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Vascular risk factors in Alzheimer's disease and Mild Cognitive Impairment: population data from the Zabùt Aging Project

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ABSTRACT

Background: Alzheimer's disease (AD) is the most common cause of dementia in older adults, accounting for about 60% of cases. However, autopsy studies suggested that mixed dementia, with vascular and neurodegenerative AD pathology, accounts for nearly 20% of dementia cases.

Aims: Aim of the present study was to evaluate the relationship between isolated or clustered Vascular Risk Factors (VRFs)/diseases and Mild Cognitive Impairment (MCI) or AD. The study was conducted using a Sicilian population-based cohort dataset collected in low-educated, rural subjects, the Zabùt Aging Project (ZAP). The effect-modification by age, sex, education, genetic factor (APOE4 allele carrier), undernutrition, inflammatory status and depressive symptoms was taken into account.

Materials and Methods: VRFs, hypertension, coronary heart disease, atrial fibrillation (FA), previous Transient Ischemic Attack (TIA)/stroke, diabetes, dyslipidemia, obesity and Metabolic Syndrome were identified with a semi-structured questionnaire, physical measurements and laboratory analysis. The Framingham general cardiovascular disease (CVD) risk profile, the Framingham stroke risk profile, the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) risk score and Late-Onset Alzheimer Disease (LOAD) vascular risk score were used as markers of vascular burden. Framingham algorithms are multivariable scores that provide a sex-specific absolute risk of cardiovascular events, and CAIDE and LOAD are dementia risk scores. The importance of each VRF in determining the outcome of each diagnosis was modelled by means of a sequential procedure based on the logistic regression, using subjects with normal cognition [NC] as reference group. The contribution of each VRFs in determining the outcome and the mutual relationship among VRFs in separating the diagnoses were studied using canonical discriminant analysis (with Mahalanobis distance).

Results and Discussion: When computed as a crude prevalence, NC accounted for near a half (45.6%) of the total population at follow-up, amnesic MCI (aMCI) and nonamnesic MCI (naMCI) for 27.9% and 11.6%, respectively, AD for 8%, while 6.9% were subjects with other dementias/psychosis. Risk of AD was increased by previous TIA/stroke (OR=2.77, C.I. 95%: 1.21-6.32). Risk of naMCI was increased by atrial fibrillation (OR=2.07, C.I. 95%: 1.00-4.27). AD scored a Framingham general CVD risk profile lower than NC or MCI ($p<0.0001$), whereas Framingham stroke risk profile showed a tendency to increase from NC or aMCI to naMCI or AD ($p=0.0001$). CAIDE risk score was higher in AD than NC ($p=0.003$). The tendency of LOAD vascular risk score to increase among diagnoses were similar to those of Framingham stroke risk profile ($p=0.0002$). In particular, when contemporarily stratifying for APOE4, inflammation, undernutrition and High level of Depressive Symptoms, CAIDE risk score strongly associated with risk of AD (OR =1.38, C.I. 95%: 1.01-1.88), Framingham stroke risk profile with naMCI (OR =1.49, C.I. 95%: 1.02-2.13) and LOAD vascular risk score with aMCI (OR =1.05, C.I. 95%: 1.01-1.09).

Data of this study, collected in low-educated, rural subjects, showed that the presence of multiple VRFs was associated with cognitive decline or AD. This suggests that a cumulative exposure to even mild effects of some VRFs would lead to cognitive decline and dementia more than the presence of an over vascular disease. Furthermore, it is likely that the effect of VRFs on cognition is not attenuated by old age but easier to detect if taking into account multiple risk factors simultaneously. These data need to be extended and confirmed by prospective analyses conducted on the ZAP incident cohort.

ABBREVIATIONS

AD: Alzheimer's disease
AF: Atrial fibrillation
AGEs: advanced glycation and products
AIC: Akaike information criterion
Akt/PKB: activating protein kinase B
APOE: apolipoprotein E gene
APP: amyloid protein precursor (APP)
A β : amyloid- β
BBB: blood brain barrier
BMI: body mass index
BP: blood pressure
CAD: coronary artery disease
CAIDE: Cardiovascular Risk Factors, Aging and dementia
CDA: canonical discriminant analysis
CES-D: Center for Epidemiologic Studies Depression Scale;
CHD: coronary heart disease
CRP: C-reactive protein
CVD: cardiovascular disease
DBP: diastolic blood pressure
DM: Diabetes mellitus
FFAs: free fatty acids
GSK3- β : glycogen synthase kinase-3 β
HDL: High Density Lipoprotein
HDL-C: HDL cholesterol
HT: Hypertension
IDE: insulin-degrading enzyme
LDL: low-density lipoprotein
LDL-C: low-density lipoprotein cholesterol
LOAD: Late-Onset Alzheimer Disease
MCI: Mild Cognitive Impairment
MetS: metabolic syndrome
MMSE: Mini-Mental State Examination
MNA: Mini Nutritional Assessment
NC: subjects with normal cognition
NFTs: neurofibrillary tangles
NO: nitric oxide
PI3-K: phosphatidylinositol-3 kinase
RAAS: renin-angiotensin-aldosterone system
RAGE: AGEs receptor
ROS: reactive oxygen species
SBP: systolic blood pressure
TD2M: type 2 diabetes mellitus
TIA: Transient Ischemic Attack
TNF α : tumor necrosis factor
VRF: vascular risk factors
ZAP: Zabùt Aging Project

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1 INTRODUCTION

1.1 The clinical spectrum of cognitive decline: Alzheimer's disease and Mild Cognitive Impairment

Dementia is syndrome characterized by a collection of signs and symptoms of multiple cognitive deficits that appear to be severe enough to interfere with daily living and social and professional functioning. Alzheimer's disease (AD) diagnosed by current clinical criteria is the most common cause of dementia in older adults, accounting for 50–70% of cases. Although, autopsy studies have suggested that mixed dementia, with vascular and neurodegenerative AD pathology, accounts for most dementia cases (Schneider et al. 2007; Launer et al. 2008; Matthews et al. 2009; Strozyk et al. 2010; Wharton et al. 2011).

From a clinical point of view, the earliest symptom is usually a difficulty in remembering recent events. Other symptoms emerge slowly and gradually, and lead to progressive cognitive deterioration associated with multimodal behavioral and affective disorders, which lead the patient to a progressive loss of functional independence. This progressive and inexorable decline has effects on both the patient's life and family, and fallouts on the society.

Ageing is a primary risk factor and the prevalence of AD and other dementias heavily increase with age worldwide, affecting approximately 6% of the population older than 65 years, and its prevalence exponentially increases with age: 40–70% older than 95 years suffer from dementia (Qiu et al. 2007). In 2015, almost 47 million people worldwide were estimated to be affected by dementia, and the numbers are expected to reach 75 million by 2030, and 131 million by 2050, with the greatest increase expected in low- and middle-income countries (Prince et al. 2015).

In EU countries, information about the number of people with dementia is available (Fig. 1). In particular, Alzheimer Europe estimates that the number of people with dementia in Italy in 2012 is 1,272,317. This represents 2.09% of the total population. This percentage is higher than the EU average of 1.55% (Alzheimer Europe 2013).

AD with onset before age 65 years (early-onset AD) accounts for up to 5% of all cases. Most of the early-onset AD cases are familial AD, a rare form of AD caused by mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), or PSEN2 genes (Bettens et al. 2013). Late-onset sporadic AD (from 65 years of age) is the most common form of AD, accounting for about 95% of all cases. Several population-based studies suggested that people older than 65 years survive from 3 to 9 years after a diagnosis of dementia. However, some of them can also live up to 20 years from the diagnosis (Ganguli et al. 2005; Helzner et al. 2008; Xie et al. 2008). Despite the enormous costs of medical and social care for AD patients depend on disease severity (Handels et al. 2013), prevalence data of dementia according to severity or stage are scarce (Winblad et al. 2016).

The identification of AD cases in its symptomatic prodromal phase, through an early detection, could influence both the health status of the patients and the exponential growth of the number of affected people in the future. For such reasons, one of the primary topics of the research on AD focused in the last decade on the timely recognition of initially symptomatic or presymptomatic individuals, which would allow to establish therapeutic strategies effective in modifying or slowing down the course of the disease.

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Various terms have been used to describe such prodromal phase: Mild Cognitive Impairment (MCI) has gained wider recognition in the recent years (Petersen et al. 2009), thus that it's currently considered the only syndromic prodromal construct of dementia, in particular of AD (Albert et al. 2011b). The concept of MCI was introduced in 1999 to define a transitional stage between normal aging and dementia (Petersen et al. 1999).

People with MCI show mild cognitive deficits without or with only minimal, impairment of the functions of everyday life. Patients with MCI could be classified into one of the two categories: amnesic MCI (a-MCI) if from neuropsychological tests the episodic memory was poor; and nonamnesic MCI (na-MCI) if from neuropsychological tests it is covered a reduction in executive functions, language or visuospatial skills. The impairment could be restricted to one cognitive domain (MCI single domain) or to multiple domains (MCI multiple domains), and thus a patient could be classified in one of the four possible clinical subtypes (Petersen 2004b).

During the last decade, an increasing number of studies have been conducted in an attempt to estimate the prevalence of MCI in the general population. From the major population-based studies using Mayo Clinic criteria, the average prevalence of MCI is 18.9% (Petersen et al. 2014). Although population studies showed that MCI appears to be an unstable and heterogeneous clinical entity, with 40-60% of individuals that evolve 5 years after diagnosis to dementia, at a population level, 25% of MCI affected patients go back to cognitive normality within 3 years (DeCarli 2003; Petersen 2004b). In addition, it was shown that the rate of patients with amnesic MCI (aMCI) clinically progressing to AD is 10-15% per year, in contrast to a rate of 1-2% per year among healthy elderly individuals (Petersen et al. 1999).

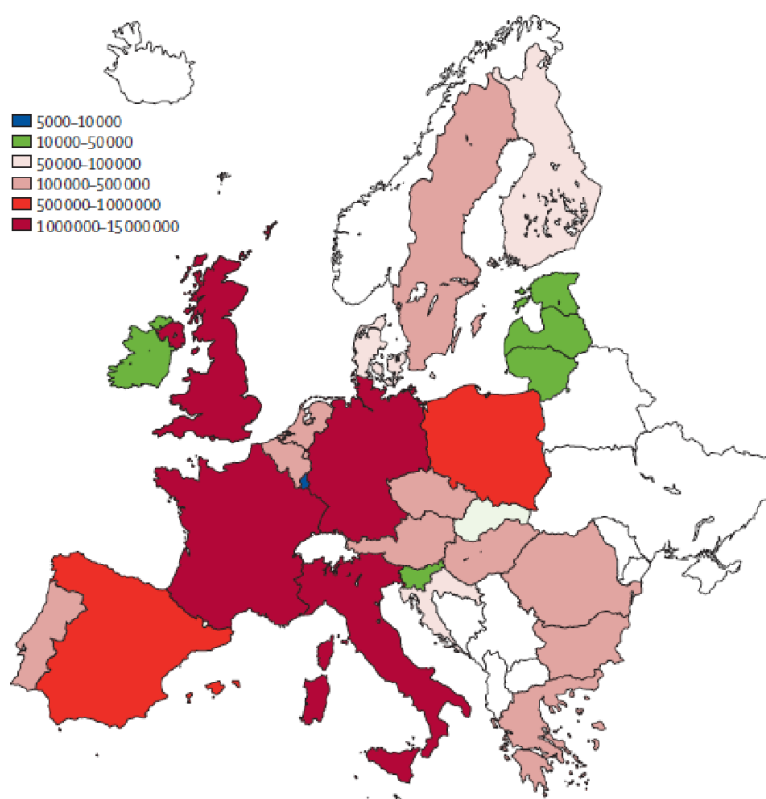


Fig. 1. Number of people with dementia in 28 European countries in 2013 (estimates from Alzheimer Europe 2013; and figure from Winblad et al. 2016).

1.2 Risk e protective factors for AD and MCI

Several factors and their interaction over the lifetime contribute to the pathological processes and clinical expression of AD, other dementing disorders, and predementia syndromes, such as MCI. In general, risk and protective factors that affect the pathological processes and the progression to AD can be classified into two groups: non-modifiable risk factors, such as age or genetic susceptibility, and modifiable risk factors, such as vascular risk factors (VRF), psychosocial factors and lifestyle (panel 1).

Panel 1: Putative risk and protective factors for late-onset dementia and Alzheimer’s disease (from Winblad et al. 2016)

Risk factors

- Older age
- Genetic factors
 - Familial aggregation (two or more family members with the disease)
 - apolipoprotein E (APOE) ε4 allele
 - Other susceptibility genes (eg, CR1, PICALM, CLU, TREM2, TOMM40)
- Vascular risk and metabolic factors
 - Atherosclerosis
 - Cerebral macrovascular and microvascular lesions
 - Cardiovascular diseases
 - Diabetes mellitus and pre-diabetes
 - Midlife hypertension
 - Midlife overweight and obesity
 - Midlife high serum cholesterol
- Lifestyle factors
 - Sedentary lifestyle
 - Smoking
 - Heavy alcohol consumption
- Diet and nutritional factors
 - Saturated fats
 - Hyperhomocysteinaemia
 - Deficiencies in vitamin B6, B12, and folate
- Other factors
 - Depression
 - Traumatic brain injury
 - Occupational exposure (eg, heavy metals, extremely-low-frequency electromagnetic fields)
 - Infectious agents (eg, herpes simplex virus type 1, Chlamydomphila pneumoniae, spirochetes)

Protective factors

- Genetic factors
 - Some genes proposed (eg, APP, APOE ε2 allele)
- Psychosocial factors
 - High education and socioeconomic status
 - High work complexity
 - Rich social network and social engagement
 - Mentally stimulating activity
- Lifestyle factors
 - Physical activity
 - Light-to-moderate alcohol intake
- Diet and nutritional factors
 - Mediterranean diet
 - Polyunsaturated fatty acid and fish-related fats
 - Vitamin B6, vitamin B12, and folate
 - Antioxidant vitamins (A, C, E)
 - Vitamin D
- Drugs
 - Antihypertensive drugs
 - Statins
 - Hormone replacement therapy
 - Non-steroidal anti-inflammatory drugs

Many risk and protective factors for dementia and Alzheimer’s disease have been proposed and investigated; however, the evidence to support the factors listed here is variable, and the relevance of several proposed factors is open to debate. The most pronounced risk factors are advancing age and carrying one or two APOE ε4 alleles.

APOE=apolipoprotein E. CR1=complement component receptor 1. PICALM=phosphatidylinositol-binding clathrin assembly protein. CLU=clusterin. TREM2=triggering receptor expressed on myeloid cells 2. TOMM40=translocase of outer mitochondrial membrane 40 homologue. APP=amyloid precursor protein.

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Older age, as previously said, is the strongest risk factor for AD and other dementias, and patients who develop dementia before age 65 years for gene mutations account for only a very small proportion of all cases. The likelihood of developing AD increased with age (Morris and Price 2001; Rowe et al. 2010; Villemagne et al. 2011). Age significantly increases the risk of cerebral β -amyloidosis in cognitively normal individuals. The frequency among people with normal cognitive function with amyloid load was 18.0%–23.1% at age 60–69 years, 25.8%–37.5% at age 70–79 years, and >30.3% to 65.0% after 80 years (Morris and Price 2001; Rowe et al. 2010; Jack et al. 2014; Dubois et al. 2016). In addition, the presence of both markers of amyloidosis and neurodegeneration at the same time increased with aging, and it was found that their frequency increase from 2.5% at age 60–69 years, 13.2% at age 70–79 years, and 31% after 80 years (Jack et al. 2015).

Regarding genetic factors, apolipoprotein E (APOE4, see section 1.5.8 for additional information) represents the major genetic risk factor for sporadic Alzheimer’s disease (Corder et al. 1993; Bertram et al. 2010; Yu et al. 2014). During last years, it was found that other genes significantly affect the risk for AD. Genome-wide association studies have identified variants in genes involved in lipid metabolism, inflammatory response, and endocytosis. Among polymorphisms in genes that are associated with increasing AD risk, the following were identified: ABCA7, CLU, CR1, CD33, CD2AP, EPHA1, BIN1, PICALM, MS4A, CASS4, CELF1, DSG2, FERMT2, HLA-DRB5-DBR1, INPP5D, MEF2C, NME8, PTK2B, SLC24H4-RIN3, SORL1, and ZCWPW1 (Dubois et al. 2016). The contribution to the risk by each gene is small. Only rare variation TREM2 gene, that encodes for an innate immune system receptor expressed primarily on microglia, showed convincing evidence for increasing risk for AD (Guerreiro et al. 2013; Jonsson et al. 2013; Colonna and Wang 2016; Sirkis et al. 2016) (Fig. 2).

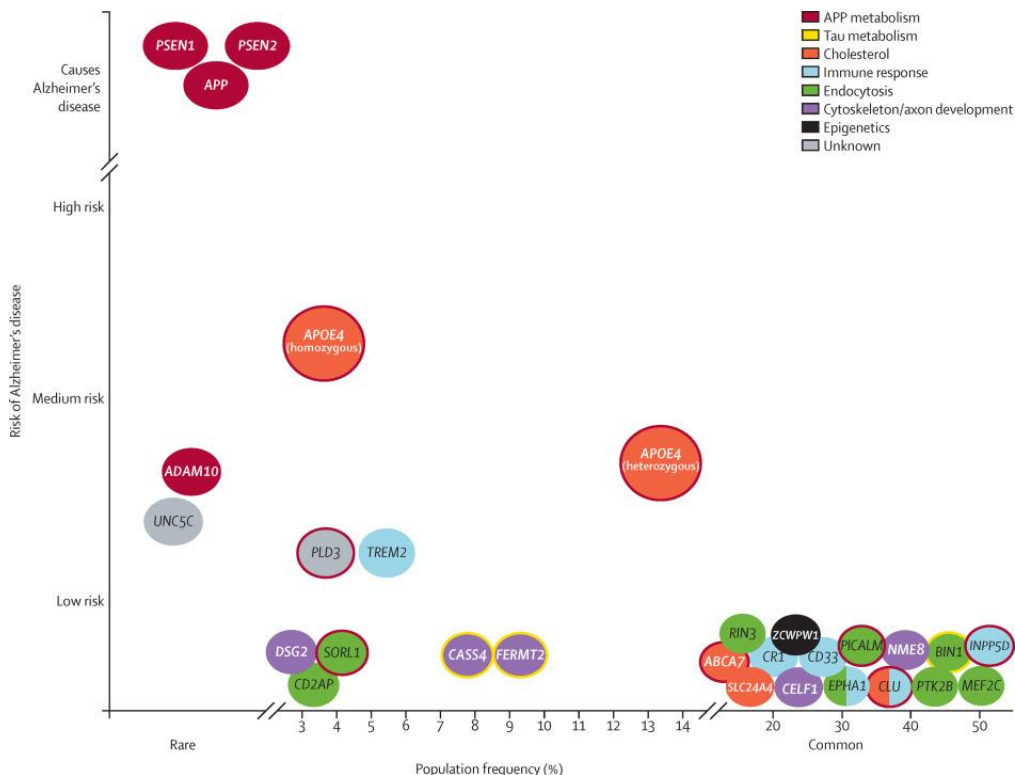


Fig. 2: Overview of gene related to the risk Alzheimer's disease. Each circle is colored according to the pathways the gene is implicated in. Red circled genes affect APP metabolism red, yellow circled the tau pathway. Genes colored twice might have functional roles in different pathways (figure from Scheltens et al. 2016).

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Most cases of dementia and AD are at least partly attributable to modifiable factors that can be targeted for intervention, such as cardiovascular risk factors (eg, hypertension, diabetes, and obesity) and psychosocial factors (eg, education, social engagements, and leisure activities). The qualitative and quantitative effects of such factors have been evaluated in several systematic reviews and meta-analyses (Qiu et al. 2010; Barnes and Yaffe 2011a; Deckers et al. 2015). It has been estimated that around a third of AD cases worldwide might be attributable to the modifiable risk factors. Thus, AD incidence might likely be reduced through strengthening the education and methods to reduce the prevalence of VRF (eg, physical inactivity, smoking, midlife hypertension, midlife obesity, and diabetes) and depression (Norton et al. 2014). However, the putative influence of the environment (socio-economic conditions, diet, environmental and urban stresses) could affect the effect of education, VRF and depression on the course of dementias (e. g. Russ et al. 2012).

Regarding depression, different long-term follow-up studies suggested that the depression can act as a risk factor for developing cognitive dysfunction evidence (Castaneda et al. 2008; Barnes et al. 2012; Diniz et al. 2013).

Moreover, preventive factors should be critically considered as they may decrease risk of developing dementia and favor a more successful aging, and they are able to modulate the neuropathologic progression to a clinical AD (Barnard et al. 2014). Protective factors, such as high education, social engagement, physical and cognitive activity, maintenance of cardiovascular health, provide brain reserve (related to brain size, number of neuronal cells, or density of connections) and cognitive reserve (related to the brain's ability to use brain networks more efficiently or to recruit alternative networks in the presence of pathology) (Stern 2012).

Most of the available information about the factors that can promote or predict the development of MCI and the different subtypes has been collected during the last 10 years. Although, it is unclear whether identified factors are true hazards for MCI or simply associated to its occurrence. The major risk factors associated with cognitive decline and dementia, such as aging and low level of education, have also been associated with MCI (Luck et al. 2010) Recent studies also suggest a possible association between gender and MCI occurrence, with higher incidences in males (Caracciolo et al. 2008; Roberts et al. 2012).

The studies regarding a possible genetic susceptibility have shown also an association between MCI and APOE4 and findings have been consistent with results for AD and dementia (see later)(Lopez et al. 2003b; Tervo et al. 2004a; Boyle et al. 2010). The presence of vascular diseases is another important variable related to MCI, but such relationship is still unclear. Furthermore, lifestyle and physical activity nowadays play a key role in the prevention of MCI, in particular several studies suggest that sustained physical, social and cognitive activities can all contribute to postponing or preventing MCI (Ahlskog et al. 2011; Marioni et al. 2012; Miller et al. 2012)

Regarding neuropsychiatric symptoms, they are common in subjects with MCI, and in particular, depression has been studied as a possible risk factor of MCI (Monastero et al. 2009; van der Linde et al. 2013).

1.3 Vascular risk factors and AD/MCI.

A possible role of vascular and lifestyle related factors was recently proposed for cognitive decline. Presently, there is substantial and growing evidence from studies of epidemiology, pharmacology, neuroimaging, and other, suggesting the evidence of overlap between degenerative and vascular

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disorders. The vascular and vascular-related factors that have been associated with dementia and cognitive decline included high blood pressure (BP) and hypertension, total cholesterol and other lipid parameters, diabetes and insulin resistance, body mass index (BMI) and obesity, and the metabolic syndrome (MetS) (Panza et al. 2006; Purnell et al. 2008; Peters 2009; Panza et al. 2010). Recent evidence from population based studies and case series suggests that VRF and cardiovascular disease (CVD) may contribute to the heterogeneity of MCI (DeCarli et al. 2004; M Kivipelto et al. 2001; Lopez et al. 2003; Solfrizzi et al. 2004)

Even the major single gene associated with increased AD risk, namely APOE, was earlier identified as a risk gene for cardiovascular diseases (Eichner et al. 2002), such as coronary heart disease (CHD) and stroke (Lahoz et al. 2001).

VRF are very frequent in the population, are predictable and can be easily modified, so that they have a big social impact. Recent data suggest that proper control of vascular diseases (including diabetes, hypertension, obesity, smoking, depression, and lack of physical activity and cognitive) can prevent or delay the onset and progression of dementia and AD. In particular, it was estimated that a 10-25% reduction of such risk factors could prevent 1.1-3.0 million AD occurrences worldwide (Barnes and Yaffe 2011a). For the same reason these possible risk factors may help to prevent, and reduce, conversion rates of MCI to dementia (Panza et al. 2006). Several population-based studies have also shown that having multiple cardiovascular risk factors concurrently in middle age or several years before dementia onset exponentially increases the risk of dementia and AD (Qiu 2012). Exposure to risk factors in midlife likely better reflects the total amount of exposure throughout a lifespan (DeBette and Seshadri 2009). This supposes a long exposure consequently leading to dementia in late life. An interesting retrospective study demonstrated an increased risk of latelife dementia in people with multiple midlife VRF, specifically diabetes, smoking, hypertension and high cholesterol, in a dose dependent manner (Whitmer et al. 2005a).

Moreover, the optimum time window for interventions that target lifestyle-related cardiovascular risk factors might be young adulthood or middle age, and interventions that multiple target-disease could be more effective.

Indices of VRF in middle age or later life to predict dementia risk, such as Framingham cardiocascular risk profile and Cardiovascular Risk Factors, Aging and dementia (CAIDE), have been developed and validated, and have an accuracy of between 70% and 80%; unhealthy lifestyle and cardiometabolic risk factors constitute a major part of these indices (Kivipelto et al. 2006a; Barnes et al. 2009; Reitz et al. 2010; Kaffashian et al. 2013; Anstey et al. 2014a; Exalto et al. 2014). In particular, the Framingham cardiovascular risk algorithms initially developed to predict cerebrovascular disease, have been shown to be associated with brain pathology and cognitive dysfunction (Seshadri et al. 2004a; Llewellyn et al. 2008).

1.4 Pathophysiology of neurodegenerative dementia and possible mechanisms linking VRF to AD

In the past three decades, population-based neuroimaging and neuropathological studies have contributed substantially to understanding of the pathophysiological mechanism underlying of neurodegenerative processes in AD patients' brains.

Briefly, AD involves aberrant processing of two protein clusters composed of paired helical filaments of hyperphosphorilated intraneuronal *tau* protein (neurofibrillary tangles; NFTs), and extracellular

protein aggregates (senile plaques). Senile plaques result from an aberrant processing of the amyloid protein precursor (APP), a type1 transmembrane protein, by β - and γ -Secretases to form a toxic abnormally folded amyloid- β (A β) peptide of 40–42 amino acids (Walter et al. 2001; Karran et al. 2011). A β then aggregates and initiates a pathogenic cascade eventually leading to neuronal loss and dementia. There are several pathological conformations of A β , oligomeric or fibrillic, specific post-translational modification and different strains (Sanders et al. 2014; Watts et al. 2014). However, the nature of the pathological conformations and the associated mechanisms of toxic effects are unclear (Aguzzi 2014). A β oligomers seem to bind to various membrane receptors, including the prion protein, but the relative importance of these different interactions to the disease process need to be further elucidated (Um et al. 2013).

At this moment, research is moving away from the simple assumption of linear causality as proposed in the original amyloid hypothesis and another exciting area is rapidly developing around VRF as a key part of AD pathology (Panza et al. 2004; Small and Duff 2008).

This is supported by neuroimaging and neuropathological studies (Schneider et al. 2007; Viswanathan et al. 2009; Stephan et al. 2012), which widely showed that most cases of clinically diagnosed dementia and AD is caused by mixed neurodegenerative and vascular pathologies, especially in older individuals (Fotuhi et al. 2009; Jellinger and Attems 2010). The coexistence of ischemic and neurodegenerative pathology could have a strong impact on the expression of the dementia, suggesting reciprocal interactions between ischemia and neurodegeneration (Nagy et al. 1997; Snowden et al. 1997)

It is well known that VRF cause cerebrovascular lesions. In addition, as will be extensively discussed below, these factors contribute to global and regional brain atrophic lesions (loss of brain tissue) and to neurodegenerative pathologies such as AD (Rodrigue et al. 2013; Roberts et al. 2014; Qiu et al. 2014).

Biologically, cerebral atherosclerosis and neurodegeneration might have joint mechanisms, such as oxidative stress, inflammation, and deposition of toxic A β . In addition, experimental studies indicating that A β has potent cerebrovascular effects, and that hypoxia–ischemia is a powerful modulator of cerebral amyloidogenesis, which in turn contributes to cognitive deterioration and dementia (Iadecola 2004; Garcia-Alloza et al. 2011).

Finally, cerebral macrovascular (atherosclerosis and infarction), microvascular (lacunar infarcts, white matter lesions, microbleeds), and neurodegenerative pathologies might synergistically contribute during ageing to brain damage and consequently promote clinical manifestation of a dementia (Cassery and Topol 2004; Pantoni 2010; Strozyk et al. 2010; Toledo et al. 2013).

1.5 Focus on vascular risk factors

In the next sections, I will introduce some important vascular risk factors (including APOE) that have been studied in the context of cognitive decline as well as the possible mechanisms behind the observed associations.

1.5.1 Hypertension

Hypertension (HT) is a widespread disease in the population. It affects a majority of middle-aged and elderly populations (Lloyd-Jones et al. 2005). HT was defined as systolic blood pressure (SBP) greater than or equal to 140 mm Hg or diastolic blood pressure (DBP) greater than or equal to 90 mm

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Hg. HT is a well-known major risk factor for ischemic heart disease, peripheral vascular disease, chronic kidney disease and CVP, mediated by both ischemic and hemorrhagic mechanisms. Furthermore, systemic HT is one of the best-known risk factors for CVD and stroke (Lawes et al. 2004). The risk of stroke increases by approximately 30% for each 10-mm Hg increase in SBP >115 mm Hg, and for each 5-mm Hg increase in DBP >75 mm Hg; a concomitant decrease in stroke risk is observed for lowering of blood pressure with treatment (Lawes et al. 2004).

A wealth of longitudinal epidemiologic evidence links high BP o HT to cognitive decline (Peters and Beckett 2009). Moreover, a series of longitudinal population based studies suggested that a higher BP at baseline was related to higher rates of cognitive decline or MCI (Elias et al. 1993; Launer et al. 1995a; Kilander et al. 1998; Tzourio et al. 1999; DeCarli et al. 2001; Tervo et al. 2004b; Reitz et al. 2007; Panza et al. 2008b; Yao et al. 2016). HT, especially during midlife, is associated with later life cognitive impairment and dementia (Nagai et al. 2010).

Indeed, long-term population based follow up studies have shown that high BP especially at midlife is associated with an increased AD risk later in life (Skoog et al. 1996; Guo et al. 1996; Launer et al. 2000; Kivipelto et al. 2002; Qiu et al. 2003; Stewart et al. 2009). However, a recent systematic review reports contrasting results, where individual clinically defined risk factors, such as HT and diabetes, were not significantly associated with increased risk for AD (Purnell et al. 2008).

This could be due to the hardness of interpretation of the effects of HT in later life, which is confounded by the mounting prevalence of orthostatic hypotension in late-life. In late-life both HT and hypotension may cause brain injury (Guo et al. 1999; Ruitenberg et al. 2001; Verghese et al. 2003). An interesting longitudinal population-based study showed that systolic BP greater than 180 mm Hg was associated with a significant adjusted relative risk for incident AD. Also extremely low diastolic pressure (≤ 65 vs. 66–90 mm Hg) produced a relatively high risk for AD and for dementia (Qiu et al. 2003).

Even among very elderly normotensives, there may be an admixture of borderline hypertensives and hypotensives, where identification of the harmful effects of HT on dementias is difficult. Several studies have failed to show an association of HT with poor cognition when assessed in late-life (Knopman and Roberts 2010).

The mechanism by which HT may cause AD is unclear. A first hypothesis could be that HT leads to AD through vascular damage, since it is a risk factor for subcortical white matter lesions commonly found in AD. AD has been associated with silent brain infarction, brain atrophy, atherosclerosis in the large cerebral and cervicocerebral arteries, endothelial and cellular dysfunction, and reduced cerebral blood flow (Waldstein et al. 2004; Milionis et al. 2008). Furthermore, there is a positive correlation among HT and vascular permeability accompanied with protein extravasation and with the number of senile plaques and NFTs (Petrovitch et al. 2000). There is also evidence that overactivation of the renin-angiotensin-aldosterone system (RAAS) might contribute to the pathogenesis of AD (Savaskan et al. 2001).

Another hypothesis of the relationship between HT and AD comes from evidence of animal models in which deposition of A β is increased with HT and consequently leads to vascular dysfunction that impairs functional hyperemia, by which process brain activity and blood flow are coordinated. This dysfunction is induced by dysregulation of vasoactive mediators such as nitric oxide (NO) and

endothelin 1, by oxidative stress, by structural alteration of the blood vessels, and by inadequate cerebral autoregulation (Iadecola and Davisson 2008) (Fig. 3).

According to the hypothesis that AD pathology could be driven by effects related to endogenous mechanical energy, HT increases brain hemodynamic stress as a result of pulsating shock waves (some 30 million per year) produced by the external surface of the arterial wall in contact with the brain parenchyma (O'Rourke and Hashimoto 2007). In a murine model, mice that have been subjected to high levels of blood pressure showed an accumulation of amyloid aggregates and an initiation of the glial response in brain tissues (Carnevale and Lembo 2011). A hypertensive rat model, demonstrated age-dependent extracellular deposition of Ab and phospho-tau accumulation (Schreiber et al. 2014)

Therefore, the continuous and repetitive exposure to environmental mechanical stress, mostly in an unnoticed manner, becomes a potential driving force for the amyloid cascade. Tau-amyloid aggregates most likely constitute the end stage of a molecular cascade (Ross and Poirier 2004). The higher the exposure to mechanical stress, the more likely an early onset of the disease (Hachiya et al. 2008; Levy Nogueira et al. 2016).

1.5.2 Diabetes mellitus

Diabetes mellitus (DM) is a common condition from middle age and older. By 65 years old, about 20% of the population carries a diagnosis of DM, mainly type 2 diabetes (T2DM) (Lloyd-Jones et al. 2005; Molenaar et al. 2008).

The incidence of T2DM is increasing in developed countries (Wild et al. 2004). This trend has been attributed in part to the increase in the number of overweight and obese individuals; indeed, the weight gain is a key risk factor for the development of T2DM. The diagnosis of T2DM is based on fasting blood glucose levels of >126 mg/dL. DM affects the kidney, heart, peripheral nerves and retina and brain.

A possible relationship between cognitive decline and DM has been suggested since the discovery of insulin (W. R. Miles and H. F. Root 1922). Diabetes mellitus is a strong risk factor for dementia (Whitmer et al. 2005a) and AD (Arvanitakis et al. 2004; Duron and Hanon 2008). It was showed by studies with cognitive screening instruments or batteries of neuropsychological tests that T2DM is associated with a 1.5- to 2-fold increase rate of cognitive decline due to aging is increased 1.5- to 2.0-fold in individuals with T2DM (Cukierman et al. 2005; Strachan et al. 2011), and this was independent of stroke (Strachan et al. 2011). T2DM has been related to a 2-fold higher risk of developing MCI among postmenopausal women (Yaffe et al. 2004a; Luchsinger and Gustafson 2009). Several population-based studies examined the relationship of T2DM with MCI and results were contrasting (Luchsinger et al. 2001; MacKnight et al. 2002; Luchsinger et al. 2007; Roberts et al. 2008; Ng et al. 2016).

Also for diabetes, alterations in midlife glycemic control and DM almost certainly have greater consequences for cognitive function than late-onset DM. The risk for dementia was found to be generally higher when DM was diagnosed at midlife versus later life in a meta-analytical study (Kloppenborg et al. 2008).

Furthermore, multiple studies have shown that DM and pre-diabetes increase the risk of developing cognitive decline and MCI (Gregg et al. 2000; Grodstein et al. 2001; Kanaya et al. 2004; Yaffe et al.

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2004a; Yaffe 2007). It was recognized that a condition of pre-diabetes in which elevated levels fasting glucose result from increasing degrees of insulin resistance and hyperinsulinemia developing over many years, leading to alterations in glucose homeostasis. Accordingly, the development of fasting hyperglycemia is preceded by impaired glucose fasting and/or impaired glucose tolerance and hyperinsulinemia. It is interesting that impaired fasting glucose and abnormal glucose tolerance have also been associated with impaired cognitive performance and greater risk of developing cognitive impairment (Yaffe et al. 2004a).

Insulin resistance and subsequent hyperinsulinaemia could increase the risk of AD and promote decline in memory and cognitive dysfunction (Kuusisto et al. 1997; Watson and Craft 2003; Luchsinger et al. 2004). Hyperinsulinemia seems to be implied in neurodegeneration and cognitive decline. The impaired glucoregulatory control is related to decrements in cognitive performance is suggested by studies which evaluated neuropsychological performance among prediabetic adults, in particular impaired glucose tolerance and hyperinsulinemia were associated with reduced Mini-Mental State Examination (MMSE) scores and have also been linked to increased risk for MCI (Yaffe et al. 2004a; S. Roriz-Filho et al. 2009). In another study in normal elderly, reduced glucose tolerance was associated with decreased general cognitive performance, in particular memory deficits, and hippocampal atrophy on neuroimaging Nuclear magnetic resonance (Convit et al. 2003).

Fig. 3 shows the different pathways through which disturbed glucose-metabolism, insulin resistance and hyperinsulinemia lead to an increased risk of AD: advanced glycation and products (AGEs), oxidative stress, inflammation, and macro- and microvascular injury (Craft 2009).

Specifically, prolonged peripheral hyperinsulinemia leads to a dysregulation of brain insulin levels decreasing insulin transport across the blood brain barrier (BBB), lowering insulin levels and its activity in the brain. Indeed, it is showed that the AD patients have a reduced cerebrospinal fluid insulin and brain insulin signaling markers (Craft et al. 1998; Zhao and Townsend 2009).

Insulin resistance signaling impairment prejudices all ATP dependent processes, which comprises insulin-degrading enzyme (IDE) activity regulation (Salkovic-Petrisic et al. 2009). The insulin normally mediates signal transduction after binding to insulin receptors by activation of phosphatidylinositol-3 kinase (PI3-K) that stimulates glucose transport and inhibits apoptosis by activating protein kinase B (Akt/PKB) (Frisardi et al. 2010). Insulin resistance signaling impairment leads to PI3-K dysfunction and reduced glycogen synthase kinase-3 β (GSK3- β) phosphorylation, and subsequently to GSK3- β activation, leading to phosphorylation of tau protein, the main component of NFTs (Gasparini et al. 2001).

Another way of action of hyperglycemia is by mediation of an increased production of nitrogen and reactive oxygen species (ROS) and subsequent oxidative stress (S. Roriz-Filho et al. 2009). The oxidative stress can induce cellular dysfunction both directly or via increased AGEs, the products of nonenzymatic glycosylation and oxidation of proteins and lipids. AGEs interacted with their receptors (RAGE) (Yan et al. 2009). Moreover, RAGE mediated c-jun N-terminal kinase (JNK) activation can also enhance GSK3- β activity, resulting in tau hyperphosphorylation and NFTs formation (Esposito et al. 2008). In addition, oxidative stress induced endothelial dysfunction (accompanied with a loss of its NO mediated properties), alterations of the BBB and of cerebral perfusion (Mooradian 1997).

Furthermore, insulin might interfere with A β degradation via its regulation of the metalloprotease IDE (Qiu et al. 1997).

Another potential mechanism is linked to chronic exposure to hyperglycemia and the development of DM complications, such as coronary artery disease (CAD), stroke, and renal disease, all of which have been associated with cognitive decline and AD (Milionis et al. 2008).

1.5.3 Obesity

Obesity is usually defined by body mass index (BMI) > 29 , but waist circumference (> 102 cm for men and > 88 cm for women) has been shown to have greater predictive ability for disease outcomes, such as heart disease (Kannel et al. 1991). Obesity affects 25%–30% of adults in industrialized countries (Rennie and Jebb 2005), and it has been associated with shoddy cognitive function in population based investigations (Elias et al. 2003).

Both high BMI (> 29) and low BMI (< 21) have been associated with increased risk of cognitive decline (Peters 2009). Studies that have examined weight, body-mass index or other measures of adiposity found that people with dementia are likely to be thinner than non-demented peers (Nourhashémi et al. 2003; Buchman et al. 2005; Stewart et al. 2005; Knopman et al. 2007). It is uncertain if subtle cognitive or behavioral changes occurring prior to dementia alters dietary habits. Furthermore, some studies showed that weight loss occurs during the preclinical phases of dementia, and recent follow-up studies suggested that low BMI could be an early sign of dementia (Nourhashémi et al. 2003; Launer et al. 2005).

Epidemiological studies, which considered the increased BMI as a risk factor for dementia, have shown contrasting results (Gustafson 2006; Gorospe and Dave 2007; Luchsinger and Gustafson 2009). Nonetheless, the studies with longer follow-up periods and younger participants at baseline had statistically significant results (Gorospe and Dave 2007; Duron and Hanon 2008). Also for obesity, the period in life in which it is recognized is important for its relationship with dementias: elevated BMI in middle age may be associated with higher dementia risk (Gustafson et al. 2003; Kivipelto et al. 2005; Whitmer et al. 2005b; Whitmer et al. 2008; Atti et al. 2008). The Cardiovascular Health Study (CHS) reported that elevated BMI at age 50 years was associated with a higher risk of dementia, so it did not for BMI at age 65 or older in the same individuals (Fitzpatrick et al. 2009).

Obesity has been related with cognitive decline through different biological mechanisms (Fig. 3) including promoting inflammation (Gustafson 2006; Whitmer 2007). Increased visceral fat mass elevates blood levels of inflammatory cytokines such as C-reactive protein (CRP), IL6, and tumor necrosis factor α (TNF α) (Eder et al. 2009; Espinola-Klein et al. 2011), and may play deleterious effects on cognitive function (Yaffe et al. 2003). It is seen that elevations of circulating levels of these factors could alter endothelial function, which in turn could lead to insulin resistance (Meigs et al. 2004).

Normally, insulin is also a primary regulator of lipid metabolism, stimulating lipogenesis, and reducing lipolysis. This inhibits adipocyte hormone-sensitive lipase activity, thereby decreasing free fatty acids (FFAs) release from adipose tissue. This process is disturbed in obesity and insulin-resistant conditions disturb the normal inhibition of adipocyte hormone-sensitive lipase activity by insulin. This leads to increased FFAs release from adipose tissue and to persistent FFA elevation that may affect AD pathogenesis (Craft 2009). FFAs inhibit IDE, the metalloprotease that plays a key role in clearance of A β (Bravata et al. 2004). In addition, in vitro FFAs stimulate the assembly of amyloid and tau filaments (Axen et al. 2003), and also induce inflammation, particularly through interactions with TNF α . It is found that TNF α is elevated in the brains and cerebrospinal fluid of patients with

AD and MCI (Vessby et al. 2001). This proinflammatory cytokine could inhibit A β transport from the brain to the periphery (López et al. 2008), resulting in an increased brain accumulation of A β (Craft 2009).

Furthermore, adipose tissue secretes several inflammatory factors called adipocytokines, such as leptin, seems to contribute to cognitive dysfunction (Li et al. 2002). Leptin regulates lean body mass, complements insulin action in the peripheral circulation, decreases brain β secretase levels, and modulates β -amyloid turnover. Consequently, leptin could be associated with production and accumulation of A β (Fewlass et al. 2004). In obesity, chronically elevated leptin levels result in leptin resistance and an inability to regulate weight (Knopman and Roberts 2010). In the late-life, leptin levels decrease consistently with the decreased BMI pre-dementia, and are inversely associated with dementia (Tezapsidis et al. 2009). Murine models suggested the presence of leptin receptors in the neocortex and hippocampus and obese mice with leptin-receptor deficient have impaired ability on behavioral tasks (Harvey 2003).

Finally, obesity leads neuroendocrine disturbances that have been associated with increased sympathetic nervous system activity (Mooradian 1997), which may cause structural brain abnormalities (Waldstein et al. 2004). Hypercortisolemia, which results by obesity (Björntorp and Rosmond 2000), has been linked to hippocampal atrophy and learning and memory dysfunction (Sapolsky 1999).

1.5.4 Dyslipidemia

Elevated blood levels of cholesterol were recognized as a major risk factor for atherosclerotic diseases more than 50 years ago (KANNEL et al. 1964). The preventive efforts has been low density lipoprotein cholesterol (LDL-C) as the principal target (Baigent et al. 2005), but other lipoprotein fractions, such as High Density Lipoprotein (HDL), are also important. The blood level of HDL cholesterol (HDL-C) is an important protective factor for atherosclerotic cardiovascular disease; moreover, higher HDL-C is associated with a reduced risk of cardiovascular death, myocardial infarction, and stroke (Pencina et al. 2009).

Most cross sectional studies, with subjects aged over 75 years, showed an association between increased HDL-C levels and a better performance on cognitive tests (Atzmon et al. 2002; Van Exel et al. 2002; van Vliet et al. 2009). An association between increased HDL-C levels and decreased prevalence of dementia, and less Alzheimer pathology, was also found (Merched et al.; Launer et al. 2001; Wolf et al. 2004). On contrary, all follow up studies, performed in large populations, showed no association between HDL-C levels and cognitive function and MCI (Yaffe et al. 2002; Henderson et al. 2003; Reitz et al. 2005; Reitz et al. 2008). Some follow up studies found no association between HDL-C levels and incident dementia, AD or Vascular Dementia (Tan et al. 2003; Reitz et al. 2004; Li et al. 2005).

Although hypercholesterolemia is a potent risk factor for cardiac disease, but its impact on cerebrovascular disease has been inconsistent, and a few studies have shown that midlife hypercholesterolemia was associated with later life MCI or dementia (Kivipelto et al. 2001a; Dufouil et al. 2005; Panza et al. 2006; Solomon et al. 2007), in particular, AD (Kivipelto et al. 2001a; Mielke et al. 2005). Therefore, also for cholesterol level, it should be underlined the importance of the period in life at which hypercholesterolemia occurred in relation to dementia. In contrast, data from the Framingham study did not confirm an association between midlife cholesterol levels and AD (Tan et al. 2003). A recent study has showed that high total cholesterol levels are present long before the

clinical manifestation of MCI and AD in patients without psychiatric or somatic comorbidities and are independent of APOE genotype (Toro et al. 2014).

Furthermore, elevated levels of total cholesterol were associated to a protective effect on dementia in late-life (Mielke et al. 2005). Low levels of cholesterol were associated with dementia (Romas et al. 1999; Mielke et al. 2005; Solomon et al. 2007). Indeed, a recent study has shown that the relationship between serum total cholesterol and dementia could be bidirectional. High midlife serum total cholesterol is a risk factor for subsequent dementia, in particular AD, but decreasing serum total cholesterol after midlife may reflect ongoing disease processes and might represent a risk marker for late-life cognitive impairment (Solomon et al. 2007). Concerning the mechanisms behind the possible association between hypercholesterolemia and an increased risk of AD, high levels of brain cholesterol accelerate AD progression by influencing the β -amyloid metabolism and NFTs formation (Burns and Duff 2002; Reid et al. 2007).

Regarding hypertriglyceridemia, there is evidence of an association between elevated triglyceride levels and cognitive functions in T2DM patients, but only in case control (Perlmutter et al. 1988). Triglycerides are likely a major cause of the cognitive disturbances in obesity (Farr et al. 2008). Indeed, in animal models, hypertriglyceridemia is partly responsible for the leptin resistance observed in obesity (Fig. 3). Another explanation is that a high plasma triglyceride concentration and a low plasma HDL concentration are the risk factors for atherosclerosis and could at least explain the vascular changes in the brains of demented patients (Bonora 2006; Razay et al. 2007) (Fig. 3).

Furthermore, HDL is the main carrier of cholesterol in the brain and affects synaptic growth and regeneration (Mauch et al. 2001). HDL-C can also prevent inflammation (Cockerill et al. 1995) as well as the aggregation and polymerization of A β (Olesen and Dagø 2000). It was also suggested that a low HDL-C concentration could bring in defective cholesterol release to neurons and subsequent formation of NFTs and senile plaques (Michikawa 2003). Finally, high HDL-C levels may protect against hippocampal atrophy (Wolf et al. 2004).

1.5.5 MetS

MetS is a clustering of VRF, characterized by a concurrence to central obesity that also includes impaired glucose metabolism, dyslipidemia, and high BP. In MetS, multiple pathophysiologic mechanisms interact to produce adverse outcomes. In particular, MetS represents a risk status for both T2DM, and CAD (Alberti and Zimmet 1998). MetS was also named “syndrome X” and described with presence of insulin resistance as the primary pathophysiological mechanism of MetS (Reaven 1988).

In most studies, MetS is defined using the Third Adults Treatment Panel of the National Cholesterol Education Program (NCEPATPIII) criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001). Based on this definition, the subjects with MetS were identified by any combination of three or more of the following components: 1) abdominal or central obesity (waist circumference > 102 cm for men and > 88 cm for women); 2) elevated plasma triglycerides (> 150 mg/dl); 3) low HDL-C (< 40 mg/dl for men and < 50 mg/dl for women); 4) high BP (>130/>85 mmHg) or being in hypertensive treatment; 5) high fasting plasma glucose (>110mg/dl); or 6) being in oral antidiabetic treatment (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001).

As explained above, several individual components of MetS have been linked to risk of developing dementia and MCI (Panza et al. 2004; Panza et al. 2006; Grodstein 2007; Milionis et al. 2008; Panza et al. 2008a; Purnell et al. 2008; Solfrizzi et al. 2008). Few studies have looked for at the components

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of MetS as a whole in the evaluation of the increased risk of developing cognitive decline (Yaffe 2007; Milionis et al. 2008; Frisardi 2014; Exalto et al. 2015; Liu et al. 2015). It is yet unclear whether the sum of individual components of MetS exerts a greater predictive value for developing cognitive decline and dementia than Mets (Yaffe 2007).

Some investigators have suggested that inflammation should be added as a component in the definition of MetS because it is such an important part of its pathophysiology (Haffner 2006). Several studies have demonstrated that elderly people with both MetS and elevated inflammation are at an increased risk for cognitive decline (Yaffe et al. 2004b; Panza et al. 2006; Dik et al. 2007; Yaffe 2007; Solfrizzi et al. 2010; Solfrizzi et al. 2011). In particular, in models stratified for inflammation, those with MetS and high inflammation had a nearly 2-fold increased likelihood of cognitive decline compared to those without MetS, whereas those with MetS and low inflammation did not have an increased probability of decline (Yaffe et al. 2004b). This association might vary with aging. A longitudinal population based study, with subject older than 85 years, suggested that the association between MetS and accelerated cognitive decline disappeared at age older than 85 (Van Den Berg et al. 2007). Furthermore, MetS was associated with a decelerated cognitive decline from age 85 to 90 years old and this effect was attributable to a survival bias (Van Den Berg et al. 2007).

The association of the MetS with the risk of developing mild cognitive impairment (MCI) or the latter's progression dementia is not well established. Few reports investigated this association (Yaffe et al. 2009; Roberts et al. 2010a; Solfrizzi et al. 2011; Feng et al. 2013). A very recent report by prospective longitudinal study found an increased risk of incident MCI (HR, 1.46; 95% CI, 1.02-2.09) and an increased risk of MCI progression to dementia (HR, 4.25; 95% CI, 1.29-14.00) (Ng et al. 2016).

In a cross sectional, population-based study, only the combination of the MetS and high levels of inflammation had a 2.3 fold elevated odds ratio of naMCI, whereas no association was found with MCI overall. These findings suggested that in the presence of inflammation, MetS may be more likely to be associated with the form of cognitive impairment, in particular naMCI (Roberts et al. 2010a). In The Italian Longitudinal Study on Aging (ILSA) reported no significant differences in overall risk of developing incident MCI among non-cognitively impaired individuals with the MetS compared with those without the MetS. Although, the investigators found that among MCI patients, those with MetS had a higher risk (more than 4 times more likely) of progression to dementia, compared with those without MetS (Solfrizzi et al. 2011).

Despite some evidence linked MetS with predementia syndromes and Vascular Dementia, the findings on a possible relationship of MetS with AD were contrasting (Vanhanen et al. 2006; Muller et al. 2007; Razay et al. 2007). In fact, the association between MetS and AD was not confirmed by four large longitudinal and population based studies: the HAAS, the Three City Study, the ILSA, and the cohort of Medicare recipients residing in northern Manhattan (Kalmijn et al. 2000; Muller et al. 2007; Raffaitin et al. 2009; Solfrizzi et al. 2010). These results are in contrast with evidences from population based, Kuopio study, and case-control studies (Vanhanen et al. 2006; Razay et al. 2007). However, the Kuopio Study was only cross-sectional and consequently, cannot resolve the direction of the association (ie. whether MetS predicts AD; Vanhanen et al. 2006). The case-control study, however, demonstrated a link between MetS and AD, but important limitations were the relatively small sample and a selection bias, because AD patients were selected from memory clinics (Razay et al. 2007).

An association between MetS and cognitive decline could also be explained by vascular disease (Launer 2002; Yaffe 2007). Concerning the mechanisms behind the possible association between

MetS levels and an increased risk of cognitive decline of degenerative or vascular origin, these are, at present, unknown. As previously shown, all components of MetS were shown to increase the risk of AD through various mechanisms summarized in Fig. 3.

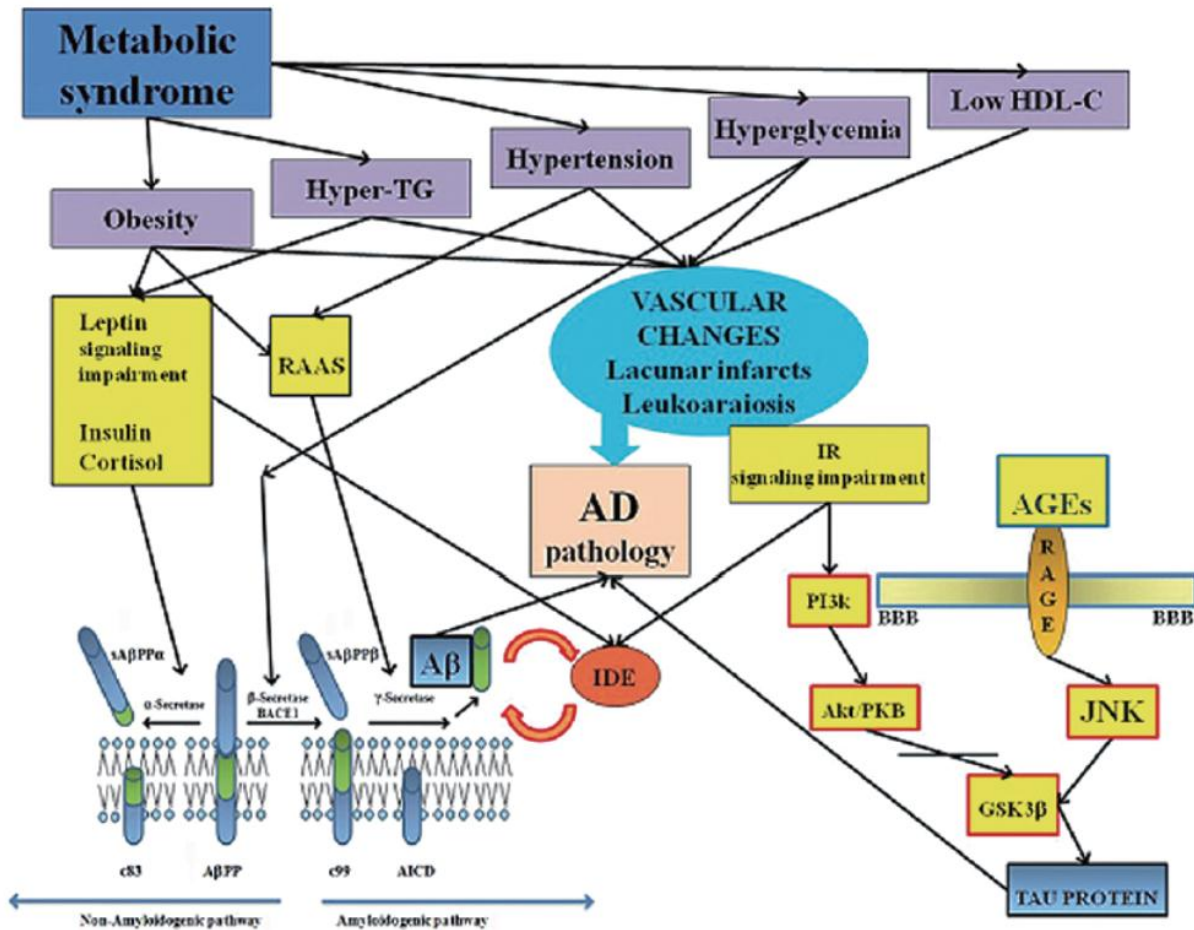


Fig. 3. Overview of the likely mechanisms linking the some VRF, in particular MetS and its components, to Alzheimer’s disease (AD). LDL = low density lipoprotein; Hyper-TG = hypertriglyceridemia; RAAS = renin – angiotensin – aldosterone system; AGEs = advanced glycation endproducts; IR = insulin resistance; sAβPPα = soluble amyloid-β protein precursor α; sAβPPβ =soluble amyloid-β protein precursor β; AβPP = amyloid-β protein precursor-β; Aβ = amyloid-β; BACE1 = β-site AβPP-cleaving enzyme 1; AICD = AβPP intracellular domain; RAGE = receptors of advanced glycation endproducts; BBB = blood brain barrier; IDE = insulin degrading enzyme; PI3k = phosphoinositide kinase-3; Akt/PKB = protein kinase B; GSK-3β = glycogen synthase kinase-3β; JNK = c-jun N-terminal kinase (adapted from Panza et al. 2010)

Finally, as shown above, several studies found an increased risk for cognitive decline in subjects with both MetS and elevated inflammation. Inflammation affects the pathophysiology of MetS. For this reason, some investigators have suggested that inflammation should be added as a component in the definition of MetS (Haffner 2006; Yaffe 2007). It has been hypothesized, as in a vicious circle, that inflammation could lead to the components of MetS, and some of these could increase inflammation (Dandona et al. 2005). In addition, markers of inflammation have been associated with an increased risk of developing dementia and cognitive decline (McGeer and McGeer 1999; Yaffe et al. 2003;

Yaffe 2007). MetS could likely contribute to accelerated atherosclerosis that, in turn, is associated with an inflammatory response and both could concur to cognitive decline (Grundey 2003; Ridker et al. 2003).

1.5.6 Heart disease

The coronary heart disease (CHD) is the worldwide leading cause of death. Several study hypothesized an increased risk of dementia in people with CHD, but the results are contrasting (Deckers et al. 2015). In the Cardiovascular Health Study cohort, the incidence of dementia was higher in those with prevalent coronary artery disease (Newman et al. 2005), and several studies confirmed that coronary artery disease is associated with cognitive impairment (Roberts et al. 2010b; Freiheit et al. 2012), reduced hippocampal volume (Koschack and Irle 2005), and increased senile plaque formation in cortical areas of the brain (Soneira and Scott 1996).

Coronary artery disease could lead to dementia through small vessel disease, which in turn interferes with cerebral blood flow regulation and perfusion, disrupts the BBB, and leads to an increased susceptibility to neurological insults (J. B. Ng, Turek, and Hakim 2013). In addition, the small vessel disease could lead a failure of clearance the excess A β produced by cortical neurons and contribute to cerebral hemorrhaging and AD pathology (Itoh et al. 1993; Bell and Zlokovic 2009).

Neuropathological studies reported correlation for aortic and mitral valve disease in AD subjects compared with a non-demented control group at autopsy (Corder et al. 2005). Several forms of heart disease were related to cognitive decline, with atrial fibrillation being studied most extensively (Kwok et al. 2011; Santangeli et al. 2012; Kalantarian et al. 2013). Atrial fibrillation (AF) is the most common arrhythmia observed in clinical practice and its prevalence increases with age. It is also a significant risk factor for thromboembolic stroke, and affects up to 9% of the population by age 80 (Stewart et al. 2002; Page 2004).

Recent data showed an association between AF and AD progression (Mielke et al. 2007). It was confirmed as independently associated with all forms of dementia (Bunch et al. 2010). A recent meta-analysis suggested that AF is associated with a higher risk for cognitive impairment and dementia, with or without a history of clinical stroke, in particular it was found a 36% higher risk for AD in people with atrial fibrillation comparing to healthy (Kalantarian et al. 2013).

Many potential mechanisms may explain the association between AF and cognitive impairment. The subjects with AF with underlying vascular/microvascular dysfunction may more likely to have brain hypoperfusion due to beat-to-beat variability in the length of the cardiac cycle and reduced cardiac output (Lavy et al. 1980), the proinflammatory state in AF (Anderson et al. 2004; Crandall et al. 2009) and periventricular white-matter lesions (de Leeuw et al. 2000).

1.5.7 Stroke

Stroke is the third cause of death in the world (Feigin et al. 2009). The occurrence of a stroke is associated with a doubling of the risk of developing dementia (Leys et al. 2005). Ischemic lesions worsen the severity of the dementia in AD patients. Thus, most studies, with some exceptions (Lee et al. 2000), found that moderate AD pathology has a much greater cognitive impact in subjects who also show basal ganglia lacunes, ischemic white matter lesions, symptomatic, or silent infarcts (Nagy et al. 1997; Snowdon et al. 1997; Heyman et al. 1998; Vermeer et al. 2003; Song et al. 2007; Schneider et al. 2009; White 2009). The vascular lesions strongly affect the early stages of AD (Esiri et al. 1999; Schneider et al. 2004). In addition, ischemic lesions also accelerate the natural history of dementia (Helzner et al. 2009).

Regarding the other links between disease progression and cerebrovascular dysfunction, AD patients with a reduced cerebrovascular reactivity to hypercapnia, an index of cerebrovascular function, showed a more rapid cognitive decline (Silvestrini et al. 2006) than controls. Therefore, coexisting cerebrovascular disease or incident ischemic lesions may shorten the preclinical stage of AD and accelerate disease progression. Furthermore, it was hypothesized as follows: from the one hand, VRF induce neurovascular dysfunction, leading to cerebrovascular insufficiency, which, in turn, leads to brain dysfunction and damage. From the other hand, cleavage of the amyloid precursor protein by β - and γ -secretases leads to $A\beta$ accumulation, which also causes brain dysfunction and damage. Either pathways are able of inducing cognitive impairment: their interaction enhances their pathogenic effects. Thus, $A\beta$ induces vascular dysregulation and enhances the vascular insufficiency, aggravating the brain dysfunction and damage associated with vascular risk factors (Iadecola 2010).

In addition, the effects of brain vascular injury and AD pathological finds such as $A\beta$, have been characterized in animal and in vitro models, but these are presently difficult to translate to human (Craft 2009). Indeed, it was found that ischemia promotes $A\beta$ accumulation by enhancing production and reducing the vascular clearance of this peptide, its major elimination pathway (Deane et al. 2004; Cirrito et al. 2005). In addition, hypoxia and ischemia promote the cleavage of $A\beta$ from the amyloid precursor protein (APP) by upregulating β -secretase expression and activity (Wen et al. 2004; Sun et al. 2006; Tesco et al. 2007; Li et al. 2009; Zhiyou et al. 2009). The increased production and the reduced clearance could enhance $A\beta$ deposition in brain and favor the formation of amyloid plaques and cerebral amyloid angiopathy (CAA) (Iadecola 2010). To which extent ischemia modulates neurofilament dynamics and phosphorylation remains unclear (Kling et al. 2013).

1.5.8 APOE

To date, APOE4 is the strongest and best established genetic, susceptibility risk factor for AD. ApoE plays a role in transporting cholesterol and mediating its metabolism in an isoform-dependent manner and for the regulation of lipid homeostasis (Mahley and Rall Jr. 2000). ApoE4 is also associated with hyperlipidaemia and hypercholesterolemia, which lead to atherosclerosis, CHD and stroke (Mahley and Rall Jr. 2000; Lahoz et al. 2001).

Genome-wide association studies have confirmed that the $\epsilon 4$ allele of APOE (APOE4) is the strongest genetic risk factor for AD (Harold et al. 2009; Lambert et al. 2009). The presence of this allele increases the susceptibility of developing the late-onset or sporadic familial AD (Chartier-Harlin et al. 1994; Houlden et al. 1998). Genetically, the $\epsilon 4$ allele of the apolipoprotein E (APOE) gene is the strongest risk factor for LOAD (Corder et al. 1993; Bu 2009; Huang and Mucke 2012). The human APOE gene exists as three polymorphic alleles, $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$, which have a worldwide frequency of 8.4%, 77.9% and 13.7%, respectively (Farrer et al. 1997). However, the frequency of the $\epsilon 4$ allele is dramatically increased to ~40% in patients with AD (Farrer et al. 1997). In addition, lifetime risk for Alzheimer's disease is more than 50% for APOE4 homozygotes and 20–30% for APOE3 and APOE4 heterozygotes, compared with 11% for men and 14% for women overall irrespective of APOE genotype (Genin et al. 2011). APOE $\epsilon 4$ carriers tend to have an earlier diagnosis than non-carriers in a gene dose-dependent manner. More specifically, the frequency of AD and mean age at clinical onset are 91% and 68 years of age in $\epsilon 4$ homozygotes, 47% and 76 years of age in $\epsilon 4$ heterozygotes, and 20% and 84 years in $\epsilon 4$ noncarriers (Albert et al. 2011a; Schrijvers et al. 2012; Scheltens et al. 2016).

APOE4 is also associated with increased prevalence of MCI, in particular aMCI and dysexecutive MCI (Pa et al. 2009) and lower age of onset (Vemuri et al. 2010). Furthermore, APOE $\epsilon 4$ -carrying

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MCI patients experience a faster cognitive decline in several cognitive and functional assessments, and the severity of such deficits are strictly associated to the APOE ϵ 4 gene dose (Farlow et al. 2004; Cosentino et al. 2008; Whitehair et al. 2010). It is noteworthy that the presence of the APOE ϵ 4 is also associated with an increased risk of progression from MCI to AD-type dementia (Petersen et al. 1995; Fleisher et al. 2007; Elias-Sonnenschein et al. 2011).

ApoE4 has several effects on AD. It confers toxic gain of function, loss of neuroprotective function or both in its pathogenesis (Liu et al. 2013). ApoE4 leads to increased aggregation and deposition of A β by modulating A β metabolism in ApoE isoform-dependent manner (ϵ 4 > ϵ 3 > ϵ 2) (Bales et al. 2009; Reiman et al. 2009; Castellano et al. 2011). In addition, ApoE4 is less efficient in A β clearance than ApoE3 (Castellano et al. 2011). In microglia, ApoE3 promotes enzyme-mediated degradation of A β more efficiently than ApoE4 (Jiang et al. 2008). It was found that ApoE4 lead to increased tau hyperphosphorylation, cytoskeletal disruption and mitochondrial dysfunction through truncated fragment of ApoE4, resulting from proteolytic cleavage of ApoE that derives from stress or injury (Brecht et al. 2004; Mahley et al. 2006; Huang 2010). Additionally, ApoE4 bring about greater medial temporal lobe atrophy, in particular in the hippocampal area (Hashimoto et al. 2001; Korf et al. 2004). Elevated baseline activity in brain of APOE ϵ 4 carriers could potentially contribute to increased A β production, because A β levels are regulated by neuronal activity (Cirrito et al. 2005; Bero et al. 2011).

ApoE4 leads to dysmodulation of lipid/cholesterol metabolism, because ApoE4 is also less efficient than ApoE3 in transporting brain cholesterol (Rapp et al. 2006), an essential component for axonal growth, synaptic formation and remodelling. Furthermore, ApoE plays a role in regulate synaptic plasticity and repair (Buttini et al. 2002; Chen et al. 2010), and neurogenesis, in particular in maintenance of the neural stem or progenitor cell pool in the adult dentate gyrus region of the hippocampus (Yang et al. 2011). In murine models, ApoE4 carriers have lower dendritic spine density and length compared with ApoE3-TR mice (Wang et al. 2005; Dumanis et al. 2009).

ApoE4 also could play a role in the innate immune response in AD. Some study suggested that ApoE4 could have proinflammatory and/or reduced anti-inflammatory functions, which could further exacerbate AD pathology (Lynch et al. 2003; Ringman et al. 2012). Finally, a population-based study highlighted that APOE ϵ 4 carriers may be more vulnerable for harmful lifestyle factors suggesting complex gene-environmental interactions (Kivipelto et al. 2008).

1.6 Aims and hypotheses

Data about the relationship between dementia and its risk factors and between the interrelationship of risk factors in favouring the onset and course of dementia subtypes are scarce, especially in populations with low-education and/or with Mediterranean lifestyle and diet. Aim of the present PhD thesis was to evaluate the relationships between isolated and clustered VRF/diseases and MCI/AD.

The study was conducted using the dataset from the Zabùt Aging Project (ZAP), a prospective cohort study on aging and dementia, carried-out in a rural little town in Sicily, Southern Italy: the municipality of Sambuca di Sicilia (province of Agrigento). To achieve this goal, the 10-year follow-up data were used cross-sectionally because several VRF were not analyzed at baseline in a comprehensive manner.

In particular, the following risk factors were analysed:

- a) Isolated VRF
 - Hypertension
 - Diabetes Mellitus
 - Dyslipidemia
 - Obesity
 - Coronary heart disease
 - Previous Transient Ischemic Attack (TIA)/Stroke
 - Atrial fibrillation
 - APOE4
 - Smoking
- b) Clustered VRF:
 - MetS
- c) Markers of vascular burden:
 - Framingham general cardiovascular disease (CVD) risk profile
 - Framingham stroke risk score
 - Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) risk score
 - Late-Onset Alzheimer Disease (LOAD) vascular risk score

The possible effect-modification by age, sex, education, genetic factor (APOE4 allele carrier), undernutrition, inflammatory status and depressive symptoms was taken into account.

2 MATERIALS AND METHODS

2.1 Target population

Participants in this study were evaluated in the 10-year follow up of the Zabut Aging Project (ZAP), a longitudinal study of population aging and dementia conducted at baseline in subjects older than 50 years living in a rural community of the South-West of Sicily: the municipality of Sambuca di Sicilia, accounting for 6114 inhabitants (ISTAT 2011). Baseline data collection was carried out between 2001-2004 and included over 2000 patients (77.7% participation rate) from a study base of 2,613 subjects. Starting from autumn 2012 until the end of 2013, all the living subjects evaluated at baseline (aged 60 years or older) underwent to the 10-year follow-up examination. Over 75% of the 1,300 subjects still alive at follow-up, after excluding subjects dropped out for death/moved and/or refusals, were re-assessed after 10 years (Fig. 4). The ethical committee of the provincial health ethics committee of the Agrigento province approved the study, and a signed informed consent was achieved from each participant.

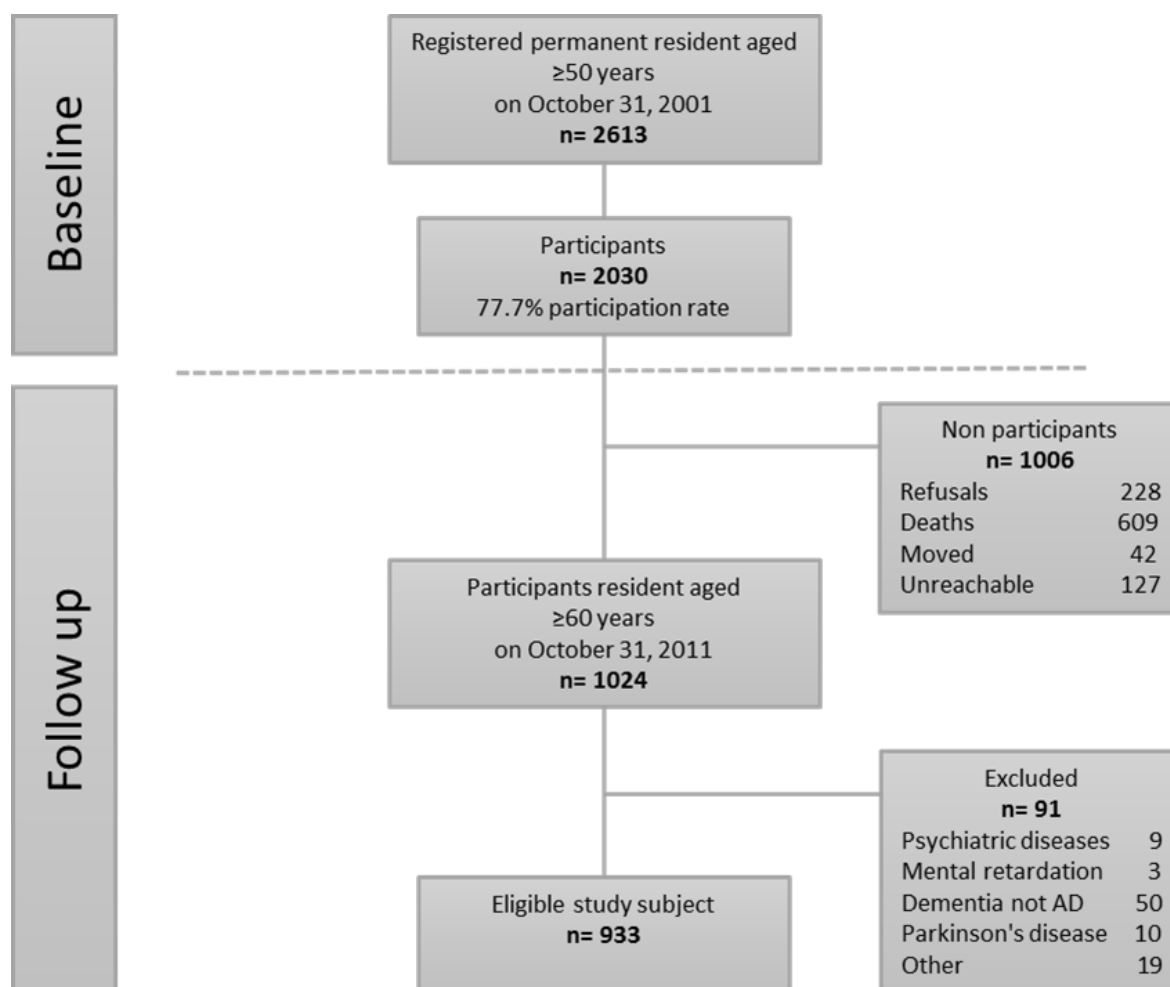


Fig. 4. Flowchart of subject recruitment for study subjects in the Sambuca di Sicilia community, aged 60 or over.

2.2 Diagnosis of MCI and Dementia

Cognitive impairment was ascertained with a multidomain neuropsychological battery including tests evaluating episodic memory, attention, language and executive functions (see section 2.8), while functional impairment was evaluated using the basic Activities of Daily Living (ADL) (Katz et al. 1970) and the Instrumental Activities of Daily Living Scale (IADL) (Lawton and Brody 1969); the Clinical Dementia Rating (CDR) was used as a clinical score for cognitive impairment and dementia (Morris 1997).

The diagnosis of dementia was made according to the DSM-IV-TR (American Psychiatric Association 2000). AD was then diagnosed according to the National Institute on Aging and the Alzheimer's Association criteria for clinical AD (McKhann et al. 2011). Mild cognitive impairment was defined according to published criteria (Petersen 2004a; Winblad et al. 2004). Subjects suspected with dementia underwent CT scan and/or 1.5 MRI.

2.3 Exclusion criteria

Exclusion criteria were: dementia/cognitive impairment due to other general medical conditions (DSM-IV-TR code 294.1), such as head trauma, severe metabolic or endocrine diseases, brain tumour, normal pressure hydrocephalus and other neurological disorders as well as subjects with a history of alcohol or substance abuse or dependence, with uncertain dementia, with delirium and with psychiatric disorders preceding the onset of dementia.

2.4 Demographic and Lifestyle Characteristics

Demographic and lifestyle characteristics of the participants were collected using a semi-structured questionnaire, consisting of the following information: (1) personal demographic data, including birth date, sex, number of formal years of education and education level; (2) lifestyles, including occupational history, physical exercise, smoking habits, passive smoking and alcohol consumption.

2.5 Laboratory Analysis, Physical Measurements and Blood Pressure

Venous blood sample was collected after overnight fasting (12 h) for evaluating the following parameters: fasting glucose, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides and APOE genotyping. The inflammatory marker was C-reactive protein (CRP) (Pearson et al. 2003; Germolec et al. 2010). Serum CRP concentrations were measured with an immunoturbidimetric assay (CRPL3, normal range 0–0.5 mg/L). A nurse measured seated blood pressure twice, supine and to the ankle one time (BP systolic, diastolic and differential), anthropometry (height and weight, hip, waist and head circumference) and skinfold with plicometry. Body mass index (BMI) was calculated as weight/height² (kg/m²). The BMI of ≥ 25 was defined overweight according to the WHO standard (WHO 1995). Undernutrition status was defined through the administration of by the Mini Nutritional Assessment (MNA) (score ≤ 23.5). The MNA was administered to identify elderly patients at risk of malnutrition (Guigoz and Vellas 1999)

2.6 *Assessment of Vascular risk factors/diseases*

Participants with hypertension, ischemic heart disease, atrial fibrillation (AF), previous TIA/stroke, diabetes, dyslipidemia and obesity were identified with a semi-structured questionnaire, physical measurements and laboratory analysis. The questionnaire included information on years of the diseases and current use of medications. In particular, VRF were valued as follows:

- hypertension was defined as systolic blood pressure (SBP) greater than or equal to 140 mm Hg or diastolic blood pressure (DBP) greater than or equal to 90 mm Hg, participant's self-reporting or receiving medication specifically for the indication of hypertension;
- diagnosis of T2DM was based on fasting blood glucose levels ≥ 126 mg/dL, participant's self-reporting or taking medications insulin and/or oral antidiabetic drugs;
- diagnosis of dyslipidemia was based on blood total cholesterol level ≥ 240 mg/dL, LDL ≥ 160 mg/dL, HDL < 40 mg/dl for men and < 50 mg/dl for women, and triglyceride ≥ 150 mg/dL, participant's self-reporting or receiving medication for the indication of hypercholesterolemia and hypertriglyceridemia.
- obesity was defined by BMI > 29 ; also it is taken into account the waist circumference > 102 cm for men and > 88 cm for women to physical measurements.
- CHD event was defined as the occurrence of myocardial infarction, angina pectoris or receiving medication specifically for the indication of coronary insufficiency;
- diagnosis of AF was based on reported medical history AF or on the assumption of medicines specifically for the indication of AF;
- previous TIA/stroke cases was based on reported medical history and/or on neuroimaging evaluation;
- MetS was diagnosed according to the Third Adults Treatment Panel of the National Cholesterol Education Program (NCEPATPIII) criteria (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001); based on this definition, the subjects with MetS were identified by any combination of three or more of the following components: abdominal or central obesity (waist circumference > 102 cm for men and > 88 cm for women); elevated plasma triglycerides (> 150 mg/dl); HDL-C (< 40 mg/dl for men and < 50 mg/dl for women); high BP ($> 130/ > 85$ mmHg) or being in hypertensive treatment; high fasting plasma glucose (> 110 mg/dl) or being in oral antidiabetic treatment;
- APOE- $\epsilon 4$ (MIM 104310) genotype was performed by APOE genotyping by peripheral blood samples. APOE4 gene carriers were participants who had at least one APOE4 allele;
- Smoking, current or past smoking vs never smoking, was assessed by information collected using a semi-structured questionnaire.

2.7 *Markers of vascular burden*

2.7.1 **Framingham cardiovascular algorithms**

The Framingham general cardiovascular disease (CVD) risk profile and the Framingham stroke risk profile, multivariable risk scores that provide a sex-specific absolute risk of cardiovascular events were computed for each participant.

The Framingham general CVD risk score includes age, sex, SBP, treatment for hypertension, high-density lipoprotein cholesterol, total cholesterol, smoking, and diabetes (D'Agostino RB et al. 2008). Higher scores indicated higher risks of cardiovascular events. The cardiovascular risk score was normally distributed and treated as a continuous.

The Framingham stroke risk score incorporates age, SBP, treatment for hypertension, diabetes, smoking, prior CVD (myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or congestive heart failure), AF, and left-ventricular hypertrophy (D'Agostino et al. 1994). The Framingham cardiovascular algorithms were used as continuous variables in the statistical models.

2.7.2 Dementia risk scores

Several composite risk scores at mid-life or later life used VRF to process risk scores for predicting the risk of dementia in the general population.

The CAIDE risk score, a mid-life score, was developed to predict the late risk of dementia on the basis of risk factor profiles at middle age using data from the population-based Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study. The CAIDE risk score is composed by age, education, sex, SBP, BMI, total cholesterol, physical activity. There are 2 models of the dementia risk score depending on the inclusion of APOE (Kivipelto et al. 2006a). In this study, both models of dementia risk score were calculated. Physical activity was evaluated by the International Physical Activity Questionnaire (IPAQ), an instrument for monitoring of physical activity and inactivity (Craig et al. 2003).

The LOAD vascular risk score, a late-life score, is a simple summary risk score for the prediction of AD in elderly persons based on their vascular risk profiles. Risk factors contributing to the risk score were age (>65 years old), sex, education, ethnicity, and several common VRF, i.e. APOE ϵ 4 genotype, history of diabetes, hypertension or smoking, high-density lipoprotein levels, and waist to hip ratio (WHR) (Reitz et al. 2010).

Kivipelto et al. (2006a) and Reitz et al. (2010) based the risk of dementia on the CAIDE and LOAD scores, respectively, categorized into five groups (based on quintiles). In the present work, these scores were used as continuous variables.

2.8 Cognitive assessment

The cognitive assessment, as well as the diagnosis of MCI and AD, were performed according to a multidimensional dementia protocol, which covers the domains of global cognition, executive function, attentive/visuoconstructional ability, memory, language as well as neuropsychiatric assessment.

The neuropsychological evaluation used in the study included the following test battery:

a) *Global cognition and subjective memory complaints*

- Mini-Mental State Examination (MMSE) (Measso et al. 1993)
- Addenbrooke's Cognitive Examination Revised (ACE-R) (Pigliatile et al. 2011)
- Montreal Cognitive Assessment (MoCA) (Pirani A, Tulipani C 2006)
- Test di Intelligenza Breve (TIB, i.e. rapid intelligence test) (G. Sartori, L. Colombo, G. Vallar, M. L. Rusconi 1997)
- Memory Assessment Clinics-Questionnaire (MAC-Q) (Crook et al. 1992)

b) *Episodic memory*

- Rey Auditory Verbal Learning Test immediate and delayed recall (Rey A 1964)
- The three-objects-three-places test (Prestia et al. 2006)
- 10/36 Spatial Recall Test (SPART 10/36) (visuospatial memory) (Gerstenecker et al. 2016)

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c) *Executive functions*

- Frontal Assessment Battery (FAB) (Dubois et al. 2000)
- Verbal Fluency (Novelli et al. 1986)

d) *Language*

- Aachener Aphasia Test - Denominazione (Luzzatti et al. 1996)
- Token Test (DE RENZI and VIGNOLO 1962)

e) *Attentive/visuoconstructional ability*

- Clock Drawing Test (Shulman et al. 1993)
- Digit Span Backward (Wechsler 1997)

Behavioral assessment includes:

- Hospital Anxiety and Depression Scale – HADS (Snaith 2003)
- Starkstein Apathy Scale (Starkstein et al. 1992)
- Center for Epidemiologic Studies Depression Scale (CES-D) (Lewinsohn et al. 1997);
- Neuropsychiatric Inventory (NPI) (Cummings et al. 1994)

The presence of high level of depressive symptoms (HLDS) was evaluated with the Center for Epidemiologic Studies Depression Scale (CESD score ≥ 16) (Lewinsohn et al. 1997). The neuropsychological and behavioural battery was administered by certified study neuropsychologist; raw data were adjusted for age and education level according to Italian normative data. All evaluation took about 90 min.

2.9 *Statistical Analysis*

Descriptive statistics were computed for population examined at baseline (split as total and evaluated at follow-up, i.e. total subjects less those dropped or dead) and 10-year follow-up (split as total and evaluated at follow-up, i.e. total less dropped or dead). Prevalence values with 95% confidence intervals were computed (crude and corrected for either sex or age (at 10-years and 5-years intervals).

Continuous variables among outcomes (ie, cognitively normal subjects vs MCI and/or AD) were compared using the analysis of variance (Glimmix procedure in SAS/STAT) and differences among means compared by applying t-grouping (Tukey-Kramer correction) at the 5% probability level to the LSMEANS.

For dichotomous variables, odds ratios (freq procedure with ‘CHISQ CMH’ options in SAS/STAT) with 95% Confidence Intervals (CI) were computed and relative risks were calculated by both Cochran-Mantel-Haenszel and Logit.

The importance of each vascular risk factor (VRF) in determining the outcome was modelled by means of a sequential procedure based on the logistic regression (logistic procedure with ‘rsquare’ option in SAS/STAT) and ‘strata’ option. Firstly, all 1-variable stratified logistic regressions were performed. Variables used in this step to stratify the population were age (dichotomization with a 75 years old cut-off; Model 1); education (dichotomization with 5 years cut-off, Model 2); APOE4 carrier (Model 3, dichotomization of the VRF were performed as explained in section 2.6); inflammation (Model 4); undernutrition (Model 5); sex (Model 6), High level of Depressive Symptoms (Model 7). Quality of each of the previous model was checked by means of the Akaike information criterion (AIC). In a further step, additional models were constructed by combining 2 or more covariates and those models minimizing AIC were retained. These included 4 additional logistic

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models with multiple stratification as follows: 1) Model 8 by using those covariates which minimized the AIC, namely APOE4, inflammation, undernutrition and High level of Depressive Symptoms; 2) model 9 stratified by mean of genetic factors (APOE4 and sex); 3) model 10 stratified for modifiable factors (inflammation, undernutrition and High level of Depressive Symptoms); 4) model 11 stratified by sex, education and age.

Finally, the contribution of each of the 14 VRF in separating the outcomes and the mutual relationship among VRF in separating the outcomes (treatments) were studied building a canonical discriminant analysis (CDA, Candisc procedure in SAS/STAT) and separating treatments when F statistic was higher than the Mahalanobis distance per each pair of comparison. A hyperspace of the canonical axes significantly different from zero was constructed with the projection of the centroids (\pm S.E.) of each treatment and vector of each VRF.

3 RESULTS

3.1 Characteristics of the population under study

On thousand and twentyfour of the original 2030 participants in the Zabut Aging Project study baseline data collection (2001) participated in the 10-years follow-up phase (2011-2013). Eligible study subjects were 933 excluding those with a previous diagnosis of psychiatric diseases, mental retardation, non-AD dementia, Parkinson's disease, other major neurological diseases, medical or psychological conditions that prevented completion of assessment tasks (Fig. 4).

Table 2a. Descriptive statistics of the total population at follow-up

	Mean	Standard Error	Median	Standard Deviation	Kurtosis	Skewness
Age (yr)	74,8	0,3	74,0	8,7	-0,7	0,4
Education (yr)	5,7	0,1	5,0	3,8	1,0	1,1
MMSE	25,7	0,2	27,2	5,4	7,0	-2,4
MNA	24,0	0,1	24,5	2,9	3,8	-1,7
CES-D	12,2	0,4	9,0	10,3	0,7	1,1
Body mass index(kg/m ²)	29,5	0,2	29,0	5,1	0,9	0,6
Systolic blood pressure (mmHg)	134,7	0,5	135,0	15,5	1,0	0,5
Diastolic blood pressure (mmHg)	74,0	0,3	72,0	8,1	1,3	0,2
Waist circumference (cm)	99,2	0,4	100,0	10,6	0,5	0,1
Glycemia (mg/dl)	98,5	1,1	92,0	31,7	22,7	3,4
Total cholesterol (mg/dl)	186,0	1,3	185,5	39,0	0,6	0,1
Triglycerides (mg/dl)	115,5	2,0	99,0	60,0	5,6	2,0
HDL (mg/dl)	53,8	0,5	52,0	15,3	0,7	0,7
LDL (mg/dl)	109,2	1,1	109,0	32,9	-0,1	0,1
CRPL3 (mg/l)	0,5	0,0	0,2	1,0	115,6	9,1
Framingham general CVD risk profile	20,7	0,3	21,5	8,5	-1,4	-0,3
Framingham stroke risk profile	13,9	0,4	11,0	11,2	7,8	2,3
CAIDE risk score Model 1	4,7	0,1	4,2	3,2	5,0	1,9
CAIDE risk score Model 2	5,8	0,2	4,4	4,6	1,4	1,7
LOAD risk score	12,2	0,3	12,6	7,6	-1,6	-0,2

Abbreviations: MMSE= Mini-Mental State Examination; CES-D= Center for Epidemiologic Studies Depression Scale; MNA= Mini Nutritional Assessment; HDL= high density lipoprotein cholesterol; LDL= low density lipoprotein cholesterol; CRPL3= C-reactive Protein; CVD= cardiovascular disease

The population under study was on average 74.8 years old with a slight positive skewness (see Table 2 for descriptive statistics of the continuous variables analysed). The median of the education was 5 years, corresponding to the first cycle of study (elementary school) of the Italian system. Most variables showed low skewness and kurtosis ($|\text{value}| < 2.6$) with the exception of glycemia and CRPL3 which showed both a high and positive skewness, and triglycerides, MMSE, MNA and Framingham Stroke risk profile which showed only a high kurtosis. The population under study showed a relatively high mean and median BMI. CAIDE risk score (both models) were also positively skewed. NC, aMCI and naMCI were in general younger than AD and ineligible patients (Fig. 5), with few differences related to sex distribution.

RESULTS

Table 2b. Descriptive statistics at baseline of subjects reassessed or lost (dead or dropped) at follow-up

		Mean	Standard Error	Median	Standard Deviation	Kurtosis	Skewness
Age at baseline	drop	66,5	0,4	66,0	9,0	-0,9	0,2
	follow up	66,1	0,3	65,0	8,7	-0,8	0,3
	dead	78,1	0,4	78,0	9,3	-0,2	-0,2
Male gender	drop	0,5	0,0		0,5	-2,0	0,2
	follow up	0,4	0,0		0,5	-1,9	0,3
	dead	0,5	0,0		0,5	-2,0	0,0
Education (yr)	drop	5,2	0,2	5,0	3,6	2,3	1,4
	follow up	5,9	0,1	5,0	3,7	1,0	1,1
	dead	4,1	0,1	4,0	3,1	5,7	1,8
MMSE at baseline	drop	26,3	0,2	27,2	3,7	2,7	-1,4
	follow up	26,8	0,1	27,7	3,1	3,4	-1,4
	dead	24,1	0,2	25,0	5,2	2,5	-1,3
CES-D at baseline	drop	8,7	0,5	5,0	10,4	1,9	1,5
	follow up	8,3	0,3	5,0	9,3	2,7	1,6
	dead	9,9	0,5	6,0	10,5	1,5	1,3

Abbreviations: MMSE= Mini-Mental State Examination; CES-D= Center for Epidemiologic Studies Depression Scale. Median and Mode for gender are not provided since it is a bivariate distribution.

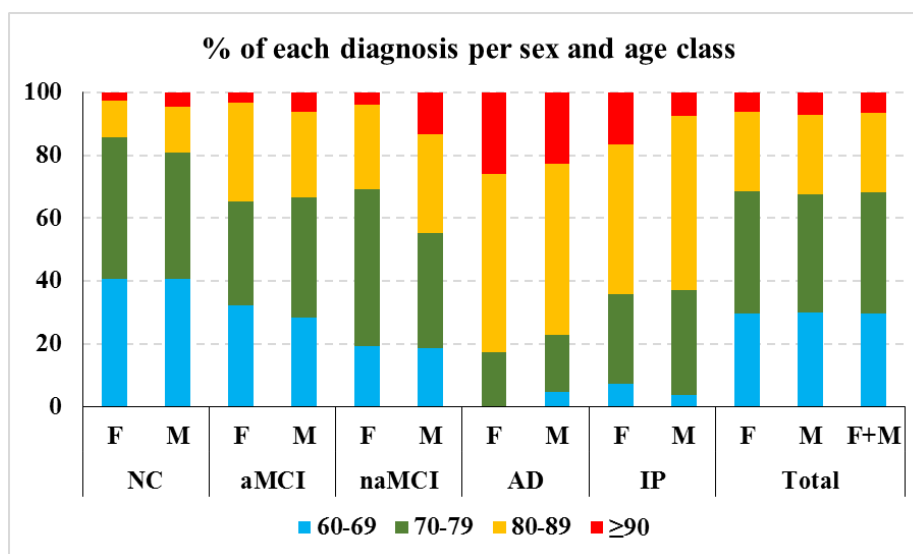


Fig. 5. Distribution by sex and age groups (grouped per 10-year intervals) according to diagnoses. NC= subjects with normal cognition, IP=ineligible patients, F and M= female and male, respectively.

The population of patients at the baseline was similar to that at the follow-up assessment. Slight differences among means of age are attributable to the different times of clinical assessments (ie, baseline vs follow-up). Populations at baseline of the followed-up and dropped patients showed similar distributions. Dead patients were, on average, 12 years older than followed-up and dropped patients, with a lower education and MMSE and higher CES-D.

When computed as crude prevalence, NC accounted for near a half (45.6% C.I. 95%: 41.0-50.2) of the total population at follow-up, aMCI and naMCI for 27.9% (C.I. 95%: 22.7-33.2) and 11.6% (C.I. 95%: 5.8-17.4) respectively, AD for 8% (C.I. 95%: 2.0-13.9) and ineligible patients were 6.9% (C.I.

RESULTS

95%: 0.9-12.9) of the total. No differences were found in crude or sex-adjusted prevalence (Fig. 6). Age-adjustment consisted in an increase of the prevalence of NC and AD patients. When age-adjustment was made with a 5-years interval, results were similar to those obtained at 10-years intervals (data not shown).

With increasing age of the participants, occurrence of NC decreased, while the prevalence of AD increased (Fig. 7), whereas those of aMCI and naMCI were variable. Estimation of the population prevalence of AD and ineligible patients was uncertain in the relatively younger patients (aged <79 years). In particular, no AD was found in patients younger than 65 years old. Prevalence of aMCI in male subjects was 16.1% higher than that of female subjects (37.2% and 21.1%, respectively; Fig. 7), whereas no differences by sex was found regarding the prevalence of other diagnoses.

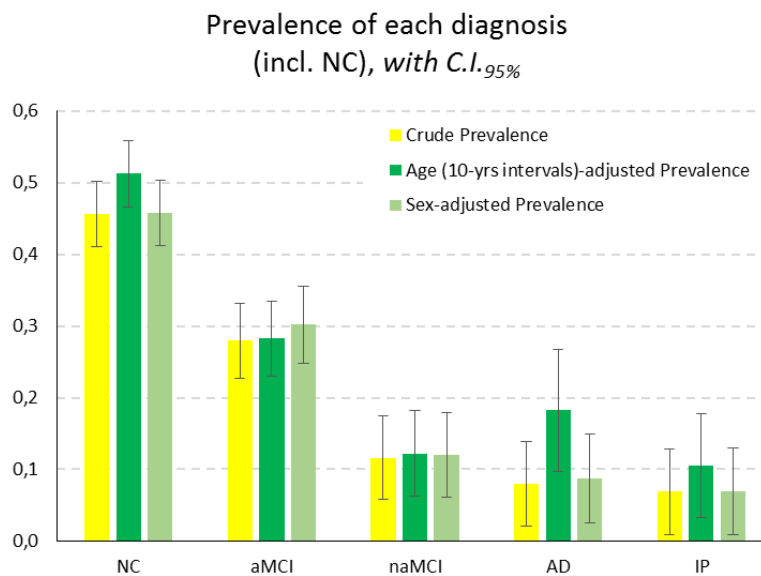


Fig. 6. Prevalence of each diagnosis, as crude prevalence and after age- or sex-adjustment. NC= subjects with normal cognition, IP= ineligible patients

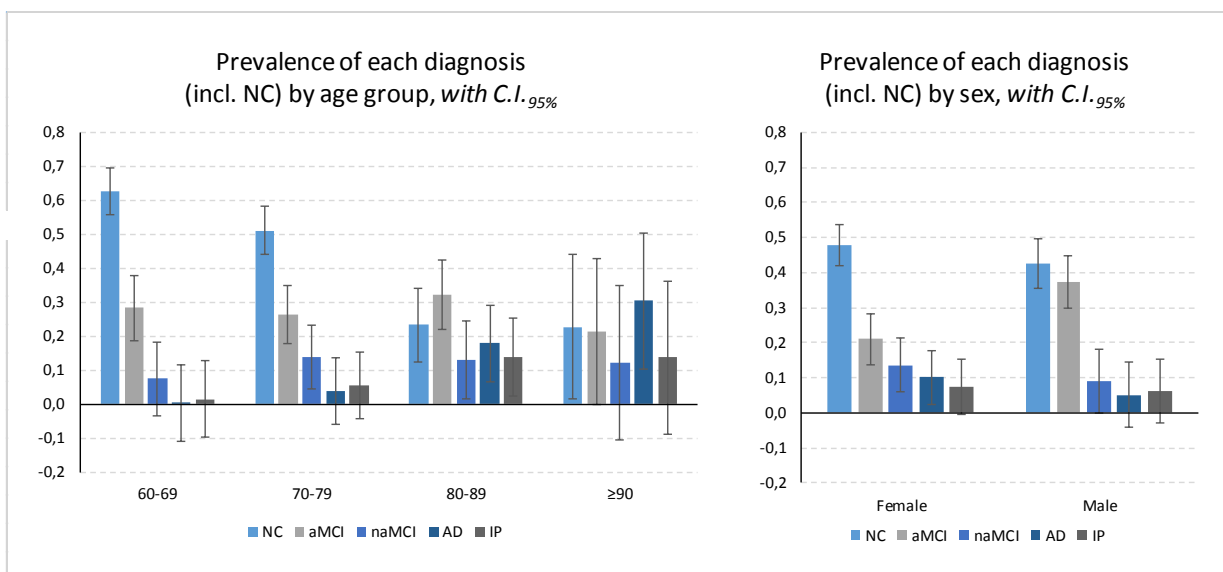


Fig. 7. Prevalence of each diagnosis by age group (left panel) or sex (right panel). NC= subjects with normal cognition, IP=ineligible patients.

RESULTS

Most socio-demographic and clinical characteristics of the eligible cohort strongly varied among diagnoses group (Tables 3a, 3b and 3c). In particular, AD patients were on average 9.2 years older than MCI and these were 3.9 years older than NC. Similarly, NC patients were more scholarized, showing lower CES-D scores than patients with any cognitive decline. AD showed MNA scores dramatically lower (−25.9%) than NC or MCI.

Table 3a. Demographic and clinical characteristics of four diagnostic groups. Values are expressed as mean ± SD.

	Four diagnostic groups				p-value
	NC group	aMCI group	naMCI group	AD group	
	<i>n</i> 457	280	116	80	
Age (yr)	72,1 ± 7,6 ^{c,*}	75,5 ± 8,6 ^b	76,4 ± 7,9 ^b	85,2 ± 6,6 ^a	<.0001
Education (yr)	6,9 ± 4,0 ^a	4,7 ± 3,5 ^b	4,4 ± 2,9 ^b	4,3 ± 3,0 ^b	<.0001
MMSE	27,8 ± 3,2 ^c	25,4 ± 3,7 ^b	26,0 ± 3,6 ^b	14,2 ± 7,5 ^a	<.0001
CES-D	10,5 ± 8,9 ^b	13,8 ± 11,0 ^a	13,6 ± 10,8 ^a	16,4 ± 13,7 ^a	<.0001
MNA	24,9 ± 1,9 ^a	24,1 ± 2,3 ^b	24,2 ± 2,2 ^b	18,1 ± 3,6 ^c	<.0001
Body mass index(kg/m2)	29,7 ± 4,9 ^a	29,6 ± 5,0 ^a	30,2 ± 5,7 ^a	27,3 ± 5,4 ^b	0,001
Waist circumference (cm)	99,6 ± 10,7 ^a	100,2 ± 10,0 ^a	98,9 ± 10,7 ^a	93,6 ± 10,8 ^b	<.0001
Triglycerides (mg/dl)	118,0 ± 55,9	119,6 ± 67,6	111,0 ± 55,4	114,3 ± 61,8	0,772
HDL cholesterol (mg/dl)	54,2 ± 15,6	51,7 ± 13,1	55,7 ± 16,8	56,1 ± 18,2	0,034 ^{**}
LDL cholesterol (mg/dl)	111,5 ± 33,2	106,4 ± 31,8	106,7 ± 31,2	109,0 ± 37,0	0,199
Total cholesterol (mg/dl)	189,3 ± 37,4	181,3 ± 38,8	182,7 ± 41,8	187,9 ± 43,9	0,051
Glycemia	97,1 ± 25,7	100,4 ± 34,4	101,8 ± 35,4	95,5 ± 45,4	0,314
CRPL3 (mg/L)	0,4 ± 0,4	0,6 ± 1,5	0,5 ± 0,9	0,6 ± 1,0	0,005 ^{***}
Hypertension (yr)	8,8 ± 9,7 ^b	8,2 ± 9,4 ^b	11,7 ± 11,3 ^a	10,9 ± 12,9 ^{a,b}	0,005
Diabetes (yr)	2,1 ± 6,9	2,2 ± 6,0	2,7 ± 6,9	2,1 ± 7,5	0,831
Dyslipidemia (yr)	2,6 ± 5,4	2,0 ± 4,2	2,2 ± 4,6	1,9 ± 6,0	0,297
Atrial Fibrillation (yr)	0,4 ± 2,3	0,5 ± 2,2	0,3 ± 1,8	1,1 ± 4,1	0,147
Systolic blood pressure (mmHg)	135,5 ± 15,8 ^{a,b}	133,6 ± 14,4 ^b	138,7 ± 15,4 ^a	127,9 ± 16,3 ^c	<.0001
Diastolic blood pressure (mmHg)	74,5 ± 8,5 ^a	73,7 ± 6,9 ^a	74,5 ± 8,9 ^a	70,7 ± 8,1 ^b	0,002

Abbreviations: NC= subjects with normal cognition; AD= Alzheimer's disease; aMCI= amnesic mild cognitive impairment; naMCI= non amnesic mild cognitive impairment; MMSE= Mini-Mental State Examination; CES-D= Center for Epidemiologic Studies Depression Scale; MNA= Mini Nutritional Assessment; HDL= high density lipoprotein; LDL= low density lipoprotein; CRPL3= C-reactive Protein. * Subsets of categories with a letter in common do not differ each other at a Tukey-Kramer-corrected $p \leq 0.05$. ** Tukey-Kramer correction and further visualization as 'lines' does not reflect all significant comparisons: uncorrected pdiff comparisons of the LSMEANS showed that HDL cholesterol of aMCI was different than that of other diagnoses (p from 0.022 to 0.034). *** Tukey-Kramer correction and further visualization as 'lines' does not reflect all significant comparisons: uncorrected pdiff comparisons of the LSMEANS showed that NC significantly differed from AD ($p=0.036$) or aMCI ($p=0.001$).

RESULTS

Blood values of HDL cholesterol and C-reactive Protein (CRPL3) significantly varied among diagnoses ($p=0.034$ and $p=0.005$, respectively), however, the Tukey-Kramer correction for multiple pair-comparison failed in retrieving differences among pairs of diagnoses. This was due to a non-normal distribution of the data within each diagnosis. In particular, uncorrected *pdiff* comparisons of the LSMEANS showed that HDL cholesterol of aMCI were lower than that of other diagnoses and that CRPL3 varied in NC vs. either aMCI or AD. AD patients also showed systolic and diastolic blood pressures lower than both MCI and NC.

Differences among diagnoses for Framingham general CVD risk profile were similar to those of MNA, whereas Framingham stroke risk profile showed a tendency to increase from NC or aMCI to naMCI or AD. 'CAIDE risk score Model 1' in aMCI and naMCI were not significantly different compared with subjects with either NC or AD, whereas LOAD Score clearly captured the difference between NC, from the one side, and the other diagnoses, from the other side (Table 3b).

The percentage of male in the eligible cohort was 57.0%. However, such percentage varied among diagnostic groups, with aMCI accounting for a strongly lower percentage of male than NC and other groups. Percentage of males in AD were higher than in NC ($p=0.045$). Differences in the percentage of APOE4 carriers of each group were not statistically observed, however, aMCI and AD showed 2.9% more APOE4 carriers than NC ($OR>1.53$ at $p>0.18$) and naMCI showed 4.7% less APOE4 carriers compared to NC ($OR=0.18$ at $p=0.063$). Similarly, AD patients showed a slight risk (odd ratio near significantly >1.00) for inflammation (high CRP3) ($OR=1.70$ C.I. 95%: 1.00-2.92 at $p=0.055$). Undernutrition in AD showed a definitely high OR ($OR=37.7$; C.I. 95%: 16.8-84.5; $p<0.001$). Similarly, also in naMCI and aMCI showed high undernutrition values ($OR=2.27$; C.I. 95%: 1,4-3,5; $p<0.001$; and $OR=2,37$ C.I. 95%: 1,71-3,29; $p<0.001$, respectively).

Risk of AD compared to NC was increased by previous TIA/stroke ($OR=2.77$ C.I. 95%: 1.21-6.32 at $p=0.027$). Risk of naMCI vs. NC was mildly increased by AF ($OR=2.07$ C.I. 95%: 1.00-4.27 at $p=0.054$).

Table 3b. Risk scores of the four diagnostic groups. Values are expressed as mean \pm SD.

	Four diagnostic groups				p-value
	NC group	aMCI group	naMCI group	AD group	
<i>n</i>	457	280	116	80	
Framingham general CVD risk profile	20,1 \pm 8,7 ^{b*}	22,3 \pm 8,1 ^a	20,8 \pm 8,2 ^{a,b}	17,5 \pm 8,0 ^b	<.0001
Framingham stroke risk profile	12,7 \pm 10,2 ^c	13,9 \pm 9,6 ^{b,c}	17,7 \pm 14,3 ^a	17,6 \pm 17,3 ^{a,b}	0,0001
CAIDE risk score Model 1	4,3 \pm 3,2 ^b	5,1 \pm 3,2 ^{a,b}	5,2 \pm 3,5 ^{a,b}	5,4 \pm 2,6 ^a	0,003
CAIDE risk score Model 2	5,3 \pm 4,4	6,6 \pm 5,0	5,8 \pm 4,3	6,0 \pm 4,2	0,108
LOAD risk score	10,3 \pm 7,5 ^b	13,4 \pm 7,4 ^a	12,86 \pm 7,3 ^a	17,43 \pm 5,6 ^a	0,0002

Abbreviations: NC= subjects with normal cognition; AD= Alzheimer's disease; aMCI= amnesic mild cognitive impairment; naMCI= non amnesic mild cognitive impairment; CVD= cardiovascular disease.* Subsets of categories with a letter in common do not differ each other at a Tukey-Kramer-corrected $p\leq 0.05$.

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Table 3c. Demographic and clinical characteristics of four diagnostic groups. Values are expressed as percentage.

	Four diagnostic groups										
	NC group		aMCI group		naMCI group			AD group			total sample
	%	%	OR	p-value*	%	OR	p-value	%	OR	p-value	%
<i>n</i>	457	280			116			80			933
Male gender	60,2	43,2	1,99	0,010	67,2	0,74	0,167	72,5	0,57	0,045	57,0
Smoker	10,3	7,1	0,67	0,187	5,2	0,48	0,106	2,5	0,22	0,021	8,0
ex-Smoker	26,5	33,6	0,80	0,406	22,4	1,40	0,045	18,8	0,64	0,164	27,4
APOE4 carrier	5,8	8,8	1,57	0,181	1,1	0,18	0,063	8,6	1,53	0,416	6,3
High triglycerides	21,1	22,1	0,06	0,778	14,0	0,61	0,105	20,0	0,93	1,000	20,5
Low HDL cholesterol	29,7	30,2	1,02	0,932	29,0	0,97	1,000	37,1	1,40	0,212	30,3
High LDL cholesterol	8,2	3,4	0,39	0,011	4,6	0,54	0,306	8,3	1,02	1,000	6,3
Hypercholesterolemia	40,0	36,4	0,86	0,350	38,8	0,95	0,833	27,5	0,57	0,034	37,7
Hyperglycemia	9,8	13,2	1,41	0,15	12,9	1,42	0,30	5,0	0,510	0,281	10,8
Dyslipidemia	34,4	32,6	0,92	0,688	34,5	1,01	1,000	20,3	0,49	0,013	32,7
Inflammation	22,7	28,2	1,34	0,106	24,1	1,08	0,799	33,3	1,70	0,055	25,4
Hypertension	77,2	74,6	0,87	0,424	82,8	1,41	0,210	62,5	0,49	0,007	75,9
Diabetes	17,5	21,8	1,31	0,177	23,3	1,43	0,182	12,5	0,67	0,331	19,1
Coronary heart disease	9,4	9,3	0,99	1,000	12,2	1,33	0,385	2,5	0,25	0,046	9,1
Previous TIA/stroke	4,4	11,4	2,82	0,527	8,7	2,08	0,097	11,3	2,77	0,027	7,6
Atrial Fibrillation	5,3	8,2	1,61	0,122	10,3	2,07	0,054	7,7	1,49	0,423	7,0
Obesity	48,3	45,5	0,89	0,491	53,2	1,21	0,397	31,6	0,49	0,009	46,7
MetS	34,2	36,3	1,10	0,623	32,4	0,92	0,818	25,8	0,67	0,207	33,9

*Pearson χ^2 . Abbreviations: NC= subjects with normal cognition; AD= Alzheimer's disease; aMCI= amnesic mild cognitive impairment; naMCI= non amnesic mild cognitive impairment; HDL= high density lipoprotein; LDL= low density lipoprotein; MetS= Metabolic syndrome; CRPL3= C-reactive Protein.

3.2 Relationship between vascular risk factors and cognitive decline

Association between VRF and outcome of aMCI, naMCI or AD (vs NC) was evaluated by logistic regressions sequentially implemented with various possible single confounders. These confounders included age, education and depression cut-offs, APOE4 carrier, inflammation, undernutrition, sex and a mixture of the previous.

Convergence criterion of all logistic regressions performed for all diagnoses were always satisfied. All logistic regressions were also constructed for people younger than 85 years and results were very similar to those constructed with the completely eligible cohort. Akaike information criterion (AIC) was on average lower for logistic regressions computed for AD (range: 81.3-163.3, Table 4) compared to naMCI (range: 266.9-321.9) and aMCI (range: 444.2-543.9). In general, model 8 and 10 better fitted the data of all the diagnoses compared of other models. Model 8 and 10 taken into account a stratification for inflammation, undernutrition and high levels of depressive symptoms and the presence or not, respectively, of APOE4 as covariates.

The most efficient AIC minimization by varying 1-single confounders (models 1 to 7, Table 4) occurred with High Level of Depressive Symptoms in all diagnoses. Addition of multiple confounders (models 8 to 11) further increased the goodness-of-fit of the model of each outcome.

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Logistic regressions built for AD (Table 5a) retrieved very few VRF as determinants and none of these were constantly confirmed in all the regression models. In particular, Hypertension was confirmed in Models 7 and 10, and waist circumference in model 11. Mets, Framingham general CVD risk profile, and LOAD score were confirmed in many models including both single and combined covariates. CAIDE risk score almost constantly captured the occurrence of contracting AD.

When studying the occurrence of aMCI (table 5b), low HDL cholesterol and LOAD risk score were almost constantly confirmed, with the exception of Model 11. In particular, LOAD scores showed high degrees of confidence with the associations (p ranging from 0.02 to <0.001 from models 1 to 10 and p=0.09 in model 11).

Association of VRF and naMCI at varying the stratifier of the subpopulation showed lesser regressors of the occurrence of AD or aMCI (table 5c). In particular, smoke was associated (at p<0.05) in models 7, 8 and 10, all of them take into account the high level of depressive symptoms. Framingham stroke risk profile was similarly tightly associated with the risk of occurrence of naMCI.

Table 4. Akaike information criterion (AIC) of each model retained in present study. AIC measures the goodness-of-fit of each model to the data used and aim of the analysis. The lower the AIC, the higher the goodness-of-fit.

	<i>Stratification for</i>	aMCI	naMCI	AD
Model 1	Age (>75 yr)	541,1	313,9	152,3
Model 2	Education (<5 yr)	543,4	314,9	163,0
Model 3	APOE4	543,9	320,9	163,3
Model 4	Inflammation	541,5	321,9	161,7
Model 5	Undernutrition	533,7	316,1	122,8
Model 6	Sex	532,2	322,0	162,9
Model 7	High level of Depressive Symptoms	503,0	308,6	120,8
Model 8	APOE4, inflammation, undernutrition and High level of Depressive Symptoms	444,2	266,9	81,3
Model 9	Genetic factors (APOE4, sex)	522,8	314,7	157,5
Model 10	Modifiable factors (inflammation, undernutrition and High level of Depressive Symptoms)	461,5	275,0	84,0
Model 11	Sex, Age (>75 yr) and Education (<5 yr)	504,3	284,2	131,7

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Table 5a. p-values of association between VRF and AD.

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9	Model 10	Model 11
Diabetes	0,10	0,32	0,27	0,34	0,62	0,31	0,58	0,91	0,24	0,85	0,11
Hypertension	0,23	0,19	0,24	0,17	0,07	0,26	0,02*	0,08	0,25	0,04*	0,22
Hypercholesterolemia	0,87	0,76	0,64	0,75	0,55	0,75	0,13	0,28	0,65	0,22	0,87
High LDL cholesterol	0,66	0,35	0,25	0,28	0,33	0,28	0,10	0,24	0,27	0,14	0,78
Low HDL cholesterol	0,28	0,26	0,25	0,28	0,16	0,26	0,72	0,46	0,21	0,53	0,17
High triglycerides	0,79	0,89	0,90	0,87	0,76	0,94	0,60	0,54	0,85	0,37	0,52
Obesity	0,18	0,11	0,08	0,08	0,06	0,10	0,96	0,31	0,14	0,38	0,41
Waist circumference	0,11	0,18	0,21	0,23	0,23	0,22	0,41	0,75	0,30	0,46	0,03*
Coronary heart disease	0,99	0,99	0,99	0,99	0,99	0,99	0,99	1,00	0,99	1,00	0,99
Atrial Fibrillation	0,17	0,07	0,07	0,07	0,07	0,07	0,99	0,99	0,09	0,99	0,16
Previous TIA/stroke	0,16	0,17	0,23	0,17	0,47	0,22	1,00	1,00	0,36	1,00	0,12
MetS	0,07	0,02*	0,03*	0,02*	0,03*	0,02*	0,20	0,12	0,03*	0,10	0,05*
Ex-Smoker and/or Smoker	0,87	0,69	0,75	0,57	0,95	0,62	0,53	0,89	0,93	0,89	0,88
Framingham general CVD risk profile	0,004*	0,007*	0,005*	0,008*	0,35	0,02*	0,37	0,88	0,02*	0,98	0,01*
Framingham stroke risk profile	0,63	0,12	0,10	0,13	0,67	0,12	0,02*	0,46	0,16	0,36	0,74
CAIDE risk score	0,002*	0,002*	0,001*	0,001*	0,001*	0,002*	0,08	0,04*	0,002*	0,05*	0,02*
LOAD risk score	0,36	0,01*	0,007*	0,005*	0,22	0,006*	0,39	0,81	0,01*	0,98	0,54

Table 5b. p-values of association between VRF and aMCI.

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9	Model 10	Model 11
Diabetes	0,80	0,58	0,59	0,50	0,32	0,93	0,43	0,29	0,98	0,26	0,80
Hypertension	0,65	0,52	0,56	0,53	0,51	0,68	0,51	0,49	0,69	0,39	0,63
Hypercholesterolemia	0,89	0,87	0,98	0,99	0,76	0,85	0,89	0,87	0,90	0,99	0,72
High LDL cholesterol	0,06	0,08	0,08	0,08	0,07	0,18	0,16	0,07	0,18	0,08	0,16
Low HDL cholesterol	0,03*	0,03*	0,02*	0,02*	0,04*	0,07	0,005*	0,02*	0,07	0,02*	0,09
High triglycerides	0,54	0,61	0,65	0,74	0,64	0,51	0,83	0,64	0,53	0,66	0,40
Obesity	0,99	0,93	0,91	0,97	0,70	0,77	0,60	0,29	0,77	0,34	0,49
Waist circumference	0,50	0,45	0,53	0,56	0,56	0,48	0,61	0,64	0,53	0,65	0,39
Coronary heart disease	0,56	0,63	0,66	0,60	0,86	0,60	0,38	0,76	0,56	0,66	0,69
Atrial Fibrillation	0,14	0,31	0,32	0,20	0,37	0,82	0,44	0,44	0,90	0,54	0,66
Previous TIA/stroke	0,60	0,65	0,78	0,72	0,95	0,91	0,97	0,97	0,97	0,83	0,76
MetS	0,29	0,42	0,37	0,33	0,45	0,29	0,12	0,15	0,28	0,15	0,23
Ex-Smoker and/or Smoker	0,17	0,14	0,14	0,20	0,10	0,85	0,49	0,22	0,87	0,37	0,93
Framingham general CVD risk profile	0,53	0,39	0,50	0,39	0,20	0,08	0,34	0,37	0,07	0,23	0,09
Framingham stroke risk profile	0,07	0,27	0,22	0,18	0,10	0,81	0,15	0,11	0,73	0,10	0,77
CAIDE risk score	0,51	0,94	0,55	0,59	0,48	0,74	0,65	0,43	0,74	0,47	0,52
LOAD risk score	0,02*	0,01*	0,002*	<0,001*	0,003*	<0,001*	0,001*	0,007*	0,002*	0,007*	0,09

* Values in bold are significant at $p < 0.05$. **Model 1** adjusted for age (>75 years old). **Model 2** adjusted for education (<5 years). **Model 3** adjusted for APOE4. **Model 4** adjusted for inflammation. **Model 5** adjusted for undernutrition. **Model 6** adjusted for sex. **Model 7** adjusted for High level of Depressive Symptoms. **Model 8** adjusted for APOE4, inflammation, undernutrition and High level of Depressive Symptoms. **Model 9** adjusted APOE4 and sex. **Model 10** adjusted for inflammation, undernutrition and High level of Depressive Symptoms. **Model 11** adjusted for sex, education (<5 years) and age (>75 years old). Abbreviations: NC= subjects with normal cognition; AD= Alzheimer's disease; aMCI= amnesic mild cognitive impairment; naMCI= non amnesic mild cognitive impairment.

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Table 5c. *p*-values of association between VRF and naMCI.

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9	Model 10	Model 11
Diabetes	0,91	0,60	0,49	0,59	0,45	0,52	0,71	0,42	0,41	0,49	0,88
Hypertension	0,35	0,23	0,29	0,31	0,26	0,21	0,37	0,14	0,20	0,15	0,29
Hypercholesterolemia	0,29	0,16	0,21	0,27	0,26	0,28	0,26	0,36	0,25	0,36	0,15
High LDL cholesterol	0,39	0,49	0,37	0,46	0,27	0,37	0,46	0,16	0,30	0,21	0,46
Low HDL cholesterol	0,99	0,64	0,73	0,72	0,70	0,62	0,86	0,97	0,64	0,93	0,86
High triglycerides	0,57	0,81	0,55	0,55	0,69	0,55	0,72	0,78	0,52	0,90	0,72
Obesity	0,31	0,18	0,38	0,35	0,29	0,37	0,51	0,60	0,39	0,58	0,15
Waist circumference	0,52	0,33	0,57	0,52	0,39	0,54	0,36	0,45	0,57	0,32	0,30
Coronary heart disease	0,97	0,97	0,95	0,96	0,95	0,68	0,74	0,78	0,71	0,74	0,78
Atrial Fibrillation	0,96	0,51	0,67	0,73	0,70	0,94	0,46	0,79	0,88	0,70	0,85
Previous TIA/stroke	0,78	0,71	0,80	0,88	0,84	0,75	0,63	0,50	0,71	0,49	0,66
MetS	0,83	0,66	0,54	0,67	0,63	0,55	0,41	0,55	0,49	0,52	0,75
Ex-Smoker and/or Smoker	0,10	0,20	0,06	0,07	0,13	0,23	0,04*	0,04*	0,16	0,04*	0,52
Framingham general CVD risk profile	0,86	0,65	0,70	0,85	0,64	0,40	0,93	0,54	0,37	0,61	0,87
Framingham stroke risk profile	0,19	0,009*	0,02*	0,02*	0,03*	0,09	0,02*	0,03*	0,09	0,02*	0,26
CAIDE risk score	0,73	0,46	0,83	0,91	0,97	0,70	0,72	0,88	0,68	0,82	0,65
LOAD risk score	0,56	0,78	0,27	0,41	0,47	0,37	0,32	0,42	0,25	0,54	0,31

* Values in bold are significant at $p < 0.05$. **Model 1** adjusted for age (>75 years old). **Model 2** adjusted for education (<5 years). **Model 3** adjusted for APOE4. **Model 4** adjusted for inflammation. **Model 5** adjusted for undernutrition. **Model 6** adjusted for sex. **Model 7** adjusted for High level of Depressive Symptoms. **Model 8** adjusted for APOE4, inflammation, undernutrition and High level of Depressive Symptoms. **Model 9** adjusted APOE4 and sex. **Model 10** adjusted for inflammation, undernutrition and High level of Depressive Symptoms. **Model 11** adjusted for sex, education (<5 years) and age (>75 years old). Abbreviations: NC= subjects with normal cognition; AD= Alzheimer's disease; aMCI= amnesic mild cognitive impairment; naMCI= non amnesic mild cognitive impairment.

3.2.1 Odd ratios of occurrence of cognitive decline by Framingham cardiovascular algorithms and dementia risk scores

Odd ratios of CAIDE risk score for AD were highly significant for almost all models and ranged, on average, between 1.20 and 1.49 (table 6a). When not significant (model 7) its confidence limits were 0.98-1.48, nearly approaching significance ($p=0.08$). In this latter model, Framingham stroke risk profile appeared significantly and positively associated with occurrence of AD. Despite being higher than 1, Framingham stroke risk profile OR in the other models were not clearly associated with occurrence of AD.

RESULTS

Table 6a. Association between each of Framingham cardiovascular risk algorithms, CAIDE risk score Model 1, LOAD risk score and AD occurrence

	Framingham general CVD risk profile		Framingham stroke risk profile		CAIDE risk score		LOAD risk score	
	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
Model 1	0,004	0,88 (0,81 - 0,96)	0,625	1,15 (0,66 - 2,01)	0,002	1,34 (1,11 - 1,62)	0,360	1,04 (0,95 - 1,14)
Model 2	0,007	0,90 (0,83 - 0,97)	0,116	1,53 (0,90 - 2,60)	0,002	1,32 (1,11 - 1,58)	0,013	1,11 (1,02 - 1,21)
Model 3	0,005	0,89 (0,81 - 0,96)	0,103	1,56 (0,92 - 2,66)	0,001	1,34 (1,12 - 1,59)	0,007	1,12 (1,03 - 1,22)
Model 4	0,008	0,90 (0,83 - 0,97)	0,134	1,50 (0,88 - 2,56)	0,001	1,35 (1,13 - 1,61)	0,005	1,13 (1,04 - 1,23)
Model 5	0,349	0,95 (0,86 - 1,05)	0,672	1,15 (0,61 - 2,16)	0,001	1,49 (1,18 - 1,89)	0,218	1,06 (0,96 - 1,17)
Model 6	0,022	0,89 (0,80 - 0,98)	0,124	1,58 (0,88 - 2,82)	0,002	1,33 (1,11 - 1,59)	0,006	1,12 (1,03 - 1,22)
Model 7	0,366	0,95 (0,86 - 1,06)	0,024	2,26 (1,11 - 4,59)	0,085	1,20 (0,98 - 1,48)	0,391	1,04 (0,95 - 1,15)
Model 8	0,880	1,01 (0,88 - 1,16)	0,463	1,37 (0,59 - 3,17)	0,041	1,38 (1,01 - 1,88)	0,806	1,02 (0,89 - 1,17)
Model 9	0,020	0,88 (0,80 - 0,98)	0,161	1,51 (0,85 - 2,69)	0,002	1,33 (1,11 - 1,59)	0,010	1,11 (1,03 - 1,21)
Model 10	0,982	1,00 (0,88 - 1,14)	0,363	1,49 (0,63 - 3,48)	0,049	1,35 (1,00 - 1,82)	0,977	1,00 (0,88 - 1,13)
Model 11	0,011	0,87 (0,78 - 0,97)	0,739	1,12 (0,59 - 2,11)	0,024	1,27 (1,03 - 1,55)	0,539	1,03 (0,94 - 1,13)

Values in bold are significant at $p < 0.05$. **Model 1** adjusted for age (>75 years old). **Model 2** adjusted for education (<5 years). **Model 3** adjusted for APOE4. **Model 4** adjusted for inflammation. **Model 5** adjusted for undernutrition. **Model 6** adjusted for sex; **Model 7** adjusted for High level of Depressive Symptoms. **Model 8** adjusted for APOE4, inflammation, undernutrition and High level of Depressive Symptoms. **Model 9** adjusted APOE4 and sex. **Model 10** adjusted for inflammation, undernutrition e High level of Depressive Symptoms. **Model 11** adjusted for sex, education (<5 years) and age (>75 years old). Abbreviations: NC= subjects with normal cognition; AD= Alzheimer’s disease; aMCI= amnesic mild cognitive impairment; naMCI= non amnesic mild cognitive impairment; CVD= cardiovascular disease

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Table 6b. Association between each of Framingham cardiovascular risk algorithms, CAIDE risk score Model 1, LOAD risk score and aMCI occurrence

	Framingham general CVD risk profile		Framingham stroke risk profile		CAIDE risk score		LOAD risk score	
	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
Model 1	0,533	1,01 (0,98 - 1,05)	0,067	0,73 (0,52 - 1,02)	0,508	1,03 (0,94 - 1,13)	0,022	1,05 (1,01 - 1,09)
Model 2	0,387	1,02 (0,98 - 1,05)	0,268	0,84 (0,61 - 1,15)	0,944	1,00 (0,91 - 1,11)	0,011	1,05 (1,01 - 1,09)
Model 3	0,504	1,01 (0,98 - 1,05)	0,224	0,82 (0,60 - 1,13)	0,549	1,03 (0,94 - 1,12)	0,002	1,06 (1,02 - 1,10)
Model 4	0,390	1,02 (0,98 - 1,05)	0,183	0,81 (0,59 - 1,11)	0,594	1,02 (0,94 - 1,12)	0,001	1,06 (1,02 - 1,10)
Model 5	0,199	1,02 (0,99 - 1,06)	0,099	0,76 (0,55 - 1,05)	0,479	1,03 (0,94 - 1,13)	0,003	1,06 (1,02 - 1,09)
Model 6	0,085	0,96 (0,91 - 1,01)	0,805	1,04 (0,74 - 1,47)	0,742	0,99 (0,90 - 1,08)	0,001	1,06 (1,03 - 1,10)
Model 7	0,342	1,02 (0,98 - 1,06)	0,147	0,77 (0,55 - 1,09)	0,646	1,02 (0,93 - 1,12)	0,001	1,06 (1,02 - 1,10)
Model 8	0,367	1,02 (0,98 - 1,06)	0,111	0,75 (0,52 - 1,07)	0,432	1,04 (0,94 - 1,15)	0,008	1,05 (1,01 - 1,09)
Model 9	0,074	0,96 (0,91 - 1,00)	0,735	1,06 (0,75 - 1,50)	0,744	0,99 (0,90 - 1,08)	0,002	1,06 (1,02 - 1,10)
Model 10	0,229	1,02 (0,99 - 1,06)	0,098	0,74 (0,52 - 1,06)	0,466	1,04 (0,94 - 1,14)	0,007	1,05 (1,01 - 1,09)
Model 11	0,086	0,96 (0,91 - 1,01)	0,766	0,95 (0,65 - 1,38)	0,523	0,97 (0,87 - 1,07)	0,091	1,04 (0,99 - 1,08)

Values in bold are significant at $p < 0.05$. **Model 1** adjusted for age (>75 years old). **Model 2** adjusted for education (<5 years). **Model 3** adjusted for APOE4. **Model 4** adjusted for inflammation. **Model 5** adjusted for undernutrition. **Model 6** adjusted for sex; **Model 7** adjusted for High level of Depressive Symptoms. **Model 8** adjusted for APOE4, inflammation, undernutrition and High level of Depressive Symptoms. **Model 9** adjusted APOE4 and sex. **Model 10** adjusted for inflammation, undernutrition e High level of Depressive Symptoms. **Model 11** adjusted for sex, education (<5 years) and age (>75 years old). Abbreviations: NC= subjects with normal cognition; AD= Alzheimer’s disease; aMCI= amnesic mild cognitive impairment; naMCI= non amnesic mild cognitive impairment; CVD= cardiovascular disease

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Table 6c. Association between each of Framingham cardiovascular risk algorithms, CAIDE risk score Model 1, LOAD risk score and naMCI occurrence

	Framingham general CVD risk profile		Framingham stroke risk profile		CAIDE risk score		LOAD risk score	
	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
Model 1	0,864	1,00 (0,94 - 1,05)	0,190	1,28 (0,89 - 1,84)	0,731	1,02 (0,90 - 1,16)	0,557	0,98 (0,93 - 1,04)
Model 2	0,647	1,01 (0,96 - 1,07)	0,009	1,60 (1,12 - 2,26)	0,458	0,95 (0,83 - 1,09)	0,779	0,99 (0,94 - 1,05)
Model 3	0,704	1,01 (0,96 - 1,06)	0,020	1,51 (1,07 - 2,13)	0,830	1,01 (0,89 - 1,15)	0,270	1,03 (0,98 - 1,08)
Model 4	0,849	1,01 (0,96 - 1,06)	0,017	1,52 (1,08 - 2,13)	0,907	1,01 (0,89 - 1,14)	0,411	1,02 (0,97 - 1,07)
Model 5	0,641	1,01 (0,96 - 1,07)	0,027	1,48 (1,05 - 2,09)	0,970	1,00 (0,88 - 1,14)	0,467	1,02 (0,97 - 1,07)
Model 6	0,402	1,03 (0,96 - 1,10)	0,092	1,39 (0,95 - 2,03)	0,698	1,03 (0,90 - 1,17)	0,368	1,02 (0,97 - 1,07)
Model 7	0,926	1,00 (0,95 - 1,06)	0,021	1,52 (1,07 - 2,16)	0,715	1,02 (0,90 - 1,16)	0,317	1,03 (0,98 - 1,08)
Model 8	0,539	1,02 (0,96 - 1,07)	0,031	1,49 (1,04 - 2,13)	0,876	1,01 (0,88 - 1,16)	0,417	1,02 (0,97 - 1,08)
Model 9	0,369	1,03 (0,97 - 1,10)	0,089	1,40 (0,95 - 2,05)	0,680	1,03 (0,90 - 1,17)	0,246	1,03 (0,98 - 1,08)
Model 10	0,612	1,01 (0,96 - 1,07)	0,024	1,51 (1,06 - 2,15)	0,823	1,02 (0,89 - 1,16)	0,542	1,02 (0,97 - 1,07)
Model 11	0,867	1,01 (0,94 - 1,08)	0,260	1,27 (0,84 - 1,94)	0,646	0,97 (0,83 - 1,12)	0,312	0,97 (0,91 - 1,03)

Values in bold are significant at $p < 0.05$. **Model 1** adjusted for age (>75 years old). **Model 2** adjusted for education (<5 years). **Model 3** adjusted for APOE4. **Model 4** adjusted for inflammation. **Model 5** adjusted for undernutrition. **Model 6** adjusted for sex; **Model 7** adjusted for High level of Depressive Symptoms. **Model 8** adjusted for APOE4, inflammation, undernutrition and High level of Depressive Symptoms. **Model 9** adjusted APOE4 and sex. **Model 10** adjusted for inflammation, undernutrition e High level of Depressive Symptoms. **Model 11** adjusted for sex, education (<5 years) and age (>75 years old). Abbreviations: NC= subjects with normal cognition; AD= Alzheimer’s disease; aMCI= amnesic mild cognitive impairment; naMCI= non amnesic mild cognitive impairment; CVD= cardiovascular disease

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LOAD risk score was positively, but not constantly across models, associated with occurrence of AD. On the contrary, Framingham general CVD risk profile was in general inversely associated with AD occurrence, showing ORs in general lower than 1.

As previously suggested, association of Framingham cardiovascular algorithms and dementia risk scores with occurrence of aMCI (table 6b) was clearly detectable for LOAD risk score only. For this score, ORs were slightly above 1 (mean ORs=1.1, mean lower confidence interval=1.02, mean upper confidence interval=1.09). Distribution of the ORs of CAIDE risk score and Framingham general CVD risk profile was near, but not significantly, to values higher than 1, whereas Framingham stroke risk profile distributions were strongly overlapping the ‘no odd’ (i.e. OR=1) threshold.

In contrast to aMCI, Framingham stroke risk profile was the sole algorithm associated with occurrence of naMCI (table 6c). Such association was showed a mean OR of 1.45 across models (mean lower confidence interval=1.01, mean upper confidence interval=2.10). However, such association was not significant in all models. The other algorithms were not associated to occurrence of naMCI.

3.2.2 Diagnoses discrimination by dimension-reduction of VRF

A strong separation of the outcomes occurred after summarizing the variability of the VRF in the canonical discriminant analysis (CDA, Table 7 and Fig. 8), which clearly separated each treatment from any other with the exception of aMCI to naMCI and naMCI to NC.

Table 7. Results of the canonical discriminant analysis: above diagonal, *F* statistic (NDF=14, DDF=833); below diagonal, *p*> Mahalanobis distance per each pair.

	<i>AD</i>	<i>aMCI</i>	<i>naMCI</i>	<i>NC</i>
<i>AD</i>		2.48*	2.34	2.41
<i>aMCI</i>	0.002		1.29	2.07
<i>naMCI</i>	0.004	0.209		1.50
<i>NC</i>	0.003	0.011	0.104	

**F* and *p* in bold are significant at $p < 0.05$

In total, only 3 canonical axes were built, and only the first (CA1) and second (CA2) axis were found to be significantly different than zero: CA1 explained 44.1% ($F=1.98$, NDF=42, DDF=2472, $p=0.0002$) of the variability of the VRF, CA2 explained 35.1% ($F=1.79$, NDF=26, DDF=1668, $p=0.009$) of the total variance.

Hypertension, High LDL cholesterol, MetS, and Smoker influenced both the CA1 and CA2 (with the absolute values of their standardized canonical coefficient [SCC] higher than 0.28 for CA1 and 0.18 for CA2. Low HDL cholesterol and obesity strongly influenced the CA1 (SCC= - 0.49 and SCC= +0.50), whereas previous TIA/stroke strongly influenced CA2 (SCC= -0.68).

Previous TIA/stroke, diabetes, waist circumference, high triglycerides, AF or being an ex-smoker mostly separated AD or aMCI subjects compared to NC. Out of these latter traits, diabetes, AF and being an ex-smoker along with obesity and a cluster of MetS, Hypercholesterolemia, Hypertension and experience of coronary hearth diseases contributed to separate (on the CA1) the AD from aMCI or naMCI.

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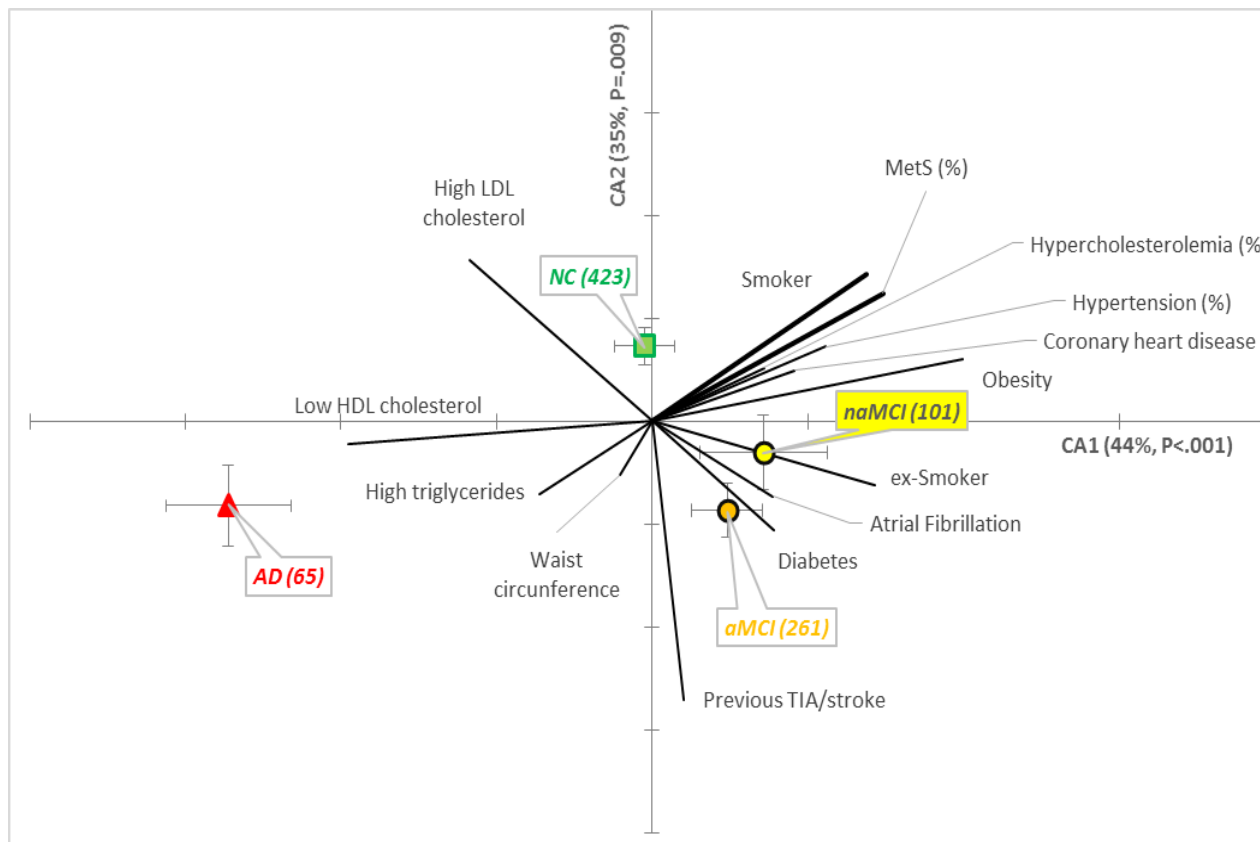


Fig. 8. Biplot of the CDA run using dichotomous VRF. The percentage of the total variance explained by each canonical axis is shown in parentheses. Subjects used were categorized as normal cognitive (NC, green square, number of subject per each diagnoses are showed in parentheses), non-amnesic mild cognitive impaired (naMCI, yellow circle), amnesic mild cognitive impaired (aMCI, orange circle), and Alzheimer's disease affected (AD, red triangle). Data of diagnoses are presented as centroid \pm S.E. Bold lines starting from '0;0' represent the vectors of each VRF. Projection of the length of each vector on each canonical axis is proportional to its contribution in distinguishing the diagnoses. Please note that CDA vectors do not represent perpendicular directions through the space of the original variables. Unit of measure of CA1 and CA2 are the same (0.25 in 'canonical correlation' score).

4 DISCUSSION

4.1 *Summary of main Finding*

In this work, the association between isolated and/or clustered VRF/diseases and the spectrum of cognitive decline were investigated, in particular mild cognitive impairment (MCIs) and Alzheimer's disease (AD). Such analysis was performed on a rural, low-educated population of Sicilian inland, Italy. The following results were found, including:

- diagnosis of previous TIA/stroke in late-life was associated with a 2.7-fold higher risk of developing AD among subjects aged 60 or older;
- diagnosis of atrial fibrillation in late-life had a 2 fold increased risk of naMCI, whereas no association was found with AD and aMCI;
- inverse association of blood pressure and diagnosis of hypertension was associated to AD risk in late-life and this remained unchanged after adjustments for high level of depressive symptoms (model 7) and inflammation, undernutrition and high level of depressive symptoms (Model 10);
- inverse association of BMI and Obesity with AD risk in late-life; in addition, undernutrition in late-life was associated to a 37.7 fold risk of AD, 2.4 fold risk of aMCI and 2.3 fold risk of naMCI;
- inverse association of diagnosis of Hypercholesterolemia with AD risk in late-life;
- a reverse relationship of presence of low level HDL cholesterol with aMCI in elderly;
- no association of MeTs with cognitive decline among subjects aged 60 or older; in addition, there is a reverse relationship with AD after controlling for education, APOE4, inflammation, undernutrition, sex and genetic factors (APOE and sex);
- high risk scores of the Framingham CVD risk profile with an increased risk of aMCI, and this association whose not retained after stratifications.
- high risk scores of the Framingham Stroke risk profile with an increased risk of naMCI and AD; in naMCI, this remained unchanged after adjustments for some possible single confounders examined and a combination of the previous; in AD, this association remained unchanged after controlling only for High level of Depressive Symptoms and high risk scores of the Framingham Stroke risk profile was associated to a 2.3-fold higher risk of developing AD;
- high risk scores of the CAIDE risk score Model 1 with an increased risk of AD, and this remained unchanged after adjustments for all possible single confounders examined, except of High level of Depressive Symptoms, and a combination of the previous.
- high risk scores of the LOAD risk score with an increased risk of cognitive decline and AD; in aMCI, this remained unchanged after adjustments for all possible single confounders examined and a mixture of the previous, except for Model 11 (sex, education and age); in AD,

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this remained unchanged after stratification for education, APOE4, inflammation and sex, and genetic factors (APOE and sex).

4.2 Population under study

The strengths of this study included the characteristics of the cohort, which was made of individuals aged 60 or older with distinctive features, including low education and living in a rural little town. Studies which evaluated the relationship between VRF and dementia conducted in rural populations are rather few (Tola-Arribas et al. 2013; Ji et al. 2015).

In epidemiology, there are possible clustered environmental exposures which are linked to different geographical areas and which are associated with the disease. In the present study, living in a rural area may result in the exposure to different risk or protective factors for cognitive decline compared to subjects who live in urban areas. This may have important repercussions on the public health course and management.

Definitions of ‘rurality’ is heterogeneous in health research. Indeed, definitions of rurality vary widely in several reports and some of them do not mention how areas were defined as ‘rural’ (Russ et al. 2012). In a study performed in Japan, an administrative unit was defined as ‘rural’ if its population numbered less than 30.000 inhabitants (Imaizumi 1992). Rural areas were defined ‘by low population density, and traditional agrarian lifestyle’ by the 10/66 dementia research group (Prince et al. 2007). The IMAGE project defined a rural area as containing villages rather than cities (Russ et al. 2012).

Indeed, a definition of the concept of rurality perfectly fitting with the aim of epidemiological studies is difficult to trace, and the epidemiological importance resides in characteristic contrasting to the urban areas: population density, access to health services and factors conducive to a healthy lifestyle, including air pollution.

According to these features the community of Sambuca di Sicilia (Agrigento province, Italy) can definitely be defined rural. It is located in the inland of Sicily, about 68 km southwest of Palermo and the northern coast and about 89 km northwest of Agrigento, which is in the southern coast. It had a population of 6207 inhabitants (data at December 2010). The local economy is mainly agricultural and pastoral.

A relatively low education degree is a normal connotation of such a kind of rural populations, especially in older people. The Sambuca’s population included in the ZAP has an average education of about five years (i.e. only primary school under the Italian laws). In particular, the subjects within the diagnostic groups (AD and MCIs) have an average number of years of schooling lower if compared to NC. It was suggested that individuals with low levels of education have an increased risk of dementia (Evans et al. 1997; Letenneur et al. 1999; Ott et al. 1999; Geerlings et al. 1999). The inverse relationship between formal education and cognitive decline could be explained in three ways: 1) the “brain reserve” hypothesis states that education has a protective effect because it enhances the structural cognitive assets (number of neuronal cells, or density of connections) and greater physiopathological changes are needed to exceed the threshold for dementia. It could be linked to innate factors or due to factors in the early years of life (Fratiglioni et al. 1991; Katzman 1993; Stern et al. 1995). 2) the “cognitive reserve” hypothesis is a functional version of the first. It hypothesizes that brain’s ability to use brain networks more efficiently or to recruit alternative networks in the face of brain damage (Stern 2002). The alternative to the idea of reserve against brain damage is the ‘brain

battering' hypothesis. According to this theory, individuals with greater educational attainment and associated higher socio-economic status would be exposed to fewer toxins, enjoy a healthier lifestyle and have greater access to quality health care. These conditions could lead a reduction of brain lesions contributing to dementia (Ser et al. 1999).

Limitations of this study include its cross-sectional design and the lack of comprehensive data regarding the VRF in midlife collected at baseline. Consequently, it was not possible to address the question of whether VRF isolated or in cluster can be used to predict AD. In fact, in this study it is possible to evaluate an association between VRF and cognitive decline, but is impossible to describe the direction of this association (ie, if the exposure is identified before the outcome, thus contributing to the onset of the disease).

4.3 Prevalence of AD and MCI

The prevalence of AD (8%) in this population older than 60 years was slightly higher than those reported previously in Italy, which was about 6.6%, being estimated in the ILSA population older than 65 years (Di Carlo et al. 2002), whereas the prevalence of MCI (39.5%) is very higher if compared to that reported by using Mayo clinic criteria (18.9%) (Petersen et al. 2014). Nonetheless, a number of studies reported extremely variable prevalence of MCI at varying the characteristic of the population and location of the study (Lopez et al. 2003a; Purser JL, Fillenbaum GG, Pieper CF 2005; Busse et al. 2006; Di Carlo et al. 2007; Das et al. 2007; Ravaglia et al. 2008; Plassman et al. 2008; Manly et al. 2008; Palmer et al. 2008; Artero et al. 2008; Sasaki et al. 2009; Dlugaj et al. 2010; Ganguli et al. 2010; Petersen et al. 2010; Kim et al. 2011; Perquin et al. 2012). Thus, it is likely that several study traits (e.g. the age of the cohort) and conditions affecting lifestyle, including the rurality of the population, its degree of schooling, diet, and various other environmental traits can strongly affect the prevalence of both MCI and AD. The higher prevalence of MCI in this cohort is probably due to the fact that cognitive performance were corrected for Italian normative data collected mainly in urban areas, and this probably lead to an overestimation of the MCI occurrence in the ZAP. Indeed, a further step of our study will be to compute normative data from the ZAP using data from subjects without cognitive decline belonging to the same cohort. A study with more strict criteria for the impairment in each cognitive domain (eg, performance below cut-off in at least two test of the same domain will be mandatory for considering impaired the cognitive function in the case of single amnesic/non amnesic MCI) is being conducted (Monastero 2017). In this latter study, a preliminary analysis of the ZAP cohort in 300 individuals without dementia using these correction and cut-offs gave approximately 20-22% of overall MCI prevalence, thus in the range with previous studies reported above.

A recent rural/urban meta-analysis (Russ et al. 2012) suggested that rural living is associated with increased rates of AD, in particular early life rural living may have great effects on the outcome of the disease. The reasons for these variable rates are yet to be clarified. There are two possible explanations: that the strongest effect of rurality to certain risk factors can be depend on either the exposure early life or the duration of exposure (Russ et al. 2012).

Many socio-environmental risk factors are likely to have their effect on dementia risk early in life (Persson and Skoog 1996; Whalley et al. 2006; Norton et al. 2008). Indeed, the rural life is not in itself a risk factor for AD, but it could lead to exposure to risk factors linked to an unhealthy lifestyle

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(with the increase of metabolic/vascular burden) or to reduced access to health services. For this reason, any consideration of geographical variation of dementia must also include geographical variation of related conditions and risk factors, such as VRF. Regarding to MCI, no meta-analyses comparing rural vs. urban MCI diagnosis was found.

Furthermore, the increased prevalence of AD and MCI in this population could be related to the low educational level of the subjects underwent neuropsychological testing. Indeed, in this population, the protective factor represented by the high level of education it is rather negligible.

However, a diagnostic bias can be occurred. For example, Gilleard (1997) suggested that surveys of elderly poorly educated populations may lead to significant over-diagnosis of clinical dementia and a possible under-diagnosis of dementia could also occur in relatively well-educated populations. Such discrepancy are related to the fact that education promotes certain lifelong learning strategies through the development of forms of decontextualized thinking. These learned habits of 'thinking on demand' enable educated people to perform better in the neuropsychological test. Similarly, subjects with low level of formal education are usually less adaptable and competent to perform the tasks of neuropsychological and mental state tests. In addition, they exhibit less confidence and motivation during testing.

We attempted to limit the possibility of diagnostic bias resulting from the low level of education through the detailed diagnostic examinations with accurate analysis of the clinical history, the ADL and IADL of the cases that presented dementia from the neuropsychological testing. Regarding MCI, reducing diagnostic bias to reduce misdiagnosis was hard. It is not uncommon for older persons who are afraid of failing to partly or completely withdraw from the tests, or reject it, threatening to affect the result.

4.4 VRF

VRF and vascular disease are the leading cause of morbidity, disability and mortality worldwide, showing a continuously increasing trend. The population in this study has peculiar characteristics of the distribution of the prevalence of VRF comparing to the general Italian and global population¹. The frequency of some risk factors, such as hypertension, diabetes and obesity appears to be strongly increased compared to the global prevalence and the Italian one, whereas the prevalence of dyslipidemia and cholesterol levels are lower than those of the Italian population (Laccetti et al.; WHO 2009; Tragni et al. 2012).

The population in this study is comprised of subjects 60 years and older, with a high prevalence of VRF, thus results are to be interpreted in this context. Indeed, the prevalence of VRF in the present population is likely different than what reported here due to biases related to survival, and to changes in the measurement of risk factors with aging.

In the present study, only few VRF (AF, previous TIA/ Stroke) were associated with risk of AD or MCI. In contrast, no or inverse associations of different VRF with cognitive decline were found. In particular, the VRF for which an inverse relationship with AD was found are hypertension and blood

¹ data from WHO, Cholesterol and Health: Education, Control and Knowledge (CHECK), a cross-sectional observational study on the Italian adult population, and of the data from a community-wide screening program to promote healthy lifestyle ('Misuriamoci'), organized by the Italian Red Cross.

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pressure, hypercholesterolemia, obesity with relative BMI and waist circumference. These findings confirm the results by others (Romas et al. 1999; Tan et al. 2003; Mielke et al. 2005; Qiu et al. 2005; Solomon et al. 2007; Beydoun et al. 2008b; Fitzpatrick et al. 2009).

Indeed, HT during midlife is associated with later life cognitive impairment and dementia (Nagai et al. 2010), in particular AD (Skoog et al. 1996; Guo et al. 1996; Launer et al. 2000; Kivipelto et al. 2002; Qiu et al. 2003; Stewart et al. 2009). Pooled analysis suggested that mid-life hypertension was associated with a 60% increased risk of AD (Barnes and Yaffe 2011b). On contrary, the relationship of late-life blood pressure to AD is complex with an often-inverse relationship between blood pressure and AD risk (Qiu et al. 2005). This could be consequence of the disease process. In fact, blood pressure may be lowered before AD onset owing to dysregulation caused by neurodegeneration (Qiu 2012). Furthermore, among very old people the prevalence of orthostatic hypotension increased and may cause brain injury possibly by affecting cerebral blood perfusion (Guo et al. 1999; Ruitenberg et al. 2001; Verghese et al. 2003; Qiu et al. 2009). Also extremely low diastolic pressure (≤ 65 vs. 66–90 mm Hg) produced a relatively high risk for AD and for dementia (Qiu et al. 2003). The systematic reviews from a life-course perspective support an age-varying association of blood pressure with risk of AD (Qiu et al. 2005; Power et al. 2011).

Also for hypercholesterolemia, the age-varying association of AD with total cholesterol was supported by prospective cohort studies, systematic reviews and meta-analysis (Anstey et al. 2008; Shepardson et al. 2011). In fact, midlife hypercholesterolemia was associated with an increased risk of later life MCI or dementia (Kivipelto et al. 2001a; Dufouil et al. 2005; Panza et al. 2006; Solomon et al. 2007), in particular AD (Kivipelto et al. 2001a; Mielke et al. 2005). On contrary, as in the present study, an inverse association between total cholesterol and risk of AD is often reported when total cholesterol was evaluated in late-life (Romas et al. 1999; Tan et al. 2003; Mielke et al. 2005; Solomon et al. 2007). Furthermore, others showed that total cholesterol declines over the years before AD onset, suggesting that decreasing serum total cholesterol after midlife might be used as marker for prodromal dementia (Solomon et al. 2007).

Similar to blood pressure and hypercholesterolemia, long-term follow-up studies suggested that the association of obesity or BMI with AD risk varies in an age-dependent manner. Elevated BMI in mid-life was associated with a higher risk of dementia, whereas in late life (≥ 65 years), it was inversely related to AD risk (Beydoun et al. 2008b; Fitzpatrick et al. 2009). This reverse relationship is evident also in the present study. The meta-analysis of cohort studies detected a 40–60% increased risk of AD associated with obesity. This association was stronger in studies with a follow-up period longer than 10 years and younger age of obesity (Beydoun et al. 2008a; Profenno et al. 2010; Anstey et al. 2011).

Subjects with AD in the ZAP population tended to be slimmer than NC. Such a finding was also detected by other studies that have examined weight e BMI in people with dementia (Nourhashémi et al. 2003; Buchman et al. 2005; Stewart et al. 2005; Knopman et al. 2007). In addition, when evaluating the nutritional status, there is an association between undernutrition and increased risk of AD, and also between undernutrition and aMCI or naMCI. This result confirms the hypothesis that weight loss evident in dementias occurs during the preclinical phases for cognitive or behavioral changes, which in turn alters dietary habits. Furthermore, low BMI in late life and weight loss after middle age could be markers for the prodromic phase of dementia, as suggested by other studies (Nourhashémi et al. 2003; Launer et al. 2005).

No association was found in ZAP population between Mets and cognitive decline. Furthermore, in AD, an inverse association after adjustments for many possible single confounders examined and the

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combination of the previous was found. The present results are in contrast with evidences from another cross-sectional study conducted in central Finland, the Kuopio study. This population-based study on Finnish elderly subjects (aged 69 to 78 years) found that MetS increased the risk for AD, but only in women (Vanhanen et al. 2006). This association has been disconfirmed by large longitudinal and population based studies (Kalmijn et al. 2000; Solfrizzi et al. 2010). In addition, also several population-based follow-up studies of older adults found no association between MetS and AD (Muller et al. 2007; Raffaitin et al. 2009; Forti et al. 2010). It is likely that a cluster of multiple metabolic factors may not be major to its individual components in detecting the risk of AD in late life.

The results found here on the associations between AF and previous TIA/stroke agree with reports in literature. (Leys et al. 2005; ONTARGET 2008; Eggermont et al. 2012; Marzona et al. 2012; Thacker et al. 2013; Kalantarian et al. 2013; Udompanich et al. 2013). The present results suggest that diagnosis of AF in late-life had was associated with risk of a two-fold occurrence of naMCI. This agrees with many reports such as several systematic reviews and meta-analyses where an association between AF and cognitive impairment was identified (Eggermont et al. 2012; Kalantarian et al. 2013; Udompanich et al. 2013). A recent meta-analysis suggested that AF is associated with higher risk of cognitive impairment and dementia, in particular increase the risk by more than 40%, independently by a clinical stroke (Kalantarian et al. 2013). In late-life, it was seen that older adults without clinical stroke enrolled in the Cardiovascular Health Study had an accelerated global cognitive decline following onset of AF (Thacker et al. 2013). A post-hoc analysis of the large randomized controlled trials suggested that AF is associated with a higher risk of cognitive impairment even in the absence of stroke. In particular, it was found a 30% increased risk of cognitive decline and dementia among patients with AF (ONTARGET 2008; TRANSCEND 2008; Marzona et al. 2012).

Evidences from the population under study showed that diagnosis of previous TIA/stroke was associated to a 2.7-fold higher risk of developing AD in late-life. A review on community-based studies reported similar results, i.e. the presence of stroke doubled the risk of dementia (Leys et al. 2005). The possible mechanisms of interconnection between VRF, brain vascular injury and AD have already been discussed in the introduction section. A recent review (Qiu and Fratiglioni 2015) suggested that stroke could fit in the sequence of events over the life-course of an individual that leads from the VRF to dementia. According to this sequence, cumulative exposure to VRF from early life leads to vascular and neurodegenerative lesions in the brain which can onset in mid-life and continue to accumulate into old age where the stored lesions start to manifest clinically (Qiu and Fratiglioni 2015). Furthermore, systematic reviews of epidemiological studies highlighted that VRF present in childhood, young adulthood, and mid-life were associated with the development of CVD and late-life dementia (Whalley et al. 2006).

In support of this hypothesis, evidences from epidemiological studies showed that the mean age of onset for myocardial infarction was about 65 years, about 70 years for stroke, and about 85 years for dementia (Matthews et al. 2005; Goldenberg et al. 2008; Shiue 2011). The association between stroke and AD in the ZAP population could fit into this sequence of events, in which cumulative exposure to VRF (such as diabetes, hypertension, and smoking) from early life might lead to development stroke, and, in a following step to dementia. Unfortunately, this kind of hypothesis cannot be further investigated with the present data due to lack of comprehensive informations regarding the VRF in midlife in our cohort. However, if considering that VRF in late life are rarely found in isolation, and often coexist, an association between the risk of AD / MCI and the combination of multiple VRF (see section 4.5) was found.

4.5 Markers of Vascular burden

4.5.1 Framingham Cardiovascular Risk Algorithms

Framingham cardiovascular algorithms were developed to evaluate the association between the vascular burden and to predict different outcomes of the disease. Multivariable risk functions are commonly used to assess risk of specific atherosclerotic CVD events (CHD, cerebrovascular disease, peripheral vascular disease, and heart failure). For instance, the Framingham CVD risk profile was incorporated into the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001). On the contrary, the Framingham Stroke risk profile is designed for prediction of stroke and therefore does not cover the full range of potentially relevant cardiovascular diseases, such as myocardial infarction, coronary insufficiency, angina, and peripheral artery disease (Kaffashian et al. 2011).

Data collected in the ZAP population showed that high risk scores of the Framingham CVD risk profile was associated with an increased risk of aMCI, and high risk scores of the Framingham Stroke risk profile with an increased risk of naMCI and AD. However, the association between Framingham CVD risk profile and aMCI was not confirmed after controlling for various confounders. On the contrary, association between Framingham Stroke risk profile and naMCI was confirmed after adjustments for some possible single confounders examined and their combinations. Moreover, although the association between AD and Framingham Stroke risk profile was confirmed after adjustment only for high level of depressive symptoms, in which case high risk scores were associated with a 2.3-fold higher risk of developing AD.

Overall, Framingham Stroke risk profile appeared useful in the prediction/association of naMCI and AD, and this occurred despite this algorithm was initially derived to predict stroke. This suggests that the pathway from VRF to cognitive decline travels across cerebrovascular disease.

Other studies examined the utility of these risk scores to assess risk of cognitive impairment and dementia. Framingham cardiovascular risk algorithms were associated with cognitive decline and cognitive impairment. In particular, high scores to Framingham Cardiovascular Risk profile were associated with an accelerated decline in memory ability, processing speed, executive function, and global cognitive function (Elias et al.; Brady et al. 2001; Seshadri et al. 2004b; Llewellyn et al. 2008; Brandt and Rogerson 2011; Kaffashian et al. 2011; Reijmer et al. 2011; Unverzagt et al. 2011; Dregan et al. 2013; Kaffashian et al. 2013).

4.5.2 Dementia Risk Scores

Several composite risk scores focusing on prediction the risk of dementia were built: a score at mid-life and four scores at later life. Such risk scores used VRF as main measures to forecast the risk, with prediction accuracy ranging from 65% to 85 (Kivipelto et al. 2006a; Barnes et al. 2009; Reitz et al. 2010; Exalto et al. 2013; Anstey et al. 2014a; Exalto et al. 2014; Qiu and Fratiglioni 2015).

In the current study, a mid-life index, namely the CAIDE risk score, and a dementia risk score focusing on short-term prediction in the elderly, namely the LOAD risk score were evaluated.

Both of these scores can be easily computed in the general population, because the components included in their algorithms are primarily cardiovascular risk factors and are noninvasive, cheap, and easily attainable. Other indices were not computed in the present study because the scores included

DISCUSSION

magnetic resonance imaging abnormalities that, from the one hand, mirror the cumulative long-term impact of VRF on the brain, but, from the other hand, are not suitable for wide scale use in the general population. These scores could be used for dementia prediction in subjects drawn from memory clinic.

CAIDE risk score is the first scoring system for dementia and was formulated in 2006 based on the CAIDE study in Finland (Kivipelto et al. 2006b). Predictors in this score are simple, easy to assess, and provide a good possibility to predict the risk of dementia onset more than 20 years later. CAIDE dementia risk score was validated in separate cohort. Furthermore, additional variables were analyzed to improve the predictive value of the CAIDE, but these did not alter the validity of the CAIDE score (Exalto et al. 2011).

The score CAIDE was born for a mid-life population and were never been used in elderly. A study in late middle age showed that this score predict cognitive decline (Kaffashian et al. 2013). In the present population, such a score was used to assess the weight of VRF in different outcomes. Results indicated that high risk scores of the CAIDE were associated with an increased risk of AD, and this kept constant when stratifying for all possible single confounders examined, except with High level of Depressive Symptoms, and a combination of the previous.

Only ‘CAIDE risk score Model 1’ was used in logistic regression because ‘CAIDE risk score Model 2’ includes the presence/absence of APOE4 allele in its algorithm, which was already taken into account in the stratifications. Furthermore, in the study of Kivipelto et al. (2006a), inclusion of APOE status in a separate analysis (Model 2) did not significantly improve the predictive value of the score (Kivipelto et al. 2006a).

The risk score for Late Onset Alzheimer’s disease (LOAD) predicted dementia to four years in this elderly population and the probability of AD increased with a higher vascular risk score and a greater number of risk factors (Reitz et al. 2010). However, this score is very rarely used and hasn’t been validated in separate cohorts. Data of the present study showed that a high LOAD risk score was associated with an increased risk of MCIs and AD. Furthermore, after stratification, LOAD was still associated to aMCI and, in many adjustments, to AD.

The different associations found here among different outcomes and four scores used could be related to several factors. Firstly, each of these scores were developed to predict different outcomes. In addition, the different processes of development and validation of these scores (e.g the mean age and range of the populations used to build them) could affect such differences.

The inclusion of education in the dementia risk scores differentiated these risk scores from the Framingham cardiovascular algorithms, which are almost exclusively made up of VRF. As education is linked with cognitive performance and risk of dementia (Stern et al. 1994; Evans et al. 1997; Ngandu et al. 2007), but education level was not associated with the rate of cognitive decline (Karlamanla et al. 2009; Singh-Manoux et al. 2011). In this population, dementia risk scores were associated with AD risk also after stratification. This does not happen for Framingham Stroke risk profile (except in the Model 7). It is likely that the education component in the risk score affected this association, which was unchanged after adjustments. Furthermore, LOAD risk score was also associated with MCIs (only aMCI after adjustments). It is possible that differences in development and validation of the load score in elderly population would influenced these results.

Regarding the Framingham cardiovascular algorithms, that in this population were associated with MCIs, its exclusive VRF composition would have made them more sensitive for assessing subclinical cognitive decline (Kaffashian et al. 2013).

4.5.3 Summary of the Risk Scores

The present finding of an association between multiple VRF using risk scores, and different cognitive outcomes, suggested a possible cumulative effect of these VRF on cognition.

Indeed, individuals could be exposed to higher risk of cognitive impairment with the clustering of risk factors associated with the risk of dementia (Launer et al. 1995b; Kivipelto et al. 2005; Luchsinger et al. 2005; Xu et al. 2011). Several studies examined the importance of multiple vascular and cardiovascular risk factors by examining the collective effect of individual risk factors in relation to cognition (Kivipelto et al. 2001a; Kivipelto et al. 2001b; Kivipelto et al. 2005; Kivipelto et al. 2006a). Furthermore, a population study suggested that cumulative exposure to VRF in young adulthood (individuals aged 18–30 years) could reduce memory, processing speed, and executive skills (40–44 years) in those who had an increased summary score (PATHrisk) for VRF including smoking, hypertension, diabetes, obesity, and physical inactivity (Anstey et al. 2014b). Other population studies reported similar finding in individuals across all age ranges from young adulthood (Laughlin et al. 2011; Joosten et al. 2013; Virta et al. 2013; Warsch et al. 2013; Zeki Al Hazzouri et al. 2013; Qiu and Fratiglioni 2015). In addition, it was reported that the presence of multiple cardiovascular risk factors at midlife substantially increased the risk of dementia in old age irrespective of age, race, sex, and education (Whitmer et al. 2005a).

It is also likely that a wider range of risk factor categories in the risk scores would better catch the continuous nature of the risk (Kaffashian et al. 2013): from the one hand by allowing to distinguishing high levels of the risk factor; and from the other hand the higher risk imparted by multiple marginal risk factors, if compared to single VRF above threshold. From the pathophysiological point of view, the presence of multiple VRF, more than an isolated VRF, could potentially act on the decline process by the combination of different pathways with an additive or synergistic effect.

5 CONCLUSIONS

5.1 *Final overview*

The present study showed that several modifiable VRF at late-life were associated with risk of cognitive decline. Few single VRF collected at late life can be associated to increased risk of cognitive impairment and AD. In summary, only AF was clearly associated with risk of cognitive impairment, in particular with naMCI. Previous TIA/Stroke was associated to almost three-fold higher risk of developing AD in late-life. Conversely, an inverse association of hypertension and blood pressure, hypercholesterolemia, obesity with relative BMI and waist circumference with AD was found.

Furthermore, in the present population, all multiple VRF clustered in risk scores were associated, at various extent and frequency of occurrence, with cognitive decline or AD. This suggests that a cumulative exposure to even mild intensities of some VRF would better affect the decline of cognition than a clear-cut exposure to a single VRF.

These results emphasize the need for global correction of vascular, modifiable risk factors at a population level rather than interventions directed to a single VRF. Assuming the attenuation of their effect with age, the intervention will be the more effective if implemented at mid-life. In fact, it is likely that the beginning at early stages of life of a sequence of events related to VRF will favor the onset of cognitive deficit.

5.2 *Future prospects*

Dementia is a disease coming out in elderly life. However, seeds of its causation deepen the root very earlier, probably even at young age. Thus, recent evidences shifted the panorama of research to earlier periods of life, in early-life and mid-life. In fact, the idea that the dementia is a disease of a lifetime is affirming. An implication of the present results is that early management of VRF would change the onset and history of the cognitive decline.

Despite population differences, age, low education, vascular risk factors were recognized influencing the development of the disease. These factors were identified as key factors in all scoring systems for predicting the likelihood of dementia. These risk scores can be used for a dual purpose: the early identification of those at increased risk of dementia, from the one hand, may help to develop preventive treatment strategies, and from the other hand to target this treatment towards individuals detected who might benefit from different interventions.

One can hypothesize applying the current risk scores, including those evaluated in the present study, that long-term maintenance of vascular health could delay or prevent dementia (Barnes and Yaffe 2011a). Such prevention has strong social implications. It is also calculated that a modest 1-year delay in the onset of AD could lead to 11.8 million fewer cases after 50 years (Brookmeyer et al. 2007). According to an estimate, 10–25% reduction in seven modifiable risk factors, five of which are VRF, could prevent up to 3 million cases of Alzheimer's disease worldwide (Barnes and Yaffe 2011a).

CONCLUSIONS

Recently, the software "CAIDE Dementia Risk Score App" has been created, which allows users to autonomously compute their own individual risk, gives tips for risk modification, and recommends consulting a health care practitioner if needed. The purpose is to encourage users to actively decrease their modifiable risk factors and retard the cognitive impairment and dementia (Sindi et al. 2015).

Studies on dementia prevention have several limitations, which cannot be neglected for correctly reading of results. These limits also include timing of the intervention. This implies that the time-window is critical for the intervention to be effective. Most prevention studies have been conducted in the elderly. For instance, a multicenter, randomized, controlled clinical trial conducted in elderly patients with mild dementia showed that there was no difference between subject receiving strict cardiovascular treatment and those receiving standard care (Richard et al. 2009b).

Secondly, AD is a multifactorial disease with the aggregation of multiple factors, likely even at mild intensities. Then, studies should consider a global change in vascular health. However, current intervention studies have targeted a single VRF at once, with a short follow-up period (Qiu 2012).

The multi-domain intervention approach was implemented in European multicenter trials: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) (Kivipelto et al. 2013), Prevention of Dementia by Intensive Vascular Care (preDIVA), and Mutidomain Alzheimer Prevention study (MAPT) (Richard et al. 2009a; Kivipelto et al. 2013; Vellas et al. 2014). Recently the European Dementia Prevention Initiative (EDPI) developed a "Healthy Aging through Internet Counseling in Elderly" (HATICE) program, a program to manage modifiable risk factors in an aged population through an accessible internet platform (Richard et al. 2012; Imtiaz et al. 2014).

The results of European multicenter trials were contrasting. The FINGER trial suggested that a multidomain intervention has a positive effect on cognitive functioning in at-risk elderly people, whereas PreDIVA and MAPT did not detect significant any effect on cognitive decline in older people (Ngandu et al. 2015; van Charante et al. 2016; Andrieu et al. 2017).

In conclusion, a substantial progress was made over the past few years in understanding the pathophysiological mechanisms underlying AD. If confirmed, these findings could open paths for early diagnosis and treatment, but the way to go is still long before this knowledge can applied in clinical settings. For such a reason, the current dementia research goal needs to develop multi-target interventions to prevent or delay the onset of dementia using the potential risk factors already identified. Keeping this in mind, control of VRF could have repercussions on the society's economic demand to manage demented people, which number is growing, and it may inspire new strategies for the prevention or treatment of these diseases, since the current treatments do not seems to affect consistently the course of such kind of diseases. In this new perspective and through multi-domain interventions, further studies will provide more precise healthy lifestyle recommendations in order to prevent cognitive decline, and new strategies to improve the adherence to lifestyle changes. Prospective data on the ZAP cohort will further contribute to the role of VRF in determining cognitive decline and dementia.

6 REFERENCES

- Aguzzi A (2014) Alzheimer's disease under strain. *Nature* 512:32–34. doi: 10.1038/512032a
- Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC (2011) Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc* 86:876–84. doi: 10.4065/mcp.2011.0252
- Albert M, DeKosky S, Dickson D (2011a) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 7:270–279. doi: 10.1016/j.jalz.2011.03.008
- Albert MS, DeKosky ST, Dickson D, et al (2011b) The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement* 7:270–279. doi: 10.1016/j.jalz.2011.03.008
- Alberti KGMM, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15:539–553. doi: 10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S
- Alzheimer Europe 2013 (2013) The Prevalence of Alzheimer's in Europe. [http://www.alzheimer- Eur Prevalence-of-dementia-in-Europe](http://www.alzheimer-eur-prevalence-of-dementia-in-europe) <http://www.alzheimer-europe.org/Research/European>.
- American Psychiatric Association (2000) American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. IV-TR ed.* American Psychiatric Association, Washington, DC
- Anderson JL, Allen Maycock CA, Lappé DL, et al (2004) Frequency of elevation of C-reactive protein in atrial fibrillation. *Am J Cardiol* 94:1255–1259. doi: 10.1016/j.amjcard.2004.07.108
- Andrieu S, Guyonnet S, Coley N, et al (2017) Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol* 16:377–389. doi: 10.1016/S1474-4422(17)30040-6
- Anstey KJ, Cherbuin N, Budge M, Young J (2011) Body mass index in midlife and late-life as a risk factor for dementia: A meta-analysis of prospective studies. *Obes Rev* 12:e426–37. doi: 10.1111/j.1467-789X.2010.00825.x
- Anstey KJ, Cherbuin N, Herath PM, et al (2014a) A self-report risk index to predict occurrence of dementia in three independent cohorts of older adults: The ANU-ADRI. *PLoS One* 9:e86141. doi: 10.1371/journal.pone.0086141
- Anstey KJ, Lipnicki DM, Low L-F (2008) Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. *Am J Geriatr Psychiatry* 16:343–54. doi: 10.1097/JGP.0b013e31816b72d4
- Anstey KJ, Sargent-Cox K, Garde E, et al (2014b) Cognitive development over 8 years in midlife and its association with cardiovascular risk factors. *Neuropsychology* 28:653–665. doi: 10.1037/neu0000044
- Artero S, Ancelin M-L, Portet F, et al (2008) Risk profiles for mild cognitive impairment and progression to dementia are gender specific. *J Neurol Neurosurg Psychiatry* 79:979–84. doi: 10.1136/jnnp.2007.136903
- Arvanitakis Z, Wilson RS, Bienias JL, et al (2004) Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol* 61:661–666. doi: 10.1001/archneur.61.5.661
- Atti AR, Palmer K, Volpato S, et al (2008) Late-life body mass index and dementia incidence: nine-year follow-up data from the Kungsholmen Project. *J Am Geriatr Soc* 56:111–6. doi: 10.1111/j.1532-5415.2007.01458.x
- Atzmon G, Gabrieli I, Greiner W, et al (2002) Plasma HDL levels highly correlate with cognitive function in exceptional longevity. *J Gerontol A Biol Sci Med Sci* 57:M712–5. doi: 10.1093/gerona/57.11.M712
- Axen K V, Dikeakos A, Sclafani A (2003) High dietary fat promotes syndrome X in nonobese rats. *J Nutr* 133:2244–2249.
- Baigent C, Keech A, Kearney PM, et al (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet (London, England)* 366:1267–78. doi: 10.1016/S0140-6736(05)67394-1

REFERENCES

- Bales KR, Liu F, Wu S, et al (2009) Human APOE isoform-dependent effects on brain beta-amyloid levels in PDAPP transgenic mice. *J Neurosci* 29:6771–6779. doi: 10.1523/JNEUROSCI.0887-09.2009
- Barnard ND, Bush AI, Ceccarelli A, et al (2014) Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. *Neurobiol Aging* 35 Suppl 2:S74-8. doi: 10.1016/j.neurobiolaging.2014.03.033
- Barnes DE, Covinsky KE, Whitmer RA, et al (2009) Predicting risk of dementia in older adults: The late-life dementia risk index. *Neurology* 73:173–179. doi: 10.1212/WNL.0b013e3181a81636
- Barnes DE, Yaffe K (2011a) The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 10:819–28. doi: 10.1016/S1474-4422(11)70072-2
- Barnes DE, Yaffe K (2011b) The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 10:819–28. doi: 10.1016/S1474-4422(11)70072-2
- Barnes DE, Yaffe K, Byers AL, et al (2012) Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Arch Gen Psychiatry* 69:493–8. doi: 10.1001/archgenpsychiatry.2011.1481
- Bell RD, Zlokovic B V (2009) Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. *Acta Neuropathol* 118:103–13. doi: 10.1007/s00401-009-0522-3
- Bero AW, Yan P, Roh JH, et al (2011) Neuronal activity regulates the regional vulnerability to amyloid- β deposition. *Nat Neurosci* 14:750–6. doi: 10.1038/nn.2801
- Bertram L, Lill CM, Tanzi RE, et al (2010) The genetics of Alzheimer disease: back to the future. *Neuron* 68:270–81. doi: 10.1016/j.neuron.2010.10.013
- Bettens K, Sleegers K, Van Broeckhoven C (2013) Genetic insights in Alzheimer's disease. *Lancet Neurol*. 12:92–104.
- Beydoun MA, Beydoun HA, Wang Y (2008a) Obesity and central obesity as risk factors for incident dementia and its subtypes: A systematic review and meta-analysis. *Obes. Rev.* 9:204–218.
- Beydoun MA, Lhotsky A, Wang Y, et al (2008b) Association of Adiposity Status and Changes in Early to Mid-Adulthood With Incidence of Alzheimer's Disease. *Am J Epidemiol Publ by Johns Hopkins Bloom Sch Public Heal* 168:1179–89. doi: 10.1093/aje/kwn229
- Björntorp P, Rosmond R (2000) Neuroendocrine abnormalities in visceral obesity. *Int J Obes Relat Metab Disord* 24 Suppl 2:S80-5. doi: 10.1038/sj/ijo/0801285
- Bonora E (2006) The metabolic syndrome and cardiovascular disease. *Ann Med* 38:64–80. doi: GV2151Q1R00716V5 [pii]r10.1080/07853890500401234
- Boyle PA, Buchman AS, Wilson RS, et al (2010) Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *J Am Geriatr Soc* 58:248–255. doi: 10.1111/j.1532-5415.2009.02671.x
- Brady CB, Spiro A, McGlinchey-Berroth R, et al (2001) Stroke risk predicts verbal fluency decline in healthy older men: evidence from the normative aging study. *J Gerontol B Psychol Sci Soc Sci* 56:P340-6. doi: 10.1093/GERONB/56.6.P340
- Brandt J, Rogerson M (2011) Preliminary findings from an internet-based dementia risk assessment. *Alzheimers Dement* 7:e94-100. doi: 10.1016/j.jalz.2010.08.229
- Bravata DM, Wells CK, Concato J, et al (2004) Two measures of insulin sensitivity provided similar information in a U.S. population. *J Clin Epidemiol* 57:1214–1217. doi: 10.1016/j.jclinepi.2004.05.001
- Brecht WJ, Harris FM, Chang S, et al (2004) Neuron-specific apolipoprotein e4 proteolysis is associated with increased tau phosphorylation in brains of transgenic mice. *J Neurosci* 24:2527–34. doi: 10.1523/JNEUROSCI.4315-03.2004
- Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM (2007) Forecasting the global burden of Alzheimer's disease. *Alzheimer's Dement* 3:186–191. doi: 10.1016/j.jalz.2007.04.381
- Bu G (2009) Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nat Rev Neurosci* 10:333–44. doi: 10.1038/nrn2620

REFERENCES

- Buchman AS, Wilson RS, Bienias JL, et al (2005) Change in body mass index and risk of incident Alzheimer disease. *Neurology* 65:892–897. doi: 10.1212/01.wnl.0000176061.33817.90
- Bunch TJ, Weiss JP, Crandall BG, et al (2010) Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm* 7:433–7. doi: 10.1016/j.hrthm.2009.12.004
- Burns M, Duff K (2002) Cholesterol in Alzheimer's disease and tauopathy. *Ann N Y Acad Sci* 977:367–75. doi: 10.1111/j.1749-6632.2002.tb04839.x
- Busse A, Hensel A, Gühne U, et al (2006) Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology* 67:2176–85. doi: 10.1212/01.wnl.0000249117.23318.e1
- Buttini M, Yu G-Q, Shockley K, et al (2002) Modulation of Alzheimer-like synaptic and cholinergic deficits in transgenic mice by human apolipoprotein E depends on isoform, aging, and overexpression of amyloid beta peptides but not on plaque formation. *J Neurosci* 22:10539–48.
- Caracciolo B, Palmer K, Monastero R, et al (2008) Occurrence of cognitive impairment and dementia in the community: a 9-year-long prospective study. *Neurology* 70:1778–85. doi: 10.1212/01.wnl.0000288180.21984.cb
- Carnevale D, Lembo G (2011) “Alzheimer-like” pathology in a murine model of arterial hypertension. *Biochem Soc Trans* 39:939–944. doi: 10.1042/BST0390939
- Casserly I, Topol E (2004) Convergence of atherosclerosis and Alzheimer's disease: Inflammation, cholesterol, and misfolded proteins. *Lancet* 363:1139–1146.
- Castaneda AE, Tuulio-Henriksson A, Marttunen M, et al (2008) A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *J Affect Disord* 106:1–27. doi: 10.1016/j.jad.2007.06.006
- Castellano JM, Kim J, Stewart FR, et al (2011) Human apoE isoforms differentially regulate brain amyloid- β peptide clearance. *Sci Transl Med* 3:89ra57. doi: 10.1126/scitranslmed.3002156
- Chartier-Harlin M-C, Parfitt M, Legrain S, et al (1994) Apolipoprotein-E, Epsilon-4 Allele As a Major Risk Factor for Sporadic Early and Late-Onset Forms of Alzheimers-Disease - Analysis of the 19Q13.2 Chromosomal Region. *Hum Mol Genet* 3:569–574. doi: 10.1093/hmg/3.4.569
- Chen Y, Durakoglugil MS, Xian X, Herz J (2010) ApoE4 reduces glutamate receptor function and synaptic plasticity by selectively impairing ApoE receptor recycling. *Proc Natl Acad Sci U S A* 107:12011–6. doi: 10.1073/pnas.0914984107
- Cirrito JR, Yamada K a., Finn MB, et al (2005) Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. *Neuron* 48:913–922. doi: 10.1016/j.neuron.2005.10.028
- Cockerill GW, Rye KA, Gamble JR, et al (1995) High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. *Arter Thromb Vasc Biol* 15:1987–1994.
- Colonna M, Wang Y (2016) TREM2 variants: new keys to decipher Alzheimer disease pathogenesis. *Nat Rev Neurosci* 17:201–7. doi: 10.1038/nrn.2016.7
- Convit A, Wolf OT, Tarshish C, de Leon MJ (2003) Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. *PNAS* 100:2019–22. doi: 10.1073/pnas.0336073100
- Corder EH, Ervin JF, Lockhart E, et al (2005) Cardiovascular damage in Alzheimer disease: autopsy findings from the Bryan ADRC. *J Biomed Biotechnol* 2005:189–97. doi: 10.1155/JBB.2005.189
- Corder EH, Saunders AM, Strittmatter WJ, et al (1993) Gene Dose of Apolipoprotein-E Type-4 Allele and the Risk of Alzheimers-Disease in Late-Onset Families. *Science* (80-) 261:921–923. doi: 10.1126/science.8346443
- Cosentino S, Scarmeas N, Helzner E, et al (2008) APOE ϵ 4 allele predicts faster cognitive decline in mild Alzheimer disease. *Neurology* 70:1842–1849. doi: 10.1212/01.wnl.0000304038.37421.cc
- Craft S (2009) The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. *Arch Neurol* 66:300–305. doi: 10.1001/archneurol.2009.27
- Craft S, Peskind E, Schwartz MW, et al (1998) Cerebrospinal fluid and plasma insulin levels in Alzheimer's disease:

REFERENCES

- relationship to severity of dementia and apolipoprotein E genotype. *Neurology* 50:164–168. doi: 10.1212/WNL.50.1.164
- Craig CL, Marshall AL, Str M MS, et al (2003) International Physical Activity Questionnaire: 12-Country Reliability and Validity. *Med Sci Sport Exerc* 35:1381–1395. doi: 10.1249/01.MSS.0000078924.61453.FB
- Crandall MA, Horne BD, Day JD, et al (2009) Atrial fibrillation and chads2 risk factors are associated with highly sensitive C-reactive protein incrementally and independently. *PACE - Pacing Clin Electrophysiol* 32:648–652. doi: 10.1111/j.1540-8159.2009.02339.x
- Crook TH, Feher EP, Larrabee GJ (1992) Assessment of memory complaint in age-associated memory impairment: the MAC-Q. *Int psychogeriatrics* 4:165–76.
- Cukierman T, Gerstein HC, Williamson JD (2005) Cognitive decline and dementia in diabetes--systematic overview of prospective observational studies. *Diabetologia* 48:2460–2469. doi: 10.1007/s00125-005-0023-4
- Cummings JL, Mega M, Gray K, et al (1994) The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 44:2308–14.
- D'Agostino RB, Wolf P a, Belanger a J, Kannel WB (1994) Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke* 25:40–43. doi: 10.1161/01.STR.25.1.40
- D'Agostino RB S, Vasan RS, Pencina MJ, et al (2008) General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 117:743–753. doi: 10.1161/CIRCULATIONAHA.107.699579
- Dandona P, Aljada A, Chaudhuri A, et al (2005) Metabolic syndrome: A comprehensive perspective based on interactions between obesity, diabetes, and inflammation. *Circulation* 111:1448–1454.
- Das SK, Bose P, Biswas A, et al (2007) An epidemiologic study of mild cognitive impairment in Kolkata, India. *Neurology* 68:2019–2026. doi: 10.1212/01.wnl.0000264424.76759.e6
- de Leeuw FE, de Groot JC, Oudkerk M, et al (2000) Atrial fibrillation and the risk of cerebral white matter lesions. *Neurology* 54:1795–801. doi: 10.1161/01.CIR.0000158483.13093.9D
- Deane R, Wu Z, Sagare A, et al (2004) LRP/amyloid β -peptide interaction mediates differential brain efflux of A β isoforms. *Neuron* 43:333–344. doi: 10.1016/j.neuron.2004.07.017
- De Renzi E, Vignolo LA (1962) The token test: A sensitive test to detect receptive disturbances in aphasics. *Brain* 85:665–78.
- Debette S, Seshadri S (2009) Vascular risk factors and dementia revisited. *J Neurol Neurosurg Psychiatry* 80:1183–4. doi: 10.1136/jnnp.2009.181289
- DeCarli C (2003) Mild cognitive impairment: prevalence, prognosis, aetiology, and treatment. *Lancet Neurol* 2:15–21. doi: 10.1016/S1474-4422(03)00262-X
- DeCarli C, Miller BL, Swan GE, et al (2001) Cerebrovascular and brain morphologic correlates of mild cognitive impairment in the National Heart, Lung, and Blood Institute Twin Study. *Arch Neurol* 58:643–7. doi: 10.1001/archneur.58.4.643
- DeCarli C, Mungas D, Harvey D, et al (2004) Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia. *Neurology* 63:220–7.
- Deckers K, van Boxtel MPJ, Schiepers OJG, et al (2015) Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry* 30:234–246. doi: 10.1002/gps.4245
- Di Carlo A, Baldereschi M, Amaducci L, et al (2002) Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy. The ILSA Study. *J Am Geriatr Soc* 50:41–8. doi: 10.1046/j.1532-5415.2002.50006
- Di Carlo A, Lamassa M, Baldereschi M, et al (2007) CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. *Neurology* 68:1909–16. doi: 10.1212/01.wnl.0000263132.99055.0d
- Dik MG, Jonker C, Comijs HC, et al (2007) Contribution of metabolic syndrome components to cognition in older

REFERENCES

- individuals. *Diabetes Care* 30:2655–2660. doi: 10.2337/dc06-1190
- Diniz BS, Butters MA, Albert SM, et al (2013) Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry* 202:329–35. doi: 10.1192/bjp.bp.112.118307
- Dlugaj M, Weimar C, Wege N, et al (2010) Prevalence of Mild Cognitive Impairment and Its Subtypes in the Heinz Nixdorf Recall Study Cohort. *Dement Geriatr Cogn Disord* 30:362–373. doi: 10.1159/000320988
- Dregan A, Stewart R, Gulliford MC (2013) Cardiovascular risk factors and cognitive decline in adults aged 50 and over: a population-based cohort study. In: *Age Ageing*. pp 338–345
- Dubois B, Hampel H, Feldman HH, et al (2016) Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's Dement*. 12:292–323.
- Dubois B, Slachevsky A, Litvan I, Pillon B (2000) The FAB: a Frontal Assessment Battery at bedside. *Neurology* 55:1621–6.
- Dufouil C, Richard F, Fiévet N, et al (2005) APOE genotype, cholesterol level, lipid-lowering treatment, and dementia: the Three-City Study. *Neurology* 64:1531–8. doi: 10.1212/01.WNL.0000160114.42643.31
- Dumanis SB, Tesoriero JA, Babus LW, et al (2009) ApoE4 decreases spine density and dendritic complexity in cortical neurons in vivo. *J Neurosci* 29:15317–22. doi: 10.1523/JNEUROSCI.4026-09.2009
- Duron E, Hanon O (2008) Vascular risk factors, cognitive decline, and dementia. *Vasc Health Risk Manag* 4:363–381. doi: 10.2147/VHRM.S1839
- Eder K, Baffy N, Falus A, Fulop AK (2009) The major inflammatory mediator interleukin-6 and obesity. *Inflamm. Res.* 58:727–736.
- Eggermont LHP, de Boer K, Muller M, et al (2012) Cardiac disease and cognitive impairment: a systematic review. *Heart* 98:1334–1340. doi: 10.1136/heartjnl-2012-301682
- Eichner JE, Dunn ST, Perveen G, et al (2002) Apolipoprotein E polymorphism and cardiovascular disease: A HuGE review. *Am. J. Epidemiol.* 155:487–495.
- Elias-Sonnenschein LS, Viechtbauer W, Ramakers IHGB, et al (2011) Predictive value of APOE-ε4 allele for progression from MCI to AD-type dementia: a meta-analysis. *J Neurol Neurosurg Psychiatry* 82:1149–1156. doi: 10.1136/jnnp.2010.231555
- Elias MF, Elias PK, Sullivan LM, et al (2003) Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. *Int J Obes Relat Metab Disord* 27:260–268. doi: 10.1038/sj.ijo.802225
- Elias MF, Sullivan LM, D'agostino RB, et al Framingham Stroke Risk Profile and Lowered Cognitive Performance. doi: 10.1161/01.STR.0000103141.82869.77
- Elias MF, Wolf PA, D'Agostino RB, et al (1993) Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *Am J Epidemiol* 138:353–64.
- Esiri MM, Nagy Z, Smith MZ, et al (1999) Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet (London, England)* 354:919–20. doi: 10.1016/S0140-6736(99)02355-7
- Espinola-Klein C, Gori T, Blankenberg S, Munzel T (2011) Inflammatory markers and cardiovascular risk in the metabolic syndrome. *Front Biosci* 16:1663–1674. doi: 3812 [pii]
- Esposito G, Scuderi C, Lu J, et al (2008) S100B induces tau protein hyperphosphorylation via Dickkopf-1 up-regulation and disrupts the Wnt pathway in human neural stem cells. *J Cell Mol Med* 12:914–27. doi: 10.1111/j.1582-4934.2008.00159.x
- Evans DA, Hebert LE, Beckett LA, et al (1997) Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. *Arch Neurol* 54:1399–405.
- Exalto L, Kivipelto M, Barnes D, et al (2011) Validation of a midlife dementia risk score in a large diverse population. *Alzheimer's Dement* 7:S504. doi: 10.1016/j.jalz.2011.05.2406

REFERENCES

- Exalto LG, Biessels GJ, Karter AJ, et al (2013) Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. *Lancet Diabetes Endocrinol* 1:183–190. doi: 10.1016/S2213-8587(13)70048-2
- Exalto LG, Quesenberry CP, Barnes D, et al (2014) Midlife risk score for the prediction of dementia four decades later. *Alzheimers Dement* 10:562–70. doi: 10.1016/j.jalz.2013.05.1772
- Exalto LG, van der Flier WM, van Boheemen CJM, et al (2015) The metabolic syndrome in a memory clinic population: relation with clinical profile and prognosis. *J Neurol Sci* 351:18–23. doi: 10.1016/j.jns.2015.02.004
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486–97.
- Farlow MR, He Y, Tekin S, et al (2004) Impact of APOE in mild cognitive impairment. *Neurology* 63:1898–1901. doi: 10.1212/01.WNL.0000144279.21502.B7
- Farr SA, Yamada KA, Butterfield DA, et al (2008) Obesity and hypertriglyceridemia produce cognitive impairment. *Endocrinology* 149:2628–2636. doi: 10.1210/en.2007-1722
- Farrer LA, Cupples LA, Haines JL, et al (1997) Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease: A Meta-analysis. *JAMA J. Am. Med. Assoc.* 278:1349–1356.
- Feigin VL, Lawes CMM, Bennett DA, et al (2009) Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 8:355–69. doi: 10.1016/S1474-4422(09)70025-0
- Feng L, Chong MS, Lim WS, et al (2013) Metabolic syndrome and amnesic mild cognitive impairment: Singapore Longitudinal Ageing Study-2 findings. *J Alzheimers Dis* 34:649–57. doi: 10.3233/JAD-121885
- Fewlass DC, Noboa K, Pi-Sunyer FX, et al (2004) Obesity-related leptin regulates Alzheimer's Abeta. *FASEB J* 18:1870–8. doi: 10.1096/fj.04-2572com
- Fitzpatrick AL, Kuller LH, Lopez OL, et al (2009) Midlife and late-life obesity and the risk of dementia: cardiovascular health study. *Arch Neurol* 66:336–42. doi: 10.1001/archneurol.2008.582
- Fleisher AS, Sowell BB, Taylor C, et al (2007) Clinical predictors of progression to Alzheimer disease in amnesic mild cognitive impairment. *Neurology* 68:1588–1595. doi: 10.1212/01.wnl.0000258542.58725.4c
- Forti P, Pisacane N, Rietti E, et al (2010) Metabolic syndrome and risk of dementia in older adults. *J Am Geriatr Soc* 58:487–492. doi: 10.1111/j.1532-5415.2010.02731.x
- Fotuhi M, Hachinski V, Whitehouse PJ (2009) Changing perspectives regarding late-life dementia. *Nat Rev Neurol* 5:649–658. doi: 10.1038/nrneurol.2009.175
- Fratiglioni L, Grut M, Forsell Y, et al (1991) Prevalence of Alzheimer's disease and other dementias in an elderly urban population: relationship with age, sex, and education. *Neurology* 41:1886–92.
- Freiheit EA, Hogan DB, Eliasziw M, et al (2012) A dynamic view of depressive symptoms and neurocognitive change among patients with coronary artery disease. *Arch Gen Psychiatry* 69:244–55. doi: 10.1001/archgenpsychiatry.2011.1361
- Frisardi V (2014) Impact of metabolic syndrome on cognitive decline in older age: protective or harmful, where is the pitfall? *J Alzheimers Dis* 41:163–7. doi: 10.3233/JAD-140389
- Frisardi V, Solfrizzi V, Capurso C, et al (2010) Is insulin resistant brain state a central feature of the metabolic-cognitive syndrome? *J Alzheimer's Dis* 21:57–63. doi: 10.3233/JAD-2010-100015
- G. Sartori, L. Colombo, G. Vallar, M. L. Rusconi and AP (1997) TIB: Test di Intelligenza Breve per la valutazione del quoziente intellettuale attuale e pre-morboso. *La Prof di Psicol* 2–24.
- Ganguli M, Chang C-CH, Snitz BE, et al (2010) Prevalence of mild cognitive impairment by multiple classifications: The Monongahela-Youghiogheny Healthy Aging Team (MYHAT) project. *Am J Geriatr Psychiatry* 18:674–83. doi: 10.1097/JGP.0b013e3181cdee4f
- Ganguli M, Dodge HH, Shen C, et al (2005) Alzheimer disease and mortality: a 15-year epidemiological study. *Arch*

REFERENCES

- Neurol 62:779–784. doi: 10.1001/archneur.62.5.779
- Garcia-Alloza M, Gregory J, Kuchibhotla K V., et al (2011) Cerebrovascular lesions induce transient β -amyloid deposition. In: *Brain*. pp 3694–3704
- Gasparini L, Gouras GK, Wang R, et al (2001) Stimulation of β -amyloid precursor protein trafficking by insulin reduces intraneuronal β -amyloid and requires mitogen-activated protein kinase signaling. *J Neurosci* 21:2561–2570.
- Geerlings MI, Schmand B, Jonker C, et al (1999) Education and incident Alzheimer's disease: a biased association due to selective attrition and use of a two-step diagnostic procedure? *Int J Epidemiol* 28:492–7.
- Genin E, Hannequin D, Wallon D, et al (2011) APOE and Alzheimer disease: a major gene with semi-dominant inheritance. *Mol Psychiatry* 16:903–7. doi: 10.1038/mp.2011.52
- Germolec DR, Frawley RP, Evans E (2010) Markers of Inflammation. In: Dietert RR (ed) *Immunotoxicity Testing*. Humana Press, a part of Springer, pp 53–73
- Gerstenecker A, Martin R, Marson DC, et al (2016) Introducing demographic corrections for the 10/36 Spatial Recall Test. *Int J Geriatr Psychiatry* 31:406–411. doi: 10.1002/gps.4346
- Gilleard CJ (1997) Education and Alzheimer's disease: A review of recent international epidemiological studies. *Aging Ment Health* 1:33–46. doi: 10.1080/13607869757362
- Goldenberg I, Moss AJ, Ryan D, et al (2008) Cumulative burden of atherosclerotic risk genotypes and the age at onset of a first myocardial infarction: A case-only carriership approach. *Ann Noninvasive Electrocardiol* 13:287–294. doi: 10.1111/j.1542-474X.2008.00233.x
- Gorospe EC, Dave JK (2007) The risk of dementia with increased body mass index. *Age Ageing* 36:23–29.
- Gregg EW, Yaffe K, Cauley JA, et al (2000) Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch Intern Med* 160:174–80. doi: 10.1001/archinte.160.2.174
- Grodstein F (2007) Cardiovascular risk factors and cognitive function. *Alzheimer's Dement* 3:S16–S22. doi: <http://dx.doi.org/10.1016/j.jalz.2007.01.001>
- Grodstein F, Chen J, Wilson RS, Manson JE (2001) Type 2 diabetes and cognitive function in community-dwelling elderly women. *Diabetes Care* 24:1060–5. doi: 10.2337/diacare.24.6.1060
- Grundey SM (2003) Inflammation, hypertension, and the metabolic syndrome. *J Am Med Assoc* 290:3000–3002. doi: 10.1001/jama.290.22.3000
- Guerreiro R, Wojtas A, Bras J, et al (2013) TREM2 variants in Alzheimer's disease. *N Engl J Med* 368:117–27. doi: 10.1056/NEJMoa1211851
- Guigoz Y, Vellas B (1999) The Mini Nutritional Assessment (MNA) for Grading the Nutritional State of Elderly Patients: Presentation of the MNA, History and Validation. In: *Mini Nutritional Assessment (MNA): Research and Practice in the Elderly*. KARGER, Basel, pp 3–12
- Guo Z, Viitanen M, Fratiglioni L, Winblad B (1996) Low blood pressure and dementia in elderly people: the Kungsholmen project. *BMJ* 312:805–8.
- Guo Z, Viitanen M, Winblad B, Fratiglioni L (1999) Low blood pressure and incidence of dementia in a very old sample: Dependent on initial cognition. *J Am Geriatr Soc* 47:723–726.
- Gustafson D (2006) Adiposity indices and dementia. *Lancet Neurol* 5:713–720. doi: 10.1016/S1474-4422(06)70526-9
- Gustafson D, Rothenberg E, Blennow K, et al (2003) An 18-year follow-up of overweight and risk of Alzheimer disease. *Arch Intern Med* 163:1524–1528. doi: 10.1001/archinte.163.13.1524
- Hachiya NS, Kozuka Y, Kaneko K, et al (2008) Mechanical stress and formation of protein aggregates in neurodegenerative disorders. *Med Hypotheses* 70:1034–7. doi: 10.1016/j.mehy.2007.06.043
- Haffner SM (2006) The metabolic syndrome: Inflammation, diabetes mellitus, and cardiovascular disease. *Am. J. Cardiol.*

REFERENCES

97:3A–11A.

- Handels RLH, Wolfs CAG, Aalten P, et al (2013) Determinants of care costs of patients with dementia or cognitive impairment. *Alzheimer Dis Assoc Disord* 27:30–36. doi: 10.1097/WAD.0b013e318242da1d
- Harold D, Abraham R, Hollingworth P, et al (2009) Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease. *Nat Genet* 41:1088–93. doi: 10.1038/ng.440
- Harvey J (2003) Leptin: a multifaceted hormone in the central nervous system. *Mol Neurobiol* 28:245–58. doi: MN:28:3:245 [pii]r10.1385/MN:28:3:245
- Hashimoto M, Yasuda M, Tanimukai S, et al (2001) Apolipoprotein E epsilon 4 and the pattern of regional brain atrophy in Alzheimer's disease. *Neurology* 57:1461–6.
- Helzner EP, Luchsinger JA, Scarmeas N, et al (2009) Contribution of vascular risk factors to the progression in Alzheimer disease. *Arch Neurol* 66:343–8. doi: 10.1001/archneur.66.3.343
- Helzner EP, Scarmeas N, Cosentino S, et al (2008) Survival in Alzheimer disease: A multiethnic, population-based study of incident cases. *Neurology* 71:1489–1495. doi: 10.1212/01.wnl.0000334278.11022.42
- Henderson VW, Guthrie JR, Dennerstein L (2003) Serum lipids and memory in a population based cohort of middle age women. *J Neurol Neurosurg Psychiatry* 74:1530–1535.
- Heyman a, Fillenbaum GG, Welsh-Bohmer KA, et al (1998) Cerebral infarcts in patients with autopsy-proven Alzheimer's disease: CERAD, part XVIII. Consortium to Establish a Registry for Alzheimer's Disease. *Neurology* 51:159–162. doi: 10.1212/WNL.51.1.159
- Houlden H, Crook R, Backhovens H, et al (1998) ApoE genotype is a risk factor in nonpresenilin early-onset Alzheimer's disease families. *Am J Med Genet - Neuropsychiatr Genet* 81:117–121. doi: 10.1002/(SICI)1096-8628(19980207)81:1<117::AID-AJMG19>3.0.CO;2-M
- Huang Y (2010) AB-independent roles of apolipoprotein E4 in the pathogenesis of Alzheimer's disease. *Trends Mol Med* 16:287–294. doi: 10.1016/j.molmed.2010.04.004
- Huang Y, Mucke L (2012) Alzheimer mechanisms and therapeutic strategies. *Cell* 148:1204–1222.
- Iadecola C (2004) Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci* 5:347–360. doi: 10.1038/nrn1387
- Iadecola C (2010) The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. *Acta Neuropathol.* 120:287–296.
- Iadecola C, Davisson RL (2008) Hypertension and Cerebrovascular Dysfunction. *Cell Metab.* 7:476–484.
- Imaizumi Y (1992) Mortality rate of Alzheimer's disease in Japan: secular trends, marital status, and geographical variations. *Acta Neurol Scand* 86:501–505.
- Imtiaz B, Tolppanen A-M, Kivipelto M, Soininen H (2014) Future directions in Alzheimer's disease from risk factors to prevention. *Biochem Pharmacol* 88:661–670. doi: 10.1016/j.bcp.2014.01.003
- Itoh Y, Yamada M, Hayakawa M, et al (1993) Cerebral amyloid angiopathy: a significant cause of cerebellar as well as lobar cerebral hemorrhage in the elderly. *J Neurol Sci* 116:135–41.
- Jack CR, Wiste HJ, Weigand SD, et al (2015) Age, Sex, and APOE ε4 Effects on Memory, Brain Structure, and β-Amyloid Across the Adult Life Span. *JAMA Neurol* 72:511. doi: 10.1001/jamaneurol.2014.4821
- Jack CR, Wiste HJ, Weigand SD, et al (2014) Age-specific population frequencies of cerebral β-amyloidosis and neurodegeneration among people with normal cognitive function aged 50–89 years: a cross-sectional study. *Lancet Neurol* 13:997–1005. doi: 10.1016/S1474-4422(14)70194-2
- Jellinger KA, Attems J (2010) Prevalence of dementia disorders in the oldest-old: An autopsy study. *Acta Neuropathol* 119:421–433. doi: 10.1007/s00401-010-0654-5
- Ji Y, Shi Z, Zhang Y, et al (2015) Prevalence of Dementia and Main Subtypes in Rural Northern China. *Dement Geriatr*

REFERENCES

- Cogn Disord 39:294–302. doi: 10.1159/000375366
- Jiang Q, Lee CYD, Mandrekar S, et al (2008) ApoE Promotes the Proteolytic Degradation of A β Neuron 58:681–693. doi: 10.1016/j.neuron.2008.04.010
- Jonsson T, Stefansson H, Steinberg S, et al (2013) Variant of TREM2 associated with the risk of Alzheimer's disease. *N Engl J Med* 368:107–16. doi: 10.1056/NEJMoa1211103
- Joosten H, van Eersel ME a, Gansevoort RT, et al (2013) Cardiovascular risk profile and cognitive function in young, middle-aged, and elderly subjects. *Stroke* 44:1543–9. doi: 10.1161/STROKEAHA.111.000496
- Kaffashian S, Dugravot A, Elbaz A, et al (2013) Predicting cognitive decline: A dementia risk score vs the framingham vascular risk scores. *Neurology* 80:1300–1306. doi: 10.1212/WNL.0b013e31828ab370
- Kaffashian S, Dugravot A, Nabi H, et al (2011) Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: Evidence from the Whitehall II study. *Eur Heart J* 32:2326–2332. doi: 10.1093/eurheartj/ehr133
- Kalantarian S, Stern TA, Mansour M, Ruskin JN (2013) Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann Intern Med* 158:338–46. doi: 10.7326/0003-4819-158-5-201303050-00007
- Kalmijn S, Foley D, White L, et al (2000) Metabolic cardiovascular syndrome and risk of dementia in Japanese- American elderly men - The Honolulu-Asia Aging Study. *Arter Thromb Vasc Biol* 20:2255–2260. doi: 10.1161/01.ATV.20.10.2255
- Kanaya AM, Barrett-Connor E, Gildengorin G, Yaffe K (2004) Change in cognitive function by glucose tolerance status in older adults: a 4-year prospective study of the Rancho Bernardo study cohort. *Arch Intern Med* 164:1327–33. doi: 10.1001/archinte.164.12.1327
- Kannel WB, Cupples LA, Ramaswami R, et al (1991) Regional obesity and risk of cardiovascular disease; the Framingham Study. *J Clin Epidemiol* 44:183–90. doi: 10.1016/0895-4356(91)90265-B
- KANNEL WB, DAWBER TR, FRIEDMAN GD, et al (1964) Risk factors in coronary heart disease an evaluation of several serum lipids as predictors of coronary heart disease. The Framingham Study. *Ann Intern Med* 61:888–899. doi: 10.7326/0003-4819-61-5-888
- Karlamangla AS, Miller-Martinez D, Aneshensel CS, et al (2009) Trajectories of cognitive function in late life in the United States: demographic and socioeconomic predictors. *Am J Epidemiol* 170:331–42. doi: 10.1093/aje/kwp154
- Karran E, Mercken M, De Strooper B (2011) The amyloid cascade hypothesis for Alzheimer's disease: an appraisal for the development of therapeutics. *Nat Rev Drug Discov* 10:698–712. doi: 10.1038/nrd3505
- Katz S, Downs T, Cash H, Grotz R (1970) Progress in Development of the Index of ADL. *Gerontologist* 10:20–30.
- Katzman R (1993) Education and the prevalence of dementia and Alzheimer's disease. *Neurology* 43:13–20.
- Kilander L, Nyman H, Boberg M, et al (1998) Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men. *Hypertens (Dallas, Tex 1979)* 31:780–6.
- Kim KW, Park JH, Kim M-H, et al (2011) A nationwide survey on the prevalence of dementia and mild cognitive impairment in South Korea. *J Alzheimers Dis* 23:281–91. doi: 10.3233/JAD-2010-101221
- Kivipelto M, Helkala E-L, Laakso MP, et al (2002) Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. *Ann Intern Med* 137:149–55. doi: 10.7326/0003-4819-137-3-200208060-00006
- Kivipelto M, Helkala EL, Hänninen T, et al (2001a) Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. *Neurology* 56:1683–9.
- Kivipelto M, Helkala EL, Hänninen T, et al (2001b) Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. *Neurology* 56:1683–9.
- Kivipelto M, Helkala EL, Laakso MP, et al (2001c) Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 322:1447–51. doi: 10.1136/bmj.322.7300.1447

REFERENCES

- Kivipelto M, Ngandu T, Fratiglioni L, et al (2005) Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol* 62:1556–60. doi: 10.1001/archneur.62.10.1556
- Kivipelto M, Ngandu T, Laatikainen T, et al (2006a) Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol* 5:735–741. doi: 10.1016/S1474-4422(06)70537-3
- Kivipelto M, Ngandu T, Laatikainen T, et al (2006b) Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol* 5:735–741. doi: 10.1016/S1474-4422(06)70537-3
- Kivipelto M, Rovio S, Ngandu T, et al (2008) Apolipoprotein E epsilon4 Magnifies Lifestyle Risks for Dementia: A Population Based Study. *JCell MolMed* 12:2762–2771. doi: 10.1111/j.1582-4934.2008.0296.x
- Kivipelto M, Solomon A, Ahtiluoto S, et al (2013) The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): Study design and progress. *Alzheimer's Dement* 9:657–665. doi: 10.1016/j.jalz.2012.09.012
- Kling MA, Trojanowski JQ, Wolk DA, et al (2013) Vascular disease and dementias: paradigm shifts to drive research in new directions. *Alzheimers Dement* 9:76–92. doi: 10.1016/j.jalz.2012.02.007
- Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ (2008) Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. *Eur J Pharmacol* 585:97–108. doi: 10.1016/j.ejphar.2008.02.049
- Knopman DS, Edland SD, Cha RH, et al (2007) Incident dementia in women is preceded by weight loss by at least a decade. *Neurology* 69:739–746. doi: 10.1212/01.wnl.0000267661.65586.33
- Knopman DS, Roberts R (2010) Vascular risk factors: Imaging and neuropathologic correlates. *J. Alzheimer's Dis.* 20:699–709.
- Korf ESC, Wahlund L-O, Visser PJ, Scheltens P (2004) Medial temporal lobe atrophy on MRI predicts dementia in patients with mild cognitive impairment. *Neurology* 63:94–100.
- Koschack J, Irle E (2005) Small hippocampal size in cognitively normal subjects with coronary artery disease. *Neurobiol Aging* 26:865–71. doi: 10.1016/j.neurobiolaging.2004.08.009
- Kuusisto J, Koivisto K, Mykkänen L, et al (1997) Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study. *BMJ* 315:1045–9.
- Kwok CS, Loke YK, Hale R, et al (2011) Atrial fibrillation and incidence of dementia: A systematic review and meta-analysis. *Neurology* 76:914–922. doi: 10.1212/WNL.0b013e31820f2e38
- Laccetti R, Pota A, Stranges S, et al Evidence on the prevalence and geographic distribution of major cardiovascular risk factors in Italy. *Public Health Nutr* 16:305–315. doi: 10.1017/S1368980012002716
- Lahoz C, Schaefer EJ, Cupples LA, et al (2001) Apolipoprotein E genotype and cardiovascular disease in the Framingham Heart Study. *Atherosclerosis* 154:529–37.
- Lambert J-C, Heath S, Even G, et al (2009) Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* 41:1094–1099. doi: 10.1038/ng.439
- Laughlin GA, McEvoy LK, von Mühlen D, et al (2011) Sex Differences in the Association of Framingham Cardiac Risk Score With Cognitive Decline in Community-Dwelling Elders Without Clinical Heart Disease. *Psychosom Med* 73:683–689. doi: 10.1097/PSY.0b013e31822f9089
- Launer LJ (2002) Demonstrating the case that AD is a vascular disease: epidemiologic evidence. *Ageing Res Rev* 1:61–77. doi: 10.1016/S0047-6374(01)00364-5
- Launer LJ, Masaki K, Petrovitch H, et al (1995) The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. *JAMA* 274:1846–51.
- Launer LJ, Petrovitch H, Ross GW, et al (2008) AD brain pathology: Vascular origins? Results from the HAAS autopsy study. *Neurobiol Aging* 29:1587–1590. doi: 10.1016/j.neurobiolaging.2007.03.008

REFERENCES

- Launer LJ, Ross GW, Petrovitch H, et al (2000) Midlife blood pressure and dementia: the Honolulu-Asia aging study. *Neurobiol Aging* 21:49–55. doi: 10.1016/S0197-4580(00)00096-8
- Launer LJ, Stewart R, Masaki K, et al (2005) A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. *Arch Neurol* 62:55–60. doi: 10.1001/archneur.62.1.55
- Launer LJ, White LR, Petrovitch H, et al (2001) Cholesterol and neuropathologic markers of AD: a population-based autopsy study. *Neurology* 57:1447–52.
- Lavy S, Stern S, Melamed E, et al (1980) Effect of Chronic Atrial Fibrillation of regional Cerebral Blood Flow. *Stroke* 11:35–8.
- Lawes CMM, Bennett DA, Feigin VL, Rodgers A (2004) Blood Pressure and Stroke: An Overview of Published Reviews. *Stroke* 35:776–785.
- Lawton M, Brody E (1969) Assessment of older people: self- maintaining and instrumental activities of daily living. *Gerontologist* 9:179–186. doi: 10.1097/01.NAJ.0000314810.46029.74
- Lee JH, Olichney JM, Hansen LA, et al (2000) Small concomitant vascular lesions do not influence rates of cognitive decline in patients with Alzheimer disease. *Arch Neurol* 57:1474–1479. doi: 10.1001/archneur.57.10.1474
- Letenneur L, Gilleron V, Commenges D, et al (1999) Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. *J Neurol Neurosurg Psychiatry* 66:177–83.
- Levy Nogueira M, Epelbaum S, Steyaert J-M, et al (2016) Mechanical stress models of Alzheimer's disease pathology. *Alzheimers Dement* 12:324–33. doi: 10.1016/j.jalz.2015.10.005
- Lewinsohn PM, Seeley JR, Roberts RE, Allen NB (1997) Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging* 12:277–87.
- Leys D, Hénon H, Mackowiak-Cordoliani M-A, Pasquier F (2005) Poststroke dementia. *Lancet Neurol* 4:752–9. doi: 10.1016/S1474-4422(05)70221-0
- Li G, Shofer JB, Kukull W a, et al (2005) Serum cholesterol and risk of Alzheimer disease: a community-based cohort study. *Neurology* 65:1045–50. doi: 10.1212/01.wnl.0000178989.87072.11
- Li L, Zhang X, Yang D, et al (2009) Hypoxia increases Abeta generation by altering beta- and gamma-cleavage of APP. *Neurobiol Aging* 30:1091–1098. doi: 10.1016/j.neurobiolaging.2007.10.011
- Li X-L, Aou S, Oomura Y, et al (2002) Impairment of long-term potentiation and spatial memory in leptin receptor-deficient rodents. *Neuroscience* 113:607–15. doi: 10.1016/S0306-4522(02)00162-8
- Liu C-C, Liu C-C, Kanekiyo T, et al (2013) Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol* 9:106–18. doi: 10.1038/nrneurol.2012.263
- Liu M, He Y, Jiang B, et al (2015) Association between metabolic syndrome and mild cognitive impairment and its age difference in a Chinese community elderly population. *Clin Endocrinol (Oxf)* 82:844–53. doi: 10.1111/cen.12734
- Llewellyn DJ, Lang IA, Xie J, et al (2008) Framingham Stroke Risk Profile and poor cognitive function: a population-based study. *BMC Neurol* 8:12. doi: 10.1186/1471-2377-8-12
- Lloyd-Jones DM, Evans JC, Levy D (2005) Hypertension in Adults Across the Age Spectrum: current outcomes and control in the community. *JAMA J Am Med Assoc* 294:466–472. doi: 10.1001/jama.294.4.466
- Lopez OL, Jagust WJ, DeKosky ST, et al (2003a) Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. *Arch Neurol* 60:1385–9. doi: 10.1001/archneur.60.10.1385
- Lopez OL, Jagust WJ, Dulberg C, et al (2003b) Risk Factors for Mild Cognitive Impairment in the Cardiovascular Health Study Cognition Study. *Arch Neurol* 60:1394. doi: 10.1001/archneur.60.10.1394
- Lopez OL, Jagust WJ, Dulberg C, et al (2003c) Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. *Arch Neurol* 60:1394–9. doi: 10.1001/archneur.60.10.1394
- López S, Bermúdez B, Pacheco YM, et al (2008) Distinctive postprandial modulation of beta cell function and insulin

REFERENCES

- sensitivity by dietary fats: monounsaturated compared with saturated fatty acids. *Am J Clin Nutr* 88:638–44.
- Luchsinger JA, Gustafson DR (2009) Adiposity, type 2 diabetes, and Alzheimer's disease. *J Alzheimers Dis* 16:693–704. doi: 10.3233/JAD-2009-1022
- Luchsinger JA, Reitz C, Honig LS, et al (2005) Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* 65:545–51. doi: 10.1212/01.wnl.0000172914.08967.dc
- Luchsinger JA, Reitz C, Patel B, et al (2007) Relation of diabetes to mild cognitive impairment. *Arch Neurol* 64:570–5. doi: 10.1001/archneur.64.4.570
- Luchsinger JA, Tang MX, Shea S, et al (2004) Hyperinsulinemia and risk of Alzheimer disease. *Neurology* 63:1187–1192. doi: 10.1212/01.wnl.0000111877.02897.2c
- Luchsinger JA, Tang MX, Stern Y, et al (2001) Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. *Am J Epidemiol* 154:635–41. doi: 10.1093/aje/k114
- Luck T, Lupp M, Briel S, Riedel-Heller SG (2010) Incidence of mild cognitive impairment: a systematic review. *Dement Geriatr Cogn Disord* 29:164–75. doi: 10.1159/000272424
- Luzzatti C, Poeck K, Weniger D, et al (1996) AAT: Aachener aphasia test: manuale e dati normativi. *Organizzazioni speciali*
- Lynch JR, Tang W, Wang H, et al (2003) APOE genotype and an ApoE-mimetic peptide modify the systemic and central nervous system inflammatory response. *J Biol Chem* 278:48529–48533. doi: 10.1074/jbc.M306923200
- MacKnight C, Rockwood K, Awalt E, McDowell I (2002) Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian Study of Health and Aging. *Dement Geriatr Cogn Disord* 14:77–83. doi: 10.1159/000064928
- Mahley RW, Rall Jr. SC (2000) Apolipoprotein E: far more than a lipid transport protein. *Annu Rev Genomics Hum Genet* 1:507–537. doi: 10.1146/annurev.genom.1.1.507
- Mahley RW, Weisgraber KH, Huang Y (2006) Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc Natl Acad Sci U S A* 103:5644–51. doi: 10.1073/pnas.0600549103
- Manly JJ, Tang M-X, Schupf N, et al (2008) Frequency and course of mild cognitive impairment in a multiethnic community. *Ann Neurol* 63:494–506. doi: 10.1002/ana.21326
- Marioni RE, Valenzuela MJ, van den Hout A, et al (2012) Active cognitive lifestyle is associated with positive cognitive health transitions and compression of morbidity from age sixty-five. *PLoS One* 7:e50940. doi: 10.1371/journal.pone.0050940
- Marzona I, O'Donnell M, Teo K, et al (2012) Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *CMAJ* 184:E329–36. doi: 10.1503/cmaj.111173
- Matthews F, Brayne C, Arie T, et al (2005) The incidence of dementia in England and Wales: Findings from the five identical sites of the MRC CFA study. *PLoS Med* 2:0753–0763. doi: 10.1371/journal.pmed.0020193
- Matthews FE, Brayne C, Lowe J, et al (2009) Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. *PLoS Med* 6:e1000180. doi: 10.1371/journal.pmed.1000180
- Mauch DH, Nägler K, Schumacher S, et al (2001) CNS synaptogenesis promoted by glia-derived cholesterol. *Science* 294:1354–1357. doi: 10.1126/science.294.5545.1354
- McGeer EG, McGeer PL (1999) Brain inflammation in Alzheimer disease and the therapeutic implications. *Curr Pharm Des* 5:821–836.
- McKhann GM, Knopman DS, Chertkow H, et al (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement* 7:263–269. doi: 10.1016/j.jalz.2011.03.005

REFERENCES

- Measso G, Cavarzeran F, Zappalà G, et al (1993) The mini-mental state examination: Normative study of an Italian random sample. *Dev Neuropsychol* 9:77–85. doi: 10.1080/87565649109540545
- Meigs JB, Hu FB, Rifai N, Manson JE (2004) Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. *JAMA* 291:1978–1986. doi: 10.1001/jama.291.16.1978
- Merched A, Xia Y, Visvikis S, et al (2000) Decreased high-density lipoprotein cholesterol and serum apolipoprotein AI concentrations are highly correlated with the severity of Alzheimer's disease. *Neurobiol Aging* 21:27–30. doi: 10.1016/S0197-4580(99)00103-7
- Michikawa M (2003) Cholesterol paradox: Is high total or low HDL cholesterol level a risk for Alzheimer's disease? *J. Neurosci. Res.* 72:141–146.
- Mielke MM, Rosenberg PB, Tschanz J, et al (2007) Vascular factors predict rate of progression in Alzheimer disease. *Neurology* 69:1850–1858. doi: 10.1212/01.wnl.0000279520.59792.fe
- Mielke MM, Zandi PP, Sjogren M, et al (2005) High total cholesterol levels in late life associated with a reduced risk of dementia. *Neurology* 64:1689–1695. doi: 10.1212/01.WNL.0000161870.78572.A5
- Milionis HJ, Florentin M, Giannopoulos S (2008) Metabolic syndrome and Alzheimer's disease: a link to a vascular hypothesis? *CNS Spectr* 13:606–613. doi: 10.1017/S1092852900016886P
- Miller DI, Taler V, Davidson PSR, Messier C (2012) Measuring the impact of exercise on cognitive aging: methodological issues. *Neurobiol Aging* 33:622.e29–43. doi: 10.1016/j.neurobiolaging.2011.02.020
- Molenaar EA, Hwang S-J, Vasan RS, et al (2008) Burden and rates of treatment and control of cardiovascular disease risk factors in obesity: the Framingham Heart Study. *Diabetes Care* 31:1367–72. doi: 10.2337/dc07-2413
- Monastero R (2017) Prevalence and associated factors of Subjective Memory Complaints and Mild Cognitive Impairment in a Sicilian rural population: data from the Zabut Aging Project (oral communication). In: XII Convegno Nazionale SinDEM. Firenze, Italia, 16-18/3/17,
- Monastero R, Mangialasche F, Camarda C, et al (2009) A systematic review of neuropsychiatric symptoms in mild cognitive impairment. *J Alzheimers Dis* 18:11–30. doi: 10.3233/JAD-2009-1120
- Mooradian AD (1997) Central nervous system complications of diabetes mellitus - A perspective from the blood-brain barrier. *Brain Res. Rev.* 23:210–218.
- Morris JC (1997) Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int psychogeriatrics* 9 Suppl 1:173-6-8.
- Morris JC, Price JL (2001) Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *J Mol Neurosci* 17:101–118. doi: 10.1385/JMN:17:2:101
- Muller M, Tang MX, Schupf N, et al (2007) Metabolic syndrome and dementia risk in a multiethnic elderly cohort. *Dement Geriatr Cogn Disord* 24:185–192. doi: 10.1159/000105927
- Nagai M, Hoshida S, Kario K (2010) Hypertension and dementia. *Am J Hypertens* 23:116–24. doi: 10.1038/ajh.2009.212
- Nagy Z, Esiri MM, Jobst KA, et al (1997) The effects of additional pathology on the cognitive deficit in Alzheimer disease. *J Neuropathol Exp Neurol* 56:165–170.
- Newman AB, Fitzpatrick AL, Lopez O, et al (2005) Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *J Am Geriatr Soc* 53:1101–7. doi: 10.1111/j.1532-5415.2005.53360.x
- Ng JB, Turek M, Hakim AM (2013) Heart disease as a risk factor for dementia. *Clin Epidemiol* 5:135–145. doi: 10.2147/CLEP.S30621
- Ng TP, Feng L, Nyunt MSZ, et al (2016) Metabolic Syndrome and the Risk of Mild Cognitive Impairment and Progression to Dementia: Follow-up of the Singapore Longitudinal Ageing Study Cohort. *JAMA Neurol* 73:456–63. doi: 10.1001/jamaneurol.2015.4899
- Ngandu T, Lehtisalo J, Solomon A, et al (2015) A 2 year multidomain intervention of diet, exercise, cognitive training,

REFERENCES

- and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 385:2255–2263. doi: 10.1016/S0140-6736(15)60461-5
- Ngandu T, Von Strauss E, Helkala EL, et al (2007) Education and dementia: What lies behind the association? *Neurology* 69:1442–1450. doi: 10.1212/01.wnl.0000277456.29440.16
- Norton MC, Ostbye T, Smith KR, et al (2008) Early parental death and late-life dementia risk: findings from the Cache County Study. *Age Ageing* 38:340–343. doi: 10.1093/ageing/afp023
- Norton S, Matthews FE, Barnes DE, et al (2014) Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol* 13:788–94. doi: 10.1016/S1474-4422(14)70136-X
- Nourhashémi F, Deschamps V, Larrieu S, et al (2003) Body mass index and incidence of dementia: the PAQUID study. *Neurology* 60:117–119. doi: 10.1212/01.WNL.0000038910.46217.AA
- Novelli G, Papagno C, Capitani E, et al (1986) Tre test clinici di ricerca e produzione lessicale. Taratura su soggetti normali. *Arch Psicol Neurol Psichiat*. 47: 477–506.
- O'Rourke MF, Hashimoto J (2007) Mechanical Factors in Arterial Aging. *J Am Coll Cardiol* 50:1–13. doi: 10.1016/j.jacc.2006.12.050
- Olesen OF, Dagø L (2000) High density lipoprotein inhibits assembly of amyloid beta-peptides into fibrils. *Biochem Biophys Res Commun* 270:62–6. doi: 10.1006/bbrc.2000.2372
- ONTARGET IT (2008) Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events. *N Engl J Med* 358:1547–1559. doi: 10.1056/NEJMoa0801317
- Ott A, van Rossum CT, van Harskamp F, et al (1999) Education and the incidence of dementia in a large population-based study: the Rotterdam Study. *Neurology* 52:663–6.
- Pa J, Boxer A, Chao LL, et al (2009) Clinical-neuroimaging characteristics of dysexecutive mild cognitive impairment. *Ann Neurol* 65:414–423. doi: 10.1002/ana.21591
- Page RL (2004) Clinical practice. Newly diagnosed atrial fibrillation. *N Engl J Med* 351:2408–16. doi: 10.1056/NEJMc041956
- Palmer K, Bäckman L, Winblad B, Fratiglioni L (2008) Mild cognitive impairment in the general population: occurrence and progression to Alzheimer disease. *Am J Geriatr Psychiatry* 16:603–11. doi: 10.1097/JGP.0b013e3181753a64
- Pantoni L (2010) Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 9:689–701. doi: 10.1016/S1474-4422(10)70104-6
- Panza F, Capurso C, D'Introno A, et al (2008a) Vascular risk factors, alcohol intake, and cognitive decline. *J Nutr Heal Aging* 12:376–381.
- Panza F, Capurso C, D'Introno A, et al (2008b) Hypertension and mild cognitive impairment subtypes. *Arch Neurol* 65:992-3-5. doi: 10.1001/archneur.65.7.992-c
- Panza F, D'Introno A, Colacicco AM, et al (2004) Vascular risk and genetics of sporadic late-onset Alzheimer's disease. *J Neural Transm* 111:69–89. doi: 10.1007/s00702-003-0071-1
- Panza F, D'Introno A, Colacicco AM, et al (2006) Cognitive frailty: Predementia syndrome and vascular risk factors. *Neurobiol. Aging* 27:933–940.
- Panza F, Frisardi V, Capurso C, et al (2010) Metabolic syndrome and cognitive impairment: Current epidemiology and possible underlying mechanisms. *J Alzheimer's Dis* 21:691–724. doi: 10.3233/JAD-2010-091669
- Pearson TA, Mensah GA, Alexander RW, et al (2003) Markers of Inflammation and Cardiovascular Disease Application to Clinical and Public Health Practice: A Statement for Healthcare Professionals From the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 107:499–511.
- Pencina MJ, Sr RBDA, Larson MG, et al (2009) Predicting the Thirty-Year Risk of Cardiovascular Disease: The Framingham Heart Study. *Circulation* 119:3078–3084. doi: 10.1161/CIRCULATIONAHA.108.816694.Predicting

REFERENCES

- Perlmutter LC, Nathan DM, Goldfinger SH, et al (1988) Triglyceride levels affect cognitive function in noninsulin-dependent diabetics. *J Diabet Complications* 2:210–213. doi: 10.1016/S0891-6632(88)80011-4
- Perquin M, Schuller A-M, Vaillant M, et al (2012) The epidemiology of mild cognitive impairment (MCI) and Alzheimer's disease (AD) in community-living seniors: protocol of the MemoVie cohort study, Luxembourg. *BMC Public Health* 12:519. doi: 10.1186/1471-2458-12-519
- Persson G, Skoog I (1996) A PROSPECTIVE POPULATION STUDY OF PSYCHOSOCIAL RISK FACTORS FOR LATE ONSET DEMENTIA. *Int J Geriatr Psychiatry* 11:15–22. doi: 10.1002/(SICI)1099-1166(199601)11:1<15::AID-GPS262>3.0.CO;2-5
- Peters R (2009) The prevention of dementia. *Int J Geriatr Psychiatry* 24:452–458. doi: 10.1002/gps.2153
- Peters R, Beckett N (2009) Hypertension, dementia, and antihypertensive treatment: Implications for the very elderly. *Curr. Hypertens. Rep.* 11:277–282.
- Petersen RC (2004a) Mild cognitive impairment as a diagnostic entity. In: *Journal of Internal Medicine*. pp 183–194
- Petersen RC (2004b) Mild cognitive impairment as a clinical entity and treatment target. *Arch Neurol* 62:1160–1163; discussion 1167. doi: 10.1001/archneur.62.7.1160
- Petersen RC, Caracciolo B, Brayne C, et al (2014) Mild cognitive impairment: A concept in evolution. *J Intern Med* 275:214–228. doi: 10.1111/joim.12190
- Petersen RC, Roberts RO, Knopman DS, et al (2010) Prevalence of mild cognitive impairment is higher in men: The Mayo Clinic Study of Aging. *Neurology* 75:889–897. doi: 10.1212/WNL.0b013e3181f11d85
- Petersen RC, Roberts RO, Knopman DS, et al (2009) Mild cognitive impairment: ten years later. *Arch Neurol* 66:1447–55. doi: 10.1001/archneurol.2009.266
- Petersen RC, Smith GE, Ivnik RJ, et al (1995) Apolipoprotein E status as a predictor of the development of Alzheimer's disease in memory-impaired individuals. *JAMA* 273:1274–8.
- Petersen RC, Smith GE, Waring SC, et al (1999) Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 56:303–8.
- Petrovitch H, White LR, Izmirlian G, et al (2000) Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. *Neurobiol Aging* 21:57–62. doi: 10.1016/S0197-4580(00)00106-8
- Pigliautile M, Ricci M, Mioshi E, et al (2011) Validation study of the Italian Addenbrooke's Cognitive Examination Revised in a young-old and old-old population. *Dement Geriatr Cogn Disord* 32:301–7. doi: 10.1159/000334657
- Pirani A, Tulipani C NM (2006) Italian translation of MoCA test and of its instructions.
- Plassman BL, Langa KM, Fisher GG, et al (2008) Prevalence of cognitive impairment without dementia in the United States. *Ann Intern Med* 148:427–34. doi: 10.7326/0003-4819-148-6-200803180-00005
- Power MC, Weuve J, Gagne JJ, et al (2011) The association between blood pressure and incident Alzheimer disease: a systematic review and meta-analysis. *Epidemiology* 22:646–659. doi: 10.1097/EDE.0b013e31822708b5
- Prestia A, Rossi R, Geroldi C, et al (2006) Validation study of the three-objects-three-places test: a screening test for Alzheimer's disease. *Exp Aging Res* 32:395–410. doi: 10.1080/03610730600875767
- Prince M, Ferri CP, Acosta D, et al (2007) The protocols for the 10/66 dementia research group population-based research programme. *BMC Public Health* 7:165. doi: 10.1186/1471-2458-7-165
- Prince M, Wimo A, Guerchet M, et al (2015) The Global Impact of Dementia - An analysis of prevalence, incidence, cost and trends. *Alzheimer's Dis Int* 84.
- Profenno LA, Porsteinsson AP, Faraone S V (2010) Meta-analysis of Alzheimer's disease risk with obesity, diabetes, and related disorders. *Biol Psychiatry* 67:505–512. doi: 10.1016/j.biopsych.2009.02.013
- Purnell C, Gao S, Callahan CM, Hendrie HC (2008) Cardiovascular risk factors and incident Alzheimer disease: a systematic review of the literature. *Alzheimer Dis Assoc Disord* 23:1–10. doi: 10.1097/WAD.0b013e318187541c

REFERENCES

- Purser JL, Fillenbaum GG, Pieper CF WR (2005) Mild cognitive impairment and 10-year trajectories of disability in the Iowa Established Populations for Epidemiologic Studies of the Elderly cohort. - PubMed - NCBI. In: J Am Geriatr Soc. <https://www.ncbi.nlm.nih.gov/pubmed/16274380>. Accessed 18 Dec 2016
- Qiu C (2012) Preventing Alzheimer's disease by targeting vascular risk factors: Hope and gap. *J. Alzheimer's Dis.* 32:721–731.
- Qiu C, De Ronchi D, Fratiglioni L (2007) The epidemiology of the dementias: an update. *Curr Opin Psychiatry* 20:380–385. doi: 10.1097/YCO.0b013e32816ebc7b
- Qiu C, Fratiglioni L (2015) A major role for cardiovascular burden in age-related cognitive decline. *Nat Rev Cardiol* 12:267–277. doi: 10.1038/nrcardio.2014.223
- Qiu C, Sigurdsson S, Zhang Q, et al (2014) Diabetes, markers of brain pathology and cognitive function. *Ann Neurol* 75:138–146. doi: 10.1002/ana.24063
- Qiu C, von Strauss E, Fastbom J, et al (2003) Low blood pressure and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Arch Neurol* 60:223–8. doi: 10.1001/archneur.60.2.223
- Qiu C, Winblad B, Fratiglioni L (2005) The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol.* 4:487–499.
- Qiu C, Winblad B, Fratiglioni L (2009) Low diastolic pressure and risk of dementia in very old people: A longitudinal study. *Dement Geriatr Cogn Disord* 28:213–219. doi: 10.1159/000236913
- Qiu C, Xu W, Fratiglioni L (2010) Vascular and psychosocial factors in Alzheimer's disease: epidemiological evidence toward intervention. *J Alzheimers Dis* 20:689–97. doi: 10.3233/JAD-2010-091663
- Qiu WQ, Ye Z, Kholodenko D, et al (1997) Degradation of amyloid β -protein by a metalloprotease secreted by microglia and other neural and non-neural cells. *J Biol Chem* 272:6641–6646. doi: 10.1074/jbc.272.10.6641
- Raffaitin C, Gin H, Empana J, et al (2009) Metabolic Syndrome and Risk for Incident Alzheimer's Disease or Vascular Dementia. *Cardiovasc Metab Risk* 32:169–174. doi: 10.2337/dc08-0272.
- Rapp A, Gmeiner B, Huttinger M (2006) Implication of apoE isoforms in cholesterol metabolism by primary rat hippocampal neurons and astrocytes. *Biochimie* 88:473–483. doi: 10.1016/j.biochi.2005.10.007
- Ravaglia G, Forti P, Montesi F, et al (2008) Mild Cognitive Impairment: Epidemiology and Dementia Risk in an Elderly Italian Population. *J Am Geriatr Soc* 56:51–58. doi: 10.1111/j.1532-5415.2007.01503.x
- Razay G, Vreugdenhil A, Wilcock G (2007) The metabolic syndrome and Alzheimer disease. *Arch Neurol* 64:93–96. doi: 10.1001/archneur.64.1.93
- Reaven GM (1988) Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 37:1595–1607. doi: 10.2337/diab.37.12.1595
- Reid PC, Urano Y, Kodama T, Hamakubo T (2007) Alzheimer's disease: Cholesterol, membrane rafts, isoprenoids and statins. *J Cell Mol Med* 11:383–392. doi: 10.1111/j.1582-4934.2007.00054.x
- Reijmer YD, Van Den Berg E, Van Sonsbeek S, et al (2011) Dementia risk score predicts cognitive impairment after a period of 15 years in a nondemented population. *Dement Geriatr Cogn Disord* 31:152–157. doi: 10.1159/000324437
- Reiman EM, Chen K, Liu X, et al (2009) Fibrillar amyloid- β burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proc Natl Acad Sci U S A* 106:6820–6825. doi: 0900345106 [pii]r10.1073/pnas.0900345106
- Reitz C, Luchsinger J, Tang MX, et al (2005) Impact of plasma lipids and time on memory performance in healthy elderly without dementia. *Neurology* 64:1378–1383. doi: 10.1212/01.wnl.0000158274.31318.3c
- Reitz C, Tang M-X, Luchsinger J, Mayeux R (2004) Relation of plasma lipids to Alzheimer disease and vascular dementia. *Arch Neurol* 61:705–14. doi: 10.1001/archneur.61.5.705
- Reitz C, Tang M-X, Manly J, et al (2007) Hypertension and the risk of mild cognitive impairment. *Arch Neurol* 64:1734–40. doi: 10.1001/archneur.64.12.1734

REFERENCES

- Reitz C, Tang M-X, Manly J, et al (2008) Plasma lipid levels in the elderly are not associated with the risk of mild cognitive impairment. *Dement Geriatr Cogn Disord* 25:232–7. doi: 10.1159/000115847
- Reitz C, Tang M-X, Schupf N, et al (2010) A summary risk score for the prediction of Alzheimer disease in elderly persons. *Arch Neurol* 67:835–41. doi: 10.1001/archneurol.2010.136
- Rennie KL, Jebb SA (2005) Prevalence of obesity in Great Britain. *Obes Rev* 6:11–12. doi: OBR164 [pii]r10.1111/j.1467-789X.2005.00164.x
- Rey A (1964) *L'Examen Clinique en Psychologie* [Clinical Examination in Psychology].
- Richard E, Andrieu S, Solomon A, et al (2012) Methodological challenges in designing dementia prevention trials — The European Dementia Prevention Initiative (EDPI). *J Neurol Sci* 322:64–70. doi: 10.1016/j.jns.2012.06.012
- Richard E, den Heuvel E Van, Moll van Charante EP, et al (2009) Prevention of Dementia by Intensive Vascular Care (PreDIVA). *Alzheimer Dis Assoc Disord* 23:198–204. doi: 10.1097/WAD.0b013e31819783a4
- Richard E, Gouw AA, Scheltens P, van Gool WA (2010) Vascular Care in Patients With Alzheimer Disease With Cerebrovascular Lesions Slows Progression of White Matter Lesions on MRI: The Evaluation of Vascular Care in Alzheimer's Disease (EVA) Study. *Stroke* 41:554–556. doi: 10.1161/STROKEAHA.109.571281
- Ridker PM, Buring JE, Cook NR, Rifai N (2003) C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 107:391–397. doi: 10.1161/01.CIR.0000055014.62083.05
- Ringman JM, Elashoff D, Geschwind DH, et al (2012) Plasma signaling proteins in persons at genetic risk for Alzheimer disease: influence of APOE genotype. *Arch Neurol* 69:757–64. doi: 10.1001/archneurol.2012.277
- Roberts RO, Geda YE, Knopman DS, et al (2012) The incidence of MCI differs by subtype and is higher in men: the Mayo Clinic Study of Aging. *Neurology* 78:342–51. doi: 10.1212/WNL.0b013e3182452862
- Roberts RO, Geda YE, Knopman DS, et al (2008) Association of duration and severity of diabetes mellitus with mild cognitive impairment. *Arch Neurol* 65:1066–73. doi: 10.1001/archneur.65.8.1066
- Roberts RO, Geda YE, Knopman DS, et al (2010a) Metabolic syndrome, inflammation, and nonamnesic mild cognitive impairment in older persons: a population-based study. *Alzheimer Dis Assoc Disord* 24:11–8. doi: 10.1097/WAD.0b013e3181a4485c
- Roberts RO, Knopman DS, Geda YE, et al (2010b) Coronary heart disease is associated with non-amnesic mild cognitive impairment. *Neurobiol Aging* 31:1894–902. doi: 10.1016/j.neurobiolaging.2008.10.018
- Roberts RO, Knopman DS, Przybelski SA, et al (2014) Association of type 2 diabetes with brain atrophy and cognitive impairment. *Neurology* 82:1132–1141. doi: 10.1212/WNL.0000000000000269
- Rodrigue KM, Rieck JR, Kennedy KM, et al (2013) Risk factors for β -amyloid deposition in healthy aging: vascular and genetic effects. *JAMA Neurol* 70:600–6. doi: 10.1001/jamaneurol.2013.1342
- Romas SN, Tang MX, Berglund L, Mayeux R (1999) APOE genotype, plasma lipids lipoproteins, and AD in community elderly. *Neurology* 53:517–521. doi: 10.1212/WNL.53.3.517
- Roriz-Filho JS, Sá-Roriz TM, Rosset I, et al (2009) (Pre)diabetes, brain aging, and cognition. *Biochim. Biophys. Acta - Mol. Basis Dis.* 1792:432–443.
- Ross CA, Poirier MA (2004) Protein aggregation and neurodegenerative disease. *Nat Med* 10:S10–S17. doi: 10.1038/nm1066
- Rowe CC, Ellis KA, Rimajova M, et al (2010) Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging* 31:1275–1283. doi: 10.1016/j.neurobiolaging.2010.04.007
- Ruitenbergh A, Skoog I, Ott A, Aevarsson O (2001) Blood pressure and risk of dementia : Results from the Rotterdam study and th ... *Blood Press* 33–39. doi: 10.1159/000051233
- Russ TC, Batty GD, Hearnshaw GF, et al (2012) Geographical variation in dementia: Systematic review with meta-analysis. *Int J Epidemiol* 41:1012–1032. doi: 10.1093/ije/dys103

REFERENCES

- Salkovic-Petrisic M, Osmanovic J, Grünblatt E, et al (2009) Modeling sporadic Alzheimer's disease: The insulin resistant brain state generates multiple long-term morphobiological abnormalities including hyperphosphorylated tau protein and amyloid- β . *J. Alzheimer's Dis.* 18:729–750.
- Sanders DW, Kaufman SK, DeVos SL, et al (2014) Distinct tau prion strains propagate in cells and mice and define different tauopathies. *Neuron* 82:1271–1288. doi: 10.1016/j.neuron.2014.04.047
- Santangeli P, Di Biase L, Bai R, et al (2012) Atrial fibrillation and the risk of incident dementia: a meta-analysis. *Heart Rhythm* 9:1761–8. doi: 10.1016/j.hrthm.2012.07.026
- Sapolsky RM (1999) Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. *Exp Gerontol* 34:721–732. doi: 10.1016/S0531-5565(99)00047-9
- Sasaki M, Kodama C, Hidaka S, et al (2009) Prevalence of four subtypes of mild cognitive impairment and APOE in a Japanese community. *Int J Geriatr Psychiatry* 24:1119–26. doi: 10.1002/gps.2234
- Savaskan E, Hock C, Olivieri G, et al (2001) Cortical alterations of angiotensin converting enzyme, angiotensin II and AT1 receptor in Alzheimer's dementia. *Neurobiol Aging* 22:541–546. doi: 10.1016/S0197-4580(00)00259-1
- Scheltens P, Blennow K, Breteler MMB, et al (2016) Alzheimer's disease. *Lancet (London, England)* 388:505–17. doi: 10.1016/S0140-6736(15)01124-1
- Schneider JA, Arvanitakis Z, Bang W, Bennett DA (2007) Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* 69:2197–2204. doi: 10.1212/01.wnl.0000271090.28148.24
- Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA (2009) The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol* 66:200–208. doi: 10.1002/ana.21706
- Schneider JA, Wilson RS, Bienias JL, et al (2004) Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. *Neurology* 62:1148–55.
- Schreiber S, Drukarch B, Garz C, et al (2014) Interplay between age, cerebral small vessel disease, parenchymal amyloid- β , and tau pathology: longitudinal studies in hypertensive stroke-prone rats. *J Alzheimers Dis* 42 Suppl 3:S205-15. doi: 10.3233/JAD-132618
- Schrijvers EMC, Verhaaren BFJ, Koudstaal PJ, et al (2012) Is dementia incidence declining?: Trends in dementia incidence since 1990 in the Rotterdam Study. *Neurology* 78:1456–1463. doi: 10.1212/WNL.0b013e3182553be6
- Ser T Del, Hachinski V, Merskey H, Munoz DG (1999) An autopsy-verified study of the effect of education on degenerative dementia. *Brain* 122:2309–2319.
- Seshadri S, Wolf PA, Beiser A, et al (2004a) Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. *Neurology* 63:1591–9. doi: 10.1212/01.WNL.0000142968.22691.70
- Seshadri S, Wolf PA, Beiser A, et al (2004b) Stroke risk profile, brain volume, and cognitive function: the Framingham Offspring Study. *Neurology* 63:1591–9.
- Shepardson NE, Shankar GM, Selkoe DJ (2011) Cholesterol level and statin use in Alzheimer disease: II. Review of human trials and recommendations. *Arch Neurol* 68:1385–1392. doi: 10.1001/archneurol.2011.242
- Shiue I (2011) Age of onset for stroke delayed in the 21st century: What is next? *Clin Neurol Neurosurg* 113:725–726. doi: 10.1016/j.clineuro.2011.07.015
- Shulman KI, Pushkar Gold D, Cohen CA, Zuccherro CA (1993) Clock-drawing and dementia in the community: A longitudinal study. *Int J Geriatr Psychiatry* 8:487–496. doi: 10.1002/gps.930080606
- Silvestrini M, Pasqualetti P, Baruffaldi R, et al (2006) Cerebrovascular reactivity and cognitive decline in patients with Alzheimer disease. *Stroke* 37:1010–1015. doi: 10.1161/01.STR.0000206439.62025.97
- Sindi S, Calov E, Fokkens J, et al (2015) The CAIDE Dementia Risk Score App: The development of an evidence-based mobile application to predict the risk of dementia. *Alzheimer's Dement Diagnosis, Assess Dis Monit* 1:328–333. doi: 10.1016/j.dadm.2015.06.005
- Singh-Manoux A, Marmot MG, Glymour M, et al (2011) Does cognitive reserve shape cognitive decline? *Ann Neurol*

REFERENCES

- 70:296–304. doi: 10.1002/ana.22391
- Sirkis DW, Bonham LW, Aparicio RE, et al (2016) Rare TREM2 variants associated with Alzheimer's disease display reduced cell surface expression. *Acta Neuropathol Commun* 4:98. doi: 10.1186/s40478-016-0367-7
- Skoog I, Lernfelt B, Landahl S, et al (1996) 15-year longitudinal study of blood pressure and dementia. *Lancet* 347:1141–1145. doi: 10.1016/S0140-6736(96)90608-X
- Small SA, Duff K (2008) Linking A β and Tau in Late-Onset Alzheimer's Disease: A Dual Pathway Hypothesis. *Neuron* 60:534–542.
- Snaith RP (2003) The Hospital Anxiety And Depression Scale. *Health Qual Life Outcomes* 1:29. doi: 10.1186/1477-7525-1-29
- Snowdon DA, Greiner LH, Mortimer JA, et al (1997) Brain Infarction and the Clinical Expression of Alzheimer Disease: The Nun Study. *JAMA J Am Med Assoc* 277:813–817. doi: 10.1001/jama.1997.03540340047031
- Solfrizzi V, Capurso C, D'Introno A, et al (2008) Lifestyle-related factors in predementia and dementia syndromes. *Expert Rev Neurother* 8:133–58. doi: 10.1586/14737175.8.1.133
- Solfrizzi V, Panza F, Colacicco AM, et al (2004) Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology* 63:1882–91.
- Solfrizzi V, Scafato E, Capurso C, et al (2010) Metabolic syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Ageing. *J Neurol Neurosurg Psychiatry* 81:433–440. doi: 10.1136/jnnp.2009.181743
- Solfrizzi V, Scafato E, Capurso C, et al (2011) Metabolic syndrome, mild cognitive impairment, and progression to dementia. The Italian Longitudinal Study on Ageing. *Neurobiol Aging* 32:1932–41. doi: 10.1016/j.neurobiolaging.2009.12.012
- Solomon A, Kåreholt I, Ngandu T, et al (2007) Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study. *Neurology* 68:751–6. doi: 10.1212/01.wnl.0000256368.57375.b7
- Soneira CF, Scott TM (1996) Severe cardiovascular disease and Alzheimer's disease: Senile plaque formation in cortical areas. *Clin Anat* 9:118–127. doi: 10.1002/(SICI)1098-2353(1996)9:2<118::AID-CA4>3.0.CO;2-D
- Song IU, Kim JS, Kim YI, et al (2007) Clinical significance of silent cerebral infarctions in patients with Alzheimer disease. *Cogn Behav Neurol* 20:93–98. doi: 10.1097/WNN.0b013e31805d859e.r00146965-200706000-00003 [pii]
- Starkstein SE, Mayberg HS, Preziosi TJ, et al (1992) Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 4:134–9. doi: 10.1176/jnp.4.2.134
- Stephan BCM, Matthews FE, Hunter S, et al (2012) Neuropathological Profile of Mild Cognitive Impairment From a Population Perspective. *Alzheimer Dis Assoc Disord* 26:205–212. doi: 10.1097/WAD.0b013e31822fc24d
- Stern Y (2012) Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* 11:1006–12. doi: 10.1016/S1474-4422(12)70191-6
- Stern Y (2002) What is cognitive reserve? Theory and research application of the reserve concept. *J Int Neuropsychol Soc* 8:448–460. doi: 10.1017/S1355617702813248
- Stern Y, Alexander GE, Prohovnik I, et al (1995) Relationship between lifetime occupation and parietal flow: implications for a reserve against Alzheimer's disease pathology. *Neurology* 45:55–60.
- Stern Y, Gurland B, Tatemichi TK, et al (1994) Influence of education and occupation on the incidence of Alzheimer's disease. *JAMA* 271:1004–1010. doi: 10.1001/jama.271.13.1004
- Stewart R, Masaki K, Xue QL, et al (2005) A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. *ArchNeurol* 62:55–60.
- Stewart R, Xue Q-L, Masaki K, et al (2009) Change in blood pressure and incident dementia: a 32-year prospective study. *Hypertens (Dallas, Tex 1979)* 54:233–40. doi: 10.1161/HYPERTENSIONAHA.109.128744
- Stewart S, Hart CL, Hole DJ, McMurray JJ V (2002) A population-based study of the long-term risks associated with

REFERENCES

- atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 113:359–64. doi: 10.1016/S0002-9343(02)01236-6
- Strachan MWJ, Reynolds RM, Marioni RE, Price JF (2011) Cognitive function, dementia and type 2 diabetes mellitus in the elderly. *Nat Rev Endocrinol* 7:108–114. doi: 10.1038/nrendo.2010.228
- Strozyk D, Dickson DW, Lipton RB, et al (2010) Contribution of vascular pathology to the clinical expression of dementia. *Neurobiol Aging* 31:1710–20. doi: 10.1016/j.neurobiolaging.2008.09.011
- Sun X, He G, Qing H, et al (2006) Hypoxia facilitates Alzheimer's disease pathogenesis by up-regulating BACE1 gene expression. *Proc Natl Acad Sci U S A* 103:18727–32. doi: 10.1073/pnas.0606298103
- Tan ZS, Seshadri S, Beiser A, et al (2003) Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study. *Arch Intern Med* 163:1053–1057. doi: 10.1001/archinte.163.9.1053
- Tervo S, Kivipelto M, Hanninen T, et al (2004a) Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. *Dement Geriatr Cogn Disord* 17:196–203.
- Tervo S, Kivipelto M, Hänninen T, et al (2004b) Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. *Dement Geriatr Cogn Disord* 17:196–203. doi: 10.1159/000076356
- Tesco G, Koh YH, Kang EL, et al (2007) Depletion of GGA3 Stabilizes BACE and Enhances γ -Secretase Activity. *Neuron* 54:721–737. doi: 10.1016/j.neuron.2007.05.012
- Tezapsidis N, Johnston JM, Smith MA, et al (2009) Leptin: a novel therapeutic strategy for Alzheimer's disease. *J Alzheimers Dis* 16:731–40. doi: 10.3233/JAD-2009-1021
- Thacker EL, McKnight B, Psaty BM, et al (2013) Atrial fibrillation and cognitive decline: a longitudinal cohort study. *Neurology* 81:119–25. doi: 10.1212/WNL.0b013e31829a33d1
- Tola-Arribas MA, Yugueros MI, Garea MJ, et al (2013) Prevalence of Dementia and Subtypes in Valladolid, Northwestern Spain: The DEMINVALL Study. *PLoS One* 8:e77688. doi: 10.1371/journal.pone.0077688
- Toledo JB, Arnold SE, Raible K, et al (2013) Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain* 136:2697–2706. doi: 10.1093/brain/awt188
- Toro P, Degen C, Pierer M, et al (2014) Cholesterol in mild cognitive impairment and Alzheimer's disease in a birth cohort over 14 years. *Eur Arch Psychiatry Clin Neurosci* 264:485–492. doi: 10.1007/s00406-013-0468-2
- Tragni E, Filippi A, Casula M, et al (2012) Risk factors distribution and cardiovascular disease prevalence in the Italian population: The CHECK study. *Open J Epidemiol* 2:90–100. doi: 10.4236/ojepi.2012.24014
- TRANSCEND I (2008) Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 372:1174–1183. doi: 10.1016/S0140-6736(08)61242-8
- Tzourio C, Dufouil C, Ducimetière P, Alpérovitch A (1999) Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. *Epidemiology of Vascular Aging. Neurology* 53:1948–52.
- Udompanich S, Lip GYH, Apostolakis S, Lane DA (2013) Atrial fibrillation as a risk factor for cognitive impairment: a semi-systematic review. *QJM* 106:795–802. doi: 10.1093/qjmed/hct129
- Um JW, Kaufman AC, Kostylev M, et al (2013) Metabotropic Glutamate Receptor 5 Is a Coreceptor for Alzheimer A β Oligomer Bound to Cellular Prion Protein. *Neuron* 79:887–902. doi: 10.1016/j.neuron.2013.06.036
- Unverzagt FW, McClure LA, Wadley VG, et al (2011) Vascular risk factors and cognitive impairment in a stroke-free cohort. *Neurology* 77:1729–36. doi: 10.1212/WNL.0b013e318236ef23
- van Charante EPM, Richard E, Eurelings LS, et al (2016) Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet* 388:797–805. doi: 10.1016/S0140-6736(16)30950-3

REFERENCES

- Van Den Berg E, Biessels GJ, De Craen AJM, et al (2007) The metabolic syndrome is associated with decelerated cognitive decline in the oldest old. *Neurology* 69:979–985. doi: 10.1212/01.wnl.0000271381.30143.75
- van der Linde RM, Stephan BCM, Matthews FE, et al (2013) The presence of behavioural and psychological symptoms and progression to dementia in the cognitively impaired older population. *Int J Geriatr Psychiatry* 28:700–9. doi: 10.1002/gps.3873
- Van Exel E, De Craen AJM, Gussekloo J, et al (2002) Association between high-density lipoprotein and cognitive impairment in the oldest old. *Ann Neurol* 51:716–721. doi: 10.1002/ana.10220
- van Vliet P, van de Water W, de Craen AJM, Westendorp RGJ (2009) The influence of age on the association between cholesterol and cognitive function. *Exp Gerontol* 44:112–122. doi: 10.1016/j.exger.2008.05.004
- Vanhanen M, Koivisto K, Moilanen L, et al (2006) Association of metabolic syndrome with Alzheimer disease: A population-based study. *Neurology* 67:843–847. doi: 10.1212/01.wnl.0000234037.91185.99
- Vellas B, Carrie I, Gillette-Guyonnet S, et al (2014) MAPT STUDY: A MULTIDOMAIN APPROACH FOR PREVENTING ALZHEIMER'S DISEASE: DESIGN AND BASELINE DATA. *J Prev Alzheimer's Dis* 1:13–22.
- Vemuri P, Wiste HJ, Weigand SD, et al (2010) Effect of apolipoprotein E on biomarkers of amyloid load and neuronal pathology in Alzheimer disease. *Ann Neurol* 67:308–316. doi: 10.1002/ana.21953
- Vergheze J, Lipton RB, Hall CB, et al (2003) Low blood pressure and the risk of dementia in very old individuals. *Neurology* 61:1667–1672. doi: 10.1212/01.WNL.0000098934.18300.BE
- Vermeer SE, Prins ND, den Heijer T, et al (2003) Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med* 348:1215–1222. doi: 10.1056/NEJMoa022066
- Vessby B, Uusitupa M, Hermansen K, et al (2001) Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU study. *Diabetologia* 44:312–319. doi: 10.1007/s001250051620
- Villemagne VL, Pike KE, Chetelat G, et al (2011) Longitudinal assessment of A β and cognition in aging and Alzheimer disease. *Ann Neurol* 69:181–192. doi: 10.1002/ana.22248
- Virta JJ, Heikkilä K, Perola M, et al (2013) Midlife cardiovascular risk factors and late cognitive impairment. *Eur J Epidemiol* 28:405–416. doi: 10.1007/s10654-013-9794-y
- Viswanathan A, Rocca WA, Tzourio C (2009) Vascular risk factors and dementia: How to move forward? *Neurology* 72:368–374.
- W. R. Miles, H. F. Root (1922) Psychologic tests applied to diabetic patients. *Arch Intern Med* 30:767–777. doi: 10.1001/archinte.1922.00110120086003
- Waldstein SR, Siegel EL, Lefkowitz D, et al (2004) Stress-induced blood pressure reactivity and silent cerebrovascular disease. *Stroke* 35:1294–1298. doi: 10.1161/01.STR.0000127774.43890.5b
- Walter J, Kaether C, Steiner H, Haass C (2001) The cell biology of Alzheimer's disease: uncovering the secrets of secretases. *Curr Opin Neurobiol* 11:585–590. doi: 10.1016/S0959-4388(00)00253-1
- Wang C, Wilson WA, Moore SD, et al (2005) Human apoE4-targeted replacement mice display synaptic deficits in the absence of neuropathology. *Neurobiol Dis* 18:390–398. doi: 10.1016/j.nbd.2004.10.013
- Warsch JRL, Rundek T, Paik MC, et al (2013) Association between Northern Manhattan study global vascular risk score and successful aging. *J Am Geriatr Soc* 61:519–524. doi: <http://dx.doi.org/10.1111/jgs.12166>
- Watson GS, Craft S (2003) The Role of Insulin Resistance in the Pathogenesis of Alzheimer's Disease Implications for Treatment. *CNS Drugs* 17:27–45.
- Watts JC, Condello C, Stöhr J, et al (2014) Serial propagation of distinct strains of A β prions from Alzheimer's disease patients. *Proc Natl Acad Sci U S A* 111:10323–8. doi: 10.1073/pnas.1408900111
- Wechsler D (1997) WAIS III administration and scoring manual.

REFERENCES

- Wen Y, Onyewuchi O, Yang S, et al (2004) Increased beta-secretase activity and expression in rats following transient cerebral ischemia. *Brain Res* 1009:1–8. doi: 10.1016/j.brainres.2003.09.086
- Whalley LJ, Dick FD, McNeill G (2006) A life-course approach to the aetiology of late-onset dementias. *Lancet Neurol* 5:87–96. doi: 10.1016/S1474-4422(05)70286-6
- Wharton SB, Brayne C, Savva GM, et al (2011) Epidemiological neuropathology: the MRC Cognitive Function and Aging Study experience. *J Alzheimers Dis* 25:359–372. doi: 10.3233/JAD-2011-091402
- White L (2009) Brain lesions at autopsy in older Japanese-American men as related to cognitive impairment and dementia in the final years of life: a summary report from the Honolulu-Asia aging study. *J Alzheimers Dis* 18:713–25. doi: 10.3233/JAD-2009-1178
- Whitehair DC, Sherzai A, Emond J, et al (2010) Influence of apolipoprotein E e4 on rates of cognitive and functional decline in mild cognitive impairment. *Alzheimer's Dement* 6:412–419.
- Whitmer R a (2007) The epidemiology of adiposity and dementia. *Curr Alzheimer Res* 4:117–122. doi: 10.2174/156720507780362065
- Whitmer RA, Gustafson DR, Barrett-Connor E, et al (2008) Central obesity and increased risk of dementia more than three decades later.[see comment]. *Neurology* 71:1057–1064. doi: 10.1212/01.wnl.0000306313.89165.ef
- Whitmer RA, Sidney S, Selby J, et al (2005a) Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 64:277–81. doi: 10.1212/01.WNL.0000149519.47454.F2
- Whitmer R, Gunderson E, Barrett-Connor E, et al (2005b) Obesity in middle age and future risk of dementia: A 27 year longitudinal population based study. *BMJ* 330:1360. doi: 10.1136/bmj.38446.466238.E0
- WHO (1995) Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ. Tech. Rep. Ser. 854:1–452.
- WHO (2009) Global Health Risks: Mortality and burden of disease attributable to selected major risks. *Bull World Health Organ* 87:646–646. doi: 10.2471/BLT.09.070565
- Wild S, Roglic G, Green A, et al (2004) Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047–1053. doi: 10.2337/diacare.27.5.1047
- Winblad B, Amouyel P, Andrieu S, et al (2016) Defeating Alzheimer's disease and other dementias: A priority for European science and society. *Lancet Neurol* 15:455–532. doi: 10.1016/S1474-4422(16)00062-4
- Winblad B, Palmer K, Kivipelto M, et al (2004) Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 256:240–6. doi: 10.1111/j.1365-2796.2004.01380.x
- Wolf H, Hensel A, Arendt T, et al (2004) Serum lipids and hippocampal volume: The link to Alzheimer's disease? *Ann Neurol* 56:745–748. doi: 10.1002/ana.20289
- Xie J, Brayne C, Matthews FE, and the Medical Research Council Cognitive Function and Ageing Study C (2008) Survival times in people with dementia: analysis from population based cohort study with 14 year follow-up. *BMJ* 336:258–62. doi: 10.1136/bmj.39433.616678.25
- Xu WL, Atti AR, Gatz M, et al (2011) Midlife overweight and obesity increase late-life dementia risk: A population-based twin study. *Neurology* 76:1568–1574. doi: 10.1212/WNL.0b013e3182190d09
- Yaffe K (2007) Metabolic syndrome and cognitive disorders: Is the sum greater than its parts? *Alzheimer Dis Assoc Disord* 21:167–171. doi: 10.1097/WAD.0b013e318065bfd6
- Yaffe K, Barrett-Connor E, Lin F, Grady D (2002) Serum lipoprotein levels, statin use, and cognitive function in older women. *Arch Neurol* 59:378–384. doi: noc10119 [pii]
- Yaffe K, Blackwell T, Kanaya AM, et al (2004a) Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology* 63:658–663. doi: 10.1212/01.WNL.0000134666.64593.BA
- Yaffe K, Kanaya A, Lindquist K, et al (2004b) The metabolic syndrome, inflammation, and risk of cognitive decline.

REFERENCES

- JAMA 292:2237–2242. doi: 10.1016/j.accreview.2004.12.135
- Yaffe K, Lindquist K, Penninx BW, et al (2003) Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology* 61:76–80. doi: 10.1212/01.WNL.0000073620.42047.D7
- Yaffe K, Weston AL, Blackwell T, Krueger KA (2009) The metabolic syndrome and development of cognitive impairment among older women. *Arch Neurol* 66:324–328. doi: 10.1001/archneurol.2008.566
- Yan S Du, Bierhaus A, Nawroth PP, Stern DM (2009) RAGE and Alzheimer's disease: a progression factor for amyloid-beta-induced cellular perturbation? *J Alzheimers Dis* 16:833–43. doi: 10.3233/JAD-2009-1030
- Yang C-P, Gilley J a., Zhang G, Kernie SG (2011) ApoE is required for maintenance of the dentate gyrus neural progenitor pool. *Development* 138:4351–4362. doi: 10.1242/dev.065540
- Yao Q, Jiang G-X, Zhou Z-M, et al (2016) Metabolic Syndrome and Mild Cognitive Impairment: A Case-Control Study among Elderly in a Shanghai Suburb. *J Alzheimers Dis* 51:1175–82. doi: 10.3233/JAD-150920
- Yu J-T, Tan L, Hardy J (2014) Apolipoprotein E in Alzheimer's Disease: An Update. *Annu Rev Neurosci* 37:79–100. doi: 10.1146/annurev-neuro-071013-014300
- Zeki Al Hazzouri A, Haan MN, Neuhaus JM, et al (2013) Cardiovascular risk score, cognitive decline, and dementia in older Mexican Americans: the role of sex and education. *J Am Hear Assoc* 2:e004978. doi: 10.1161/jaha.113.004978
- Zhao WQ, Townsend M (2009) Insulin resistance and amyloidogenesis as common molecular foundation for type 2 diabetes and Alzheimer's disease. *Biochim. Biophys. Acta - Mol. Basis Dis.* 1792:482–496.
- Zhiyou C, Yong Y, Shanquan S, et al (2009) Upregulation of BACE1 and beta-amyloid protein mediated by chronic cerebral hypoperfusion contributes to cognitive impairment and pathogenesis of Alzheimer's disease. *Neurochem Res* 34:1226–35. doi: 10.1007/s11064-008-9899-y

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