consumption also appears to slow the rate of cognitive decline. Green leafy vegetables show the strongest association [19].

As mentioned above, the brain antioxidants levels are low, making it particularly vulnerable to free-radical damage [3]. Therefore, higher fruits and vegetables intake might have beneficial effects in preventing age-related neurologic dysfunctions due to their high content of antioxidants and bioactive components (such as polyphenols and vitamins C and E) [3, 19].

Two studies showed that the high levels of polyphenolic components found in fruits, such as blueberries, pomegranates, apples, bananas and oranges, protect against oxidative stress via signal transduction, neuronal communication and increases in hippocampal plasticity. In particular, quercetin is one of the main polyphenols found in fruits and vegetables and it has the ability to improve cell viability and decrease neuronal cell membrane damage induced by oxidative stress [8]. Studies with tomato products or dishes, such as gazpacho, have also shown significant reductions in oxidative stress markers, such as isoprostanes [21].

Two studies have reported the benefits of Concord grape juice and wild blueberry juice; Concord grape juice supplementation for 12 weeks improved verbal learning and recall in individuals with memory decline and daily intake of wild blueberry juice also for 12 weeks in individuals with early memory changes improved paired associate learning and word list recall [13].

Vitamin C (or L-ascorbic acid) is a strong reducing agent and acts as a scavenger to

several reactive oxygen species. In turn, Vitamin E, present in high amounts in vegetables, protects cell membranes from oxidation by free radicals. In animal studies, both vitamins showed protection against neuronal death and improved learning and memory. Another study showed that both vitamins were associated with a reduced risk of AD [13].

Dairy

Dairy products are rich in magnesium, vitamin D and phosphorus and might reduce the risk of cognitive impairment by reducing vascular and structural brain changes that take place during cognitive decline. Studies have shown that moderate intake of dairy rich in unsaturated fats in midlife decreases the risk of AD, unlike dairy rich in saturated fats [19].

Conclusion

Despite a global pessimistic scenario around AD, there are some reasons for optimism, given that extensive research has focused in several aspects of the disorder and particularly on early intervention strategies, such as nutritional ones [15].

The MeDi has been globally recognized as one of the healthiest dietary models in the world, due to its association with low morbidity and mortality for several chronic diseases [32]. Its role on the brain health translates into slower cognitive decline (particularly the one related to the aging brain), reduced risk of developing MCI, reduced risk of conversion of MCI to AD, reduced risk of AD and symptomatic relief [4, 14, 25]. This association is probably mediated by the combined effect of several nutritional components, such as wine, olive oil, fish, fruits and vegetables [25].

A specific dietary strategy would represent a totally new approach for the management of AD. As nutrients are usually well-tolerated, such an approach is extremely promising and could exert its effects in synergy with existing and future pharmacological agents [9]. Importantly, the promotion of the MeDi pattern should be extended, particularly due to the globalisation of food supplies that led to changes on traditional food choices, especially among the young generations [23].

The Aristotelic concept of "the whole is greater than the sum of its parts" confirms that the MeDi, rather than single foods or nutrients, may constitute an effective preventive strategy with low costs, few side effects and strong epidemiological health outcomes, which might translate into a significant progress on public health [14, 23, 37]. In any case, given the degree of burden induced by adverse cognitive aging, even a modest benefit of the MeDi pattern could have a substantial impact on public health systems and, therefore, be worth the effort [36].

Conflict of interest

The authors declare that there are no conflicts of interest.

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Agradecimentos

À Professora Joana Guimarães, pela sua disponibilidade e conselhos sábios, que me fizeram desenvolver desde o início um carinho especial por este trabalho. Muito obrigada.

A todos os meus amigos, em especial àqueles que, tendo familiares demenciados e sofrendo as consequências desta doença, me inspiraram a escrever esta monografia. O vosso *feedback* e o meu gosto enorme pela Neurologia foram aliados essenciais. O meu sincero obrigada.

Aos meus pais e à minha irmã, por me aturarem tão fielmente ao longo destes seis anos, e porque "somos aquilo que comemos" e eu não poderia ter melhores *chefs* na minha vida. Obrigada.

Anexos

Anexo I – Instruções aos Autores da Revista de Nutrição

ISSN 1415-5273 ***versão impressa***
ISSN 1678-9865 ***versão on-line***

INSTRUÇÕES AOS AUTORES

Escopo e política

A **Revista de Nutrição** é um periódico especializado que publica artigos que contribuem para o estudo da Nutrição em suas diversas subáreas e interfaces. Com periodicidade bimestral, está aberta a contribuições da comunidade científica nacional e internacional.

Os manuscritos podem ser rejeitados sem comentários detalhados após análise inicial, por pelo menos dois editores da **Revista de Nutrição**, se os artigos forem considerados inadequados ou de prioridade científica insuficiente para publicação na Revista.

Categoria dos artigos

A Revista aceita artigos inéditos em português, espanhol ou inglês, com título, resumo e termos de indexação no idioma original e em inglês, nas seguintes categorias:

Original: contribuições destinadas à divulgação de resultados de pesquisas inéditas, tendo em vista a relevância do tema, o alcance e o conhecimento gerado para a área da pesquisa (limite máximo de 5 mil palavras).

Especial: artigos a convite sobre temas atuais (limite máximo de 6 mil palavras).

Revisão (a convite): síntese de conhecimentos disponíveis sobre determinado tema, mediante análise e interpretação de bibliografia pertinente, de modo a conter uma análise crítica e comparativa dos trabalhos na área, que discuta os limites e alcances metodológicos, permitindo indicar perspectivas de continuidade de estudos naquela linha de pesquisa (limite máximo de 6 mil palavras). Serão publicados até dois trabalhos por fascículo.

Comunicação: relato de informações sobre temas relevantes, apoiado em pesquisas recentes, cujo mote seja subsidiar o trabalho de profissionais que atuam na área, servindo de apresentação ou atualização sobre o tema (limite máximo de 4 mil palavras).

Nota Científica: dados inéditos parciais de uma pesquisa em andamento (limite máximo de 4 mil palavras).

Ensaio: trabalhos que possam trazer reflexão e discussão de assunto que gere questionamentos e hipóteses para futuras pesquisas (limite máximo de 5 mil palavras).

Seção Temática (a convite): seção destinada à publicação de 2 a 3 artigos coordenados entre si, de diferentes autores, e versando sobre tema de interesse atual (máximo de 10 mil palavras no total).

Categoria e a área temática do artigo: Os autores devem indicar a categoria do artigo e a área temática, a saber: alimentação e ciências sociais, avaliação nutricional, bioquímica nutricional, dietética, educação nutricional, epidemiologia e estatística, micronutrientes, nutrição clínica, nutrição experimental, nutrição e geriatria, nutrição materno-infantil, nutrição em produção de refeições, políticas de alimentação e nutrição e saúde coletiva.

Pesquisas envolvendo seres vivos

Resultados de pesquisas relacionadas a seres humanos e animais devem ser

acompanhados de cópia de aprovação do parecer de um Comitê de Ética em pesquisa.

Registros de Ensaios Clínicos

Artigos com resultados de pesquisas clínicas devem apresentar um número de identificação em um dos Registros de Ensaios Clínicos validados pelos critérios da Organização Mundial da Saúde (OMS) e do *Intemational Committee of Medical Journal Editors*(ICMJE), cujos endereços estão disponíveis no site do ICMJE. O número de identificação deverá ser registrado ao final do resumo.
Os autores devem indicar três possíveis revisores para o manuscrito. Opcionalmente, podem indicar três revisores para os quais não gostaria que seu trabalho fosse enviado.

Procedimentos editoriais

Autoria
A indicação dos nomes dos autores logo abaixo do título do artigo é limitada a 6. O crédito de autoria deverá ser baseado em contribuições substanciais, tais como concepção e desenho, ou análise e interpretação dos dados. Não se justifica a inclusão de nomes de autores cuja contribuição não se enquadre nos critérios acima.
Os manuscritos devem conter, na página de identificação, explicitamente, a contribuição de cada um dos autores.
Processo de julgamento dos manuscritos
Todos os outros manuscritos só iniciarão o processo de tramitação se estiverem de acordo com as Instruções aos Autores. Caso contrário, **serão devolvidos para adequação às normas**, inclusão de carta ou de outros documentos eventualmente necessários.
Recomenda-se fortemente que o(s) autor(es) busque(m) assessoria lingüística profissional (revisores e/ou tradutores certificados em língua portuguesa e inglesa) antes de submeter(em) originais que possam conter incorreções e/ou inadequações morfológicas, sintáticas, idiomáticas ou de estilo. Devem ainda evitar o uso da primeira pessoa "meu estudo...", ou da primeira pessoa do plural "percebemos....", pois em texto científico o discurso deve ser impessoal, sem juízo de valor e na terceira pessoa do singular.
Originais identificados com incorreções e/ou inadequações morfológicas ou sintáticas **serão devolvidos antes mesmo de serem submetidos à avaliação** quanto ao mérito do trabalho e à conveniência de sua publicação.
Pré-análise: a avaliação é feita pelos Editores Científicos com base na originalidade, pertinência, qualidade acadêmica e relevância do manuscrito para a nutrição.
Aprovados nesta fase, os manuscritos serão encaminhados aos revisores ad hoc selecionados pelos editores. Cada manuscrito será enviado para dois revisores de reconhecida competência na temática abordada, podendo um deles ser escolhido a partir da indicação dos autores. Em caso de desacordo, o original será enviado para uma terceira avaliação.
Todo processo de avaliação dos manuscritos terminará na segunda e última versão.
O processo de avaliação por pares é o sistema de *blind review*, procedimento sigiloso quanto à identidade tanto dos autores quanto dos revisores. Por isso os autores deverão empregar todos os meios possíveis para evitar a identificação de autoria do manuscrito.
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Os pareceres são analisados pelos editores associados, que propõem ao Editor Científico a aprovação ou não do manuscrito.

Manuscritos recusados, mas com possibilidade de reformulação, poderão retornar como novo trabalho, iniciando outro processo de julgamento.

Conflito de interesse

No caso da identificação de conflito de interesse da parte dos revisores, o Comitê Editorial encaminhará o manuscrito a outro revisor *ad hoc*.

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Serão aceitos trabalhos acompanhados de carta assinada por todos os autores, com descrição do tipo de trabalho e da área temática, declaração de que o trabalho está sendo submetido apenas à Revista de Nutrição e de concordância com a cessão de direitos autorais e uma carta sobre a principal contribuição do estudo para a área.

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É fundamental que o escopo do artigo **não contenha qualquer forma de identificação da autoria**, o que inclui referência a trabalhos anteriores do(s) autor(es), da instituição de origem, por exemplo.

O texto deverá contemplar o número de palavras de acordo com a categoria do artigo. As folhas deverão ter numeração personalizada desde a folha de rosto (que deverá apresentar o número 1). O papel deverá ser de tamanho A4, com formatação de margens superior e inferior (no mínimo 2,5cm), esquerda e direita (no mínimo 3cm).

Os artigos devem ter, aproximadamente, 30 referências, exceto no caso de artigos de revisão, que podem apresentar em torno de 50. Sempre que uma referência possuir o número de *Digital Object Identifier* (DOI), este deve ser informado.

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Página de rosto deve conter

a) título completo - deve ser conciso, evitando excesso de palavras, como "avaliação do....", "considerações acerca de..." 'estudo exploratório....";

b) *short title* com até 40 caracteres (incluindo espaços), em português (ou espanhol) e inglês;

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Os artigos submetidos em inglês deverão vir acompanhados de resumo em português, além do *abstract* em inglês.
Para os artigos originais, os resumos devem ser estruturados destacando objetivos, métodos básicos adotados, informação sobre o local, população e amostragem da pesquisa, resultados e conclusões mais relevantes, considerando os objetivos do trabalho, e indicando formas de continuidade do estudo.
Para as demais categorias, o formato dos resumos deve ser o narrativo, mas com as mesmas informações.
O texto não deve conter citações e abreviaturas. Destacar no mínimo três e no máximo seis termos de indexação, utilizando os descritores em Ciência da Saúde - DeCS - da Bireme <http://decs.bvs.br>.
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Introdução: deve conter revisão da literatura atualizada e pertinente ao tema, adequada à apresentação do problema, e que destaque sua relevância. Não deve ser extensa, a não ser em manuscritos submetidos como Artigo de Revisão.
Métodos: deve conter descrição clara e sucinta do método empregado, acompanhada da correspondente citação bibliográfica, incluindo: procedimentos adotados; universo e amostra; instrumentos de medida e, se aplicável, método de validação; tratamento estatístico.
Em relação à análise estatística, os autores devem demonstrar que os procedimentos utilizados foram não somente apropriados para testar as hipóteses do estudo, mas também corretamente interpretados. Os níveis de significância estatística (ex. $p<0,05$; $p<0,01$; $p<0,001$) devem ser mencionados.
Informar que a pesquisa foi aprovada por Comitê de Ética credenciado junto ao Conselho Nacional de Saúde e fornecer o número do processo.
Ao relatar experimentos com animais, indicar se as diretrizes de conselhos de pesquisa institucionais ou nacionais - ou se qualquer lei nacional relativa aos cuidados e ao uso de animais de laboratório - foram seguidas.
Resultados: sempre que possível, os resultados devem ser apresentados em tabelas ou figuras, elaboradas de forma a serem auto-explicativas e com análise estatística. Evitar repetir dados no texto.
Tabelas, quadros e figuras devem ser limitados a cinco no conjunto e numerados consecutiva e independentemente com algarismos arábicos, de acordo com a ordem de menção dos dados, e devem vir em folhas individuais e separadas, com indicação de sua localização no texto. **É imprescindível a informação do local e ano do estudo.** A cada um se deve atribuir um título breve. Os quadros e tabelas terão as bordas laterais abertas.
O(s) autor(es) se responsabiliza(m) pela qualidadedas figuras (desenhos, ilustrações, tabelas, quadros e gráficos), que deverão ser elaboradas em tamanhos de uma ou duas colunas (7 e 15cm, respectivamente); **não é permitido o formato paisagem**. Figuras digitalizadas deverão ter extensão jpeg e resolução mínima de 400 dpi.
Gráficos e desenhos deverão ser gerados em programas de desenho vetorial (*Microsoft Excel, CorelDraw, Adobe Illustrator* etc.), acompanhados de seus parâmetros quantitativos, em forma de tabela e com nome de todas as variáveis.

A publicação de imagens coloridas, após avaliação da viabilidade técnica de sua reprodução, será custeada pelo(s) autor(es). Em caso de manifestação de interesse por parte do(s) autor(es), a Revista de Nutrição providenciará um orçamento dos custos envolvidos, que poderão variar de acordo com o número de imagens, sua distribuição em páginas diferentes e a publicação concomitante de material em cores por parte de outro(s) autor(es).
Uma vez apresentado ao(s) autor(es) o orçamento dos custos correspondentes ao material de seu interesse, este(s) deverá(ão) efetuar depósito bancário. As informações para o depósito serão fornecidas oportunamente.
Discussão: deve explorar, adequada e objetivamente, os resultados, discutidos à luz de outras observações já registradas na literatura.
Conclusão: apresentar as conclusões relevantes, considerando os objetivos do trabalho, e indicar formas de continuidade do estudo. **Não serão aceitas citações bibliográficas nesta seção.**
Agradecimentos: podem ser registrados agradecimentos, em parágrafo não superior a três linhas, dirigidos a instituições ou indivíduos que prestaram efetiva colaboração para o trabalho.
Anexos: deverão ser incluídos apenas quando imprescindíveis à compreensão do texto. Caberá aos editores julgar a necessidade de sua publicação.
Abreviaturas e siglas: deverão ser utilizadas de forma padronizada, restringindo-se apenas àquelas usadas convencionalmente ou sancionadas pelo uso, acompanhadas do significado, por extenso, quando da primeira citação no texto. Não devem ser usadas no título e no resumo.
Referências de acordo com o estilo *Vancouver*
Referências: devem ser numeradas consecutivamente, seguindo a ordem em que foram mencionadas pela primeira vez no texto, conforme o estilo *Vancouver*.
Nas referências com dois até o limite de seis autores, citam-se todos os autores; acima de seis autores, citam-se os seis primeiros autores, seguido de *et al*.
As abreviaturas dos títulos dos periódicos citados deverão estar de acordo com o *Index Medicus*.
Não serão aceitas citações/referências de **monografias** de conclusão de curso de graduação, **de trabalhos** de Congressos, Simpósios, *Workshops*, Encontros, entre outros, e de **textos não publicados** (aulas, entre outros).
Se um trabalho não publicado, de autoria de um dos autores do manuscrito, for citado (ou seja, um artigo *in press*), será necessário incluir a carta de aceitação da revista que publicará o referido artigo.
Se dados não publicados obtidos por outros pesquisadores forem citados pelo manuscrito, será necessário incluir uma carta de autorização, do uso dos mesmos por seus autores.
Citações bibliográficas no texto: deverão ser expostas em ordem numérica, em algarismos arábicos, meia linha acima e após a citação, e devem constar da lista de referências. Se forem dois autores, citam-se ambos ligados pelo "&"; se forem mais de dois, cita-se o primeiro autor, seguido da expressão *et al*.
A exatidão e a adequação das referências a trabalhos que tenham sido consultados e mencionados no texto do artigo são de responsabilidade do autor. Todos os autores cujos trabalhos forem citados no texto deverão ser listados na seção de Referências.
Exemplos
Artigo com mais de seis autores
Oliveira JS, Lira PIC, Veras ICL, Maia SR, Lemos MCC, Andrade SLL, *et al*. Estado nutricional e insegurança alimentar de adolescentes e adultos em duas localidades de baixo índice de desenvolvimento humano. Rev Nutr. 2009; 22(4): 453-66. doi: 10.1590/S1415-52732009000400002.
Artigo com um autor
Burlandy L. A construção da política de segurança alimentar e nutricional no Brasil: estratégias e desafios para a promoção da intersetorialidade no âmbito federal de governo. Ciênc Saúde Coletiva. 2009; 14(3):851-60. doi: 10.1590/S1413-

81232009000300020.

Artigo em suporte eletrônico

Sichieri R, Moura EC. Análise multinível das variações no índice de massa corporal entre adultos, Brasil, 2006. Rev Saúde Pública [Internet]. 2009 [acesso 2009 dez 18]; 43(Suppl.2):90-7. Disponível em: <http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0034-89102009000900012&lng=pt&nrm=iso>. doi: 10.1590/S0034-89102009000900012.

Livro

Alberts B, Lewis J, Raff MC. Biologia molecular da célula. 5ª ed. Porto Alegre: Artmed; 2010.

Livro em suporte eletrônico

Brasil. Alimentação saudável para pessoa idosa: um manual para o profissional da saúde [Internet]. Brasília: Ministério da Saúde; 2009 [acesso 2010 jan 13]. Disponível em: <http://200.18.252.57/services/e-books/alimentacao_saudavel_idosa_profissionais_saude.pdf>.

Capítulos de livros

Aciolly E. Banco de leite. In: Aciolly E. Nutrição em obstetrícia e pediatria. 2ª ed. Rio de Janeiro: Guanabara Koogan; 2009. Unidade 4.

Capítulo de livro em suporte eletrônico

Emergency contraceptive pills (ECPs). In: World Health Organization. Medical eligibility criteria for contraceptive use [Internet]. 4th ed. Geneva: WHO; 2009 [cited 2010 Jan 14]. Available from: <http://whqlibdoc.who.int/publications/2009/9789241563888_eng.pdf>.

Dissertações e teses

Duran ACFL. Qualidade da dieta de adultos vivendo com HIV/AIDS e seus fatores associados [mestrado]. São Paulo: Universidade de São Paulo; 2009.

Texto em formato eletrônico

Sociedade Brasileira de Nutrição Parental e Enteral [Internet]. Assuntos de interesse do farmacêutico atuante na terapia nutricional. 2008/2009 [acesso 2010 jan 14]. Disponível em: <http://www.sbnpe.com.br/ctdpg.php?pg=13&ct=A>.

Programa de computador

Software de avaliação nutricional. DietWin Professional [programa de computador]. Versão 2008. Porto Alegre: Brubins Comércio de Alimentos e Supergelados; 2008.

Para outros exemplos recomendamos consultar as normas do Committee of Medical Journals Editors (Grupo Vancouver) <http://www.icmje.org>.

Para outros exemplos recomendamos consultar as normas do Committee of Medical Journals Editors (Grupo Vancouver) <http://www.icmje.org>.

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