Ageing Research Reviews 25 (2016) 1–12

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

# Efficacy of lifestyle interventions on clinical and neuroimaging outcomes in elderly

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ARTICLE INFO

*Article history:*
Received 22 April 2015
Received in revised form 30 October 2015
Accepted 9 November 2015
Available online 14 November 2015

*Keywords:*
Alzheimer's disease
Prevention trials
Neuroimaging
Lifestyle
Nonpharmacological interventions
Clinical outcomes

ABSTRACT

The prevalence of Alzheimer's disease (AD) is constantly growing worldwide in absence of any effective treatment. Methodology and technique advancements facilitated the early diagnosis of AD leading to a shift toward preclinical AD stages investigation in order to delay the disease onset in individuals at risk for AD. Recent evidence demonstrating the aging related multifactorial nature of AD supported the hypothesis that modifiable environmental factors can accelerate or delay the disease onset. In particular, healthy dietary habits, constant physical and cognitive activities are associated with reduced brain atrophy, amyloid load and incidence of AD cases. Due to these promising results, an emerging field of studies is currently investigating the efficacy of interventions addressing different lifestyle habits in cognitive intact elderly individuals as a potential preventive strategy against AD onset.

We provide a critical overview of the current evidence on nonpharmacologic treatments in elderly individuals, discussing their efficacy on clinical and neuroimaging outcomes and identifying current methodological issues. Future perspectives, relevant for the scientific community and the worldwide public health institutes will be further discussed.



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## 1. Introduction

Alzheimer's disease (AD) represents one of the most common forms of dementia. The global prevalence of AD cases has been estimated to nearly quadruple by 2050 (Brookmeyer et al., 2007; Prince

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http://dx.doi.org/10.1016/j.arr.2015.11.003
1568-1637/

et al., 2013) increasing significantly the social and the economic burden of the disease (Wimo et al., 2013). Indeed, the estimated annual worldwide costs of dementia are US$604 billion, considering direct medical and social care costs and informal care costs (Wimo et al., 2013).

In the last few decades, the concept of ADonset underwent consistent modifications and evolutions. The AD diagnosis, originally established by the presence of specific clinical symptoms (McKhann et al., 1984) and post mortem verification, was reconceptualized thanks to the implementation of in vivo markers able to detect the two main neuropathological mechanism of AD: amyloid plaques and neurofibrillary tangles formation. In particular, brain amyloid deposition is revealed in vivo by decreased concentration of cerebrospinal fluid (CSF) amyloid $_{\beta 1\text{-}42}$ protein or increased cortical retention of amyloid ligands with positron emission tomography (PET), while neurodegeneration is confirmed by increased concentrations of CSF total-tau (t-tau) and phosphorylated-tau (p-tau) proteins, cortical hypometabolism on fluorodeoxyglucose (FDG) PET and hippocampal atrophy on magnetic resonance imaging (MRI) (Dubois et al., 2007; McKhann et al., 2011). As a result of these technological advancements and according to the recently updated Alzheimer's disease research diagnostic criteria, is currently possible to diagnose preclinical stage of AD by the presence of in vivo markers of neuropathology (Sperling et al., 2011; Jack and Holtzman, 2013; Dubois et al., 2014). This new conceptualization of AD has shifted toward the study of preclinical AD stages offering the opportunity to investigate possible strategy to delay cognitive impairment, leading to the emerging field of AD prevention.

Noteworthy, it was estimated that even a 1 year delay in AD onset would result in fewer 11.8 million incident cases worldwide (Brookmeyer et al., 2007). In addition, Norton and colleagues showed that one-third of AD cases might be attributable to modifiable risk factors, such as diabetes, midlife hypertension and obesity, physical inactivity, smoking, depression and low educational attainment (Norton et al., 2014). Moreover, observational studies showed consistent associations between some lifestyle habits, such as high levels of physical (Hamer and Chida, 2009; Sofi et al., 2011) and cognitive activities (Vemuri et al., 2014) or high adherence to specific dietary patterns (Singh et al., 2014; Tangney, 2014), and decreased risk to develop cognitive decline and dementia These observations lead to growing interest by scientific community and public health professionals to investigate nonpharmacological interventions aimed to promote healthy lifestyle habits as a preventive strategy against cognitive decline and AD (Andrieu et al., 2011; Richard et al., 2012; Solomon et al., 2014; Lista et al., 2015).

Large randomized trials, aimed to demonstrate the efficacy of dementia prevention by multi domain lifestyle interventions, are currently ongoing (Richard et al., 2009; Kivipelto et al., 2013; Vellas et al., 2014) and recently post-intervention results of one of these trials have been published (Ngadu et al., 2015). The assumptions underlying these approaches is that interventions addressing multiple risk factors simultaneously could lead to greater effects on cognitive and functional status, supporting healthy cognitive aging (Schneider and Yvon, 2013) and being more appropriate to delay the onset of multifactorial disorders such as AD (Richard et al., 2012; Solomon et al., 2014).

Although conceptually sound, the associations between healthy lifestyle habits and decreased risk of AD, described in observational studies, need to be supported by interventional studies results (Thiese, 2014). Aim of the present study is to discuss and critically revise the current evidence on the efficacy of individual and multiple nonpharmacological interventions on neuroimaging and clinical outcomes in elderly individuals.

## 2. Single domain lifestyle interventions

In order to design cost effective preventive lifestyle interventions in elderly, the identification of the best combination of interventions able to promote significant cognitive improvements and structural or functional brain changes is needed.

Nutrition, physical and cognitive activities are the main potential areas of interventions aimed to promote lifestyle changes in elderly. In the present section we are going to present evidence from nonpharmacological treatments separately addressing the above described potential areas in improving cognitive and brain health in cognitive intact elderly individuals.

### 2.1. Nutrition

Changes in nutritional intake may be promoted by adding individual dietary components with nutritional supplementation or by improving adherence to specific dietary guidelines. Several studies investigating the efficacy of nutritional supplementation to improve cognitive health found inconsistent results (Jia et al., 2008; Malouf and Grimley Evans, 2008; van de Rest et al., 2015). More recently, a multicomponent nutritional approach was suggested to be more effective as a preventive strategy against cognitive decline (Shea and Remington, 2015).

The Mediterranean Diet (MeDi) and the Dietary Approaches to Prevent and Treat Hypertension (DASH) represent the two main dietary patterns associated with better cognitive outcomes and decreased AD incidence in observational studies (Singh et al., 2014; Tangney, 2014; van de Rest et al., 2015).

The MeDi is characterized by high consumption of fruit, vegetables, legumes, cereals, nuts, fish, olive oil, low to moderate intake of dairy products, regular but modest intake of alcohol, together with low consumption of meat and saturated fatty acids (Willett et al., 1995). Highintake of omega-3 poliunsaturated fatty acids (PUFA), polyphenols, folates and vitamins preserves brain health and reduces vascular risk factors (Frisardi et al., 2010).

The DASH, recommended especially to individuals affected by hypertension (Appel et al., 2006), is composed by nearly the same prescription of MeDi, except for the recommendations of olive oil and moderate alcohol consumption (Tangney, 2014).

High MeDi adherence during life was found to be associated with lower AD incidence with a possible dose-response effect (Scarmeas et al., 2006). A meta-analyses of selected longitudinal studies further underlined that individuals with lower levels of MeDi adherence had an increased risk of cognitive impairment, mild cognitive impairment (MCI) and AD incidence (Singh et al., 2014; Feart et al., 2015), even if more recent studies have found inconstant results (Feart et al., 2015).

Few studies recently investigated the protective effects of DASH diet on cognitive decline with longitudinal assessments reporting convergent evidence of better cognitive outcomes in individuals with high DASH adherence score (Tangney, 2014).

Further, recent evidence showed the association between reported nutrients intake and neuroimaging and biological markers of AD in cognitively healthy individuals (Gu et al., 2012; Titova et al., 2013; Mosconi et al., 2014). Negative association between levels of self reported meat intake and total brain volumes was found in elderly, but no associations were found between other individual nutrients intake or a global measure of MeDi like dietary habits and gray or white matter volumes (Titova et al., 2013). Significant association between nutrients biomarkers were further found between omega-3 PUFA dietary intake and reduced plasma levels of amyloid beta (Gu et al., 2012). Mosconi and colleagues (Mosconi et al., 2014) found a significant association between increased intake of Vitamin $B_{12}$, D and omega-3 PUFA and reduced brain amyloid burden, while higher β-carotene and folate consumption was associated