

Review

Beyond mild cognitive impairment: vascular cognitive impairment, no dementia (VCIND)

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Abstract

Identifying the causes of dementia is important in the search for effective preventative and treatment strategies. The concept of mild cognitive impairment (MCI), as prodromal dementia, has been useful but remains controversial since in population-based studies it appears to be a limited predictor of progression to dementia. Recognising the relative contribution of neurodegenerative and vascular causes, as well as their interrelationship, may enhance predictive accuracy. The concept of vascular cognitive impairment (VCI) has been introduced to describe the spectrum of cognitive change related to vascular causes from early cognitive decline to dementia. A recent review of this concept highlighted the need for diagnostic criteria that encompass the full range of the VCI construct. However, very little is known regarding the mildest stage of VCI, generally termed 'vascular cognitive impairment, no dementia' (VCIND). Whether mild cognitive change in the context of neurodegenerative pathologies is distinct from that in the context of cerebrovascular diseases is not known. This is key to the definition of VCIND and whether it is possible to identify this state. Distinguishing between vascular (that is, VCIND) and non-vascular (that is, MCI) cognitive disorders and determining how well each might predict dementia may not be possible due to the overlap in pathologies observed in the older population. Here, we review the concept of VCIND in an effort to identify recent developments and areas of controversy in nosology and the application of VCIND for screening individuals at increased risk of dementia secondary to vascular disease and its risk factors.

Introduction

A better understanding of dementia, including its causes, underlying pathophysiological processes and earliest possible identification, has become a major public health priority. Changes in cognition associated with age are complex, especially with regard to distinguishing usual from pathological brain ageing. Multiple and often intertwined

pathological factors, including atrophy, neurodegeneration, inflammation, stroke and genetic-related factors, cause dementia [1]. Here, we explore the link between vascular disease, cognitive decline and dementia risk. Given the relatively high proportion of dementia attributable to possibly reversible midlife vascular causes [2], it has been suggested that vascular risk manipulation may result in up to a 50% reduction in the forecasted dementia prevalence rate in individuals who are 65 years old or older [3,4]. Vascular risk factors for dementia may also contribute to impairments observed in the pre-clinical stage of cognitive decline. This has raised questions regarding (a) whether vascular disease can predict cognitive change and dementia risk in otherwise non-impaired individuals and (b) the duration and possible reversal of cognitive symptoms and dementia depending on vascular disease manipulation and treatment. The aim of this review is to describe the current understanding of the division between pre-clinical cognitive impairment in the context of vascular disease versus the absence of vascular disease. The focus will be on the term 'vascular cognitive impairment, no dementia' (VCIND), an umbrella term that broadly encompasses cognitive deficits associated with vascular disease which fall short of a dementia diagnosis, in order to determine whether within the context of this condition there is a pre-clinical state linked to a high risk of dementia progression.

Age-related changes in the vascular system

Ageing in the developed world is associated with changes in the vascular system which result in atherogenesis, increased pulse pressure and increased risk of developing vascular disease as a consequence of a direct effect on the vascular system (for example, arterial hypertension and vasculitis) or

AD = Alzheimer disease; A-MCI = amnesic subtype of mild cognitive impairment; MCI = mild cognitive impairment; VaD = vascular dementia; VCI = vascular cognitive impairment; VCIND = vascular cognitive impairment, no dementia.

indirect metabolic and haemodynamic effects secondary to other disorders (for example, diabetes, congestive heart failure and obesity) [5]. Vascular disease can reduce cerebral perfusion, causing oxidative stress and neurodegeneration [6]. Vascular disease has also been reported to accelerate atrophy and result in white matter abnormalities, asymptomatic infarct, inflammation and reduced glucose metabolism, cerebral blood flow and vascular density [5,7]. Such pathological changes have been associated with not only dementia of the vascular type but also Alzheimer disease (AD) [8,9]. The mechanisms by which vascular disease and its risk factors cause pathology and how such changes impact cognitive function are incompletely understood but are thought to depend on age, disease co-morbidity, lifestyle and genetic susceptibility and predisposition. An important question is whether different vascular disease factors can be separated from each other and from the effect of ageing itself in order to identify their unique impact on cognitive function. A more complete understanding of the relationship between vascular disease, cognitive decline and dementia risk will have important implications in identifying vulnerable population subgroups and a potential treatment target.

Classification systems of early cognitive change

Age-related cognitive change can be placed along a continuum from normal to severely demented, with intermediate stages of cognitive decline. To date, there is no consensus on where boundaries between disease and non-disease lie, if such a definite boundary exists. Rather than a strict dichotomisation, the determination of impairment may instead be based on the likelihood or probability that ageing is not occurring in accordance with normative expectations. Furthermore, classification systems of cognitive change themselves raise questions regarding the level of cognitive and functional dysfunction used to reliably categorise individuals and those risk factors apart from ageing itself that contribute to mild and severe cognitive change.

Mild cognitive impairment

The term mild cognitive impairment (MCI) broadly defines an intermediate state of cognitive decline, predominately linked to impaired memory function, which is thought to be predictive of dementia, primarily AD. Various definitions have been proposed in the literature, each with differences in focus (for example, age-associated change versus pathological decline) and diagnostic criteria (for example, memory versus non-memory impairment) [10-14]. As a possible tool for identifying individuals at increased risk of dementia, MCI is an important concept. Indeed, in clinical samples, individuals with a case diagnosis of the amnesic subtype of MCI (A-MCI) [15-17] have been found to progress to dementia at a rate of 10% to 15% per year compared with a progression rate of only 1% to 2% in normal controls [18,19]. In contrast, in the general population, the positive predictive validity of A-MCI is poor [19]. Many incident dementia cases are found to

be excluded from an A-MCI case diagnosis, and of persons with A-MCI, many remain stable or revert to normal cognitive status at follow-up [10]. These findings are consistent across all MCI definitions (for example, amnesic versus non-amnesic and single- versus multiple-domain MCI) [19].

No MCI criteria can be recommended for population screening of individuals at high dementia risk [20]. This raises a number of questions regarding the precision and utility of current diagnostic criteria and what the best indicators of dementia risk are and whether these are being captured in current diagnostic methods. Poor predictability possibly results from limitations in case findings due to a lack of clinical judgement and inflexibility in operationalisation of criteria when a diagnosis of MCI is made outside the clinical setting. However, it has been suggested that MCI predictability may be improved through consideration of the underlying pathogenesis of cognitive decline [21]. Subclassification of MCI with and without co-morbid vascular disease may therefore be important for discriminating individuals at high versus low dementia risk in the general population.

Although the fact is not always explicitly stated in MCI-defining criteria, an MCI case diagnosis is usually made following the exclusion of individuals with psychiatric and vascular co-morbidity [10,12,22]. As such, the association between vascular disease and MCI is not widely studied. Where vascular disease has been evaluated in the context of MCI, no clear pattern between vascular disease and incident MCI or between vascular disease, MCI and risk of dementia progression has been found. An increased risk of incident MCI has been associated with elevated midlife blood pressure [23], elevated total cholesterol level [23], history of coronary artery bypass grafting [24], stroke [25] and midlife hypertension [21] in some, but not other [26], studies. Only atrial fibrillation and low folate levels have been associated with an increased risk of dementia progression from MCI [27]. Inconsistencies in conclusions possibly result from differences in patient sources (for example, clinic- versus population-based), type of impairment (for example, narrow [A-MCI] versus global measures of cognitive impairment as captured in the term 'cognitive impairment, no dementia' [CIND]), definitions of disease and measurement of vascular factors over varying time frames and with instruments of different sensitivities (for example, subjective report versus objective measure). To better identify the link between vascular disease and cognitive impairment, the term vascular cognitive impairment (VCI) was introduced [9,28-32].

Cognitive impairment and vascular disease

VCI refers to cognitive decline attributable to vascular disease. However, unlike MCI (which is a narrow term capturing a pre-clinical form of dementia), VCI encompasses individuals affected with any degree of cognitive decline caused by or associated with vascular disease and its risk

factors. As such, the level of impairment in VCI ranges in severity from mild to vascular dementia (VaD) or mixed VaD, in which cerebrovascular and AD pathologies co-occur. Calls for more specific staging have recently led to further sub-classification of VCI to capture vascular disease-related impairment not fulfilling criteria for dementia. This stage is defined using the term VCIND and has been further subdivided to include specific terms for pre-clinical impairment, including vascular MCI (V-MCI), MCI of vascular type, pre-clinical VCI, vascular pre-dementia MCI and mild VCI (M-VCI/MCI-vas) [29]. Each is analogous to the concept of MCI in terms of stage. However, similar to MCI, VCIND and its component states lack consistent standardised indicators (for example, symptoms) and a unique case definition.

Whether within VCIND there is a state predictive of dementia is largely unknown. Commonly, VCIND is not seen as a pre-clinical dementia state. Where longitudinal outcome across the spectrum of VCI has been investigated, progression is not always clinical (that is, decline/dementia), with many cases improving or remaining stable at follow-up [9,33-35]. Predictive ability may depend on the nature of the vascular disturbance in addition to methodological factors (for example, case description, sample and nature of cognitive impairment). As with MCI, terminology and diagnostic criteria for VCIND have not been harmonised, making cross-study comparison of disease outcomes difficult. Yet unlike MCI, in which algorithms have been created for each different classification [10], no such algorithm yet exists for VCIND and its many possible subtypes.

Defining the boundary between VCIND and MCI

Some MCI classifications do not consider possible vascular contributing factors to cognitive impairment, and therefore the distinction between MCI and VCIND becomes blurred [36]. This raises questions of the benefit in distinguishing MCI from VCIND and whether formulating a new diagnostic category such as VCIND is even necessary. Whether vascular disease is considered in the diagnosis of MCI may influence general population prevalence estimates and longitudinal patterns of progression. Empirical evidence as to the degree of comorbidity across different pathologies (including, for example, AD and VaD pathologies) will help new classifications, particularly as biomarkers of specific pathologies emerge.

Generally, the differential diagnosis between MCI and VCIND is clinical and based on the distinction between AD and VaD. AD is characterised by a steady and progressive loss of memory and cognitive faculties, including language deterioration, impaired visuospatial skills and poor judgement [37]. AD has a distinct neuropathological pattern of beta-amyloid plaques and neurofibrillary tangles [38,39]. Other significant correlates of cognitive decline include synaptic loss, neuronal death and disruption to the cholinergic pathway [40]. In contrast, the disease course of VaD is highly variable, generally following a stepwise pattern of decline and

fluctuating course [41,42]. For a diagnosis of VaD, it is recommended that radiographic features of vascular disease, including evidence of an ischaemic lesion, white matter hyperintensities and/or hypometabolism, be confirmed [37]. However, in some cases, AD and VaD have been found to result in similar cognitive, functional and behavioural disturbances, and frequently both pathologies co-occur [43-45]. AD and VaD may share associated risk factors (stroke, arterial hypertension, increasing age and low educational attainment), structural changes, neuropathological profiles (white matter lesions and apoptosis) and neurochemical changes (that is, in the cholinergic system) [46]. Overlap may also result from the large degree of silent risk pathology in older people.

In older people, multi-morbidity is common and a strict dichotomisation between degenerative and vascular dementing disorders at both pre-clinical and dementia stages is difficult to undertake, possibly artificial and perhaps not the most useful approach. Below, we explore the cognitive, neuro-imaging and neuropathological profiles of MCI and VCIND to determine whether evidence exists for the separation of both conditions.

Cognitive differences (MCI with vascular disease versus MCI without vascular disease)

Neuropsychological studies have identified attentional-executive deficits and psychomotor slowing, with relatively preserved language and recognition memory in individuals with vascular disease [47,48]. However, not all studies agree on the importance of each cognitive domain and no single deficit or pattern of deficits as yet accurately signals an underlying vascular cause [49]. This is not unexpected given the multiplicity of aetiologies for vascular disease and the fact that the pattern and extent of cognitive deficits would likely reflect not only disease type, but also its severity [50,51]. For example, cognitive impairment as a consequence of stroke would likely depend on not only timing and the anatomical location of the stroke, but also the laterality, severity and extent of the lesion. Furthermore, impairments in attention and executive and motor function are not necessarily restricted to vascular causes of dementia and have also been associated with Lewy body dementia [52] and fronto-temporal dementia [53].

Where VCIND has been followed longitudinally, cognitive impairment associated with memory (free and cued recall) and category fluency was found to predict risk of incident dementia [54]. These findings suggest that the pattern of impairment in VCIND conforms more to AD than to VaD. Indeed, almost half of the cases progressed to AD or mixed AD at 5 years of follow-up. However, whether these findings extend across the different vascular causes of VCIND (that is, stroke- versus hypertension-related cognitive impairment) and other cognitive domains (that is, perception and motor performance) remains to be tested.

With regard to MCI, no consistent cognitive profile exists across the many different case definitions. The focus of MCI is predominantly impaired memory, but deficits in other cognitive domains will also be observed when, by definition, they are also included [55]. Subdivisions between different cognitive subtypes of MCI (for example, amnesic versus non-amnesic and single- versus multi-domain) have implications for inference about aetiology and outcomes. Indeed, while A-MCI [15,16,56] is thought to be a precursor of AD, non-amnesic subtypes of MCI have been found to identify individuals at high risk of both AD and VaD [57].

Where the cognitive profile of individuals with MCI and comorbid vascular disease has been compared with that of individuals with MCI and no vascular disease, group differences have been reported in some [58,59], but not all [60], studies. Where differences have been observed, the MCI vascular group shows more extensive cognitive impairment primarily in speed, attention and executive function [58], consistent with the general pattern of cognitive difficulties resulting from vascular disease alone [29]. In other studies, vascular pathology in MCI (for example, white matter lesions) has been associated with decreased risk of progression of cognitive pathology and a more stable cognitive change profile [61,62], although this is not always replicated [63]. These findings suggest a complex relationship between vascular disease and cognitive progression in MCI which might relate to the specific vascular disease factor. Of importance is determining whether the presence of vascular disease accelerates or intensifies the cognitive disturbance in all cases of MCI and which factors might mediate this relationship (for example, age and reserve). The specific type of cognitive impairment associated with vascular disease needs to be defined and measures that are sensitive, specific and appropriate for longitudinal and observational assessment of cognition in the context of vascular disease (that is, memory versus non-memory domains) need to be identified in order to facilitate the development of diagnostic criteria for cognitive decline in the presence (VCIND) versus the absence (MCI) of vascular disease.

Neuroimaging profile (MCI versus VCIND)

Neuroimaging in VCIND shows a pattern of vascular lesions that are similar to, but less severe than, changes observed in VaD [64]. Pathology includes evidence of leukoaraiosis and white matter infarction [28,65,66], with mild hippocampal and entorhinal cortex atrophy relative to the level seen in MCI/AD [64]. In contrast, neuroimaging in MCI generally shows a pattern of changes similar to that observed in AD, namely temporal and hippocampal atrophy, reduction in whole-brain glucose metabolism and white matter degeneration, including hyperintensities and white matter lesions identified using diffusion tensor imaging [67-74]. Development of dementia from MCI has been associated with hippocampal volume changes [69,75-79], medial temporal lobe atrophy [80] and metabolic alteration [78,81].

Although neuroimaging studies of VCIND and MCI suggest different pathological processes, findings are not always consistent and such changes are imperfect predictors of disease. Considerable intra-individual variation exists, and overall, neuroimaging-identified abnormalities correlate poorly with cognitive profile [43]. Indeed, such changes have also been observed in individuals who do not exhibit cognitive deficits, raising questions about the uniqueness of findings [82]. Inconsistency in results possibly arises due to differences in the use of subjective visual rating scales to assess the extent of pathology across groups, regional focus of disease (global versus focal), in addition to differences in enrolment criteria and the type and severity of vascular disease across imaging cohorts. Indeed, different vascular disease factors are associated with varying types and levels of pathology: hypertension has been associated with reduced cerebral blood flow [83] and an increased risk of periventricular white matter lesions [84,85]; lower arterial oxygen saturation and chronic obstructive pulmonary disease have been associated with cerebral white matter lesions, but not lacunar infarcts [86]; diabetes has been associated with cortical and hippocampal atrophy [87,88], white matter lesions [89] and lacunar infarcts [89]; and current smoking status, diabetes and hypertension are associated with both neurodegenerative (that is, decreased brain volume) and vascular (that is, lacunar infarcts and white matter lesions) changes [90].

The severity and type of lesions required for a diagnosis of MCI and VCIND remain controversial. Vascular disease and its risks are associated with brain changes but the clinical relevance of such changes in the prediction of cognitive decline and dementia progression remains uncertain. Isolating unique disease effects from the effects of ageing and other risk factors (that is, genetic susceptibility) will be important in determining cellular/molecular/functional vulnerability as a consequence of vascular disease as well as establishing with accuracy those changes that distinguish who will and will not develop cognitive decline and subsequent dementia.

Neuropathology profile (MCI versus VCIND)

The neuropathological profile of MCI has been derived mainly from a relatively small number of studies with MCI defined predominately using the A-MCI subtype. Compared with highly selected controls, MCI cases generally show an increase in neurofibrillary tangle pathology in memory-related cortical regions, including the entorhinal cortex, fusiform gyrus and temporal pole [91,92]. These changes are thought to represent one of the earliest pathological substrates of this condition [93] and have been taken to suggest that many MCI cases are early or prodromal AD [94,95]. Vascular pathology has also been reported in MCI such that the neuropathology of some cases includes features associated with both AD and VaD [96]. However, there is considerable heterogeneity in findings and not all individuals with MCI at death or those who progress from MCI to dementia have been reported to show any particular neuropathology [97].

Rather, they have been indistinguishable from control groups. Inconsistency in outcome may arise from differences in study population (for example, specialised clinic versus population), age group differences (that is, young-old versus old-old), operational definition of MCI and neuropathological criteria (for example, Khachaturian, Consortium to Establish a Registry for Alzheimer's Disease, or National Institute on Aging-Reagan).

Whether there is a consistent neuropathological profile across the spectrum of vascular causes and severity levels of VCI is unknown but seems unlikely. Indeed, VCI is a multi-factor disorder related to a wide variety of lesions and causes and as such the pathological profile, similarly to the psychological and radiological profiles, would be expected to be heterogeneous. In autopsy studies, an increased prevalence of cerebral vascular pathology has been found in individuals with stroke [98], diabetes mellitus [99,100], angina (with comorbid dementia) [101,102] and hypertension [103]. Pathological features have included large- and small-vessel disease, gliosis, microvascular brain damage (severe cribriform change), white matter damage, microinfarction and haemorrhage [104]. Cardiovascular risk factors have also been associated with AD-like neuropathological lesion formation in some, but not all, studies, with the extent of pathology typically being more severe in APOE (apolipoprotein E) e4 carriers [100,103,105-107]. In contrast, in other cases, an inverse association between vascular disease and the extent of cerebral degenerative pathology has been found [101]. The profile of pathology across the different vascular disease factors is heterogeneous and the significance of such changes in the development of cognitive impairment is not known. Furthermore, neuropathological associations appear to be risk factor-specific and population-specific, being absent when vascular disease is assessed using composite cerebrovascular index scores and in non-Caucasian populations [108,109].

Across the spectrum of age-associated brain changes, no neuropathological profile yet exists that reliably distinguishes impairment of different severity levels and causes. In the general population, currently identifiable pathological features have not been found to correlate well with observed clinical and cognitive profiles: many non-demented healthy controls also show evidence of pathological brain changes associated with both AD and VaD [43,110,111]. Techniques that better characterise the impact of vascular disease on brain structure and more sensitive measures for accurately staging cognitive status which incorporate known risk factors are needed for diagnostic differentiation between an *at-risk* and a *not at-risk* brain. However, as with AD, expecting neuropathology to be a gold standard at any given age for the diagnosis of VCI is an oversimplification [112].

Vascular risk factor control

Current pharmacological and non-pharmacological modifications of vascular disease and its risks have been found to

have only a marginal effect on reducing dementia prevalence in the general population [113]. Indeed, most strategies, whether pharmacological or non-pharmacological, are ineffective in the prevention of dementia and are potentially harmful. With regard to MCI, while pharmacological and lifestyle modifications have been found to be effective in ameliorating cognitive impairment in selected older cohorts [114,115], no consistently positive results have emerged from randomised controlled trials for such manipulation in the prevention of MCI or future dementia progression in older people in the general population [116,117]. Where the primary prevention of VCIND has been considered, physical activity has been found to reduce the risk of VCIND in women, but not men [118]. Why gender differences emerged in this study is unclear but is thought to be linked to gender reporting bias in physical activity levels or to statistical error (type 2 error) due to the small number of male cases. However, before recommendations based on this result can be made, it must be replicated in population-representative samples using objective measures of physical activity.

Overall, the results of intervention trials of vascular risk reduction on the prevention of cognitive decline and dementia have not been encouraging so far. There are, however, other reasons why cardiovascular and cerebrovascular disease should be prevented and treated, especially for the prevention of recurrent stroke and hypertension, which themselves are strong risk factors for functional impairment and mortality [119]. Further trials are needed to determine whether the manipulation of different vascular diseases and vascular risk factors prevents VCIND and dementia progression. However, it is unlikely that a single strategy will cure or prevent all dementia; rather, early treatment may require a combination of therapies with different targets and time frames for instigation (that is, early, mid- and later life).

Future directions

A more complete understanding of the relationship of vascular disease to cognitive decline and dementia risk is needed. Even when vascular pathology appears to be the main underlying process, the effect can be heterogeneous, with diverse neuropsychological, clinical, radiological and morphological profiles, often in the presence of other pathologies. To date, the risk of dementia progression cannot yet be accurately predicted from pre-dementia states captured in the concepts of MCI and VCIND. Cognitive decline can also occur prior to vascular insult (for example, pre-stroke dementia), raising the question of causality [1]. How vascular disease relates to dementia and its influence across an individual's life span and the unique and interactive mechanisms of action on neurodegeneration must be investigated further to identify the best treatment and preventative target.

Conclusions

Before case screening for individuals at high risk of dementia secondary to vascular disease can be undertaken, the

concept of VCIND will require evidence-based consensus criteria and validation as a pre-clinical state that confers high dementia risk in both clinical and population-based studies. Many questions remain open, particularly with regard to identifying where the state of VCIND begins and ends. This review suggests that cognitive change would be expected to be influenced by vascular disease type and severity, disease onset, co-occurring factors, underlying vulnerability (for example, age, education and genetics) and whether pathology occurs secondary to another process (for example, AD). Accurate early detection of the general population at increased risk of dementia is central for the implementation of interventions to prevent dementia and other memory-related problems in older individuals.

Competing interests

The authors declare that they have no competing interests.

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References

- Stewart R: **Vascular dementia: a diagnosis running out of time.** *Br J Psychiatry* 2002, **180**:152-156.
- Brayne C: **The elephant in the room - healthy brains in later life, epidemiology and public health.** *Nat Rev Neurosci* 2007, **8**: 233-239.
- Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM: **Forecasting the global burden of Alzheimer's disease.** *Alzheimers Dement* 2007, **3**:186-191.
- Brookmeyer RP, Gray SBS, Kawas CMD: **Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset.** *Am J Public Health* 1998, **88**:1337-1342.
- Jani B, Rajkumar C: **Ageing and vascular ageing.** *Postgrad Med J* 2006, **82**:357-362.
- de la Torre JC: **Alzheimer disease as a vascular disorder: nosological evidence.** *Stroke* 2002, **33**:1152-1162.
- Nilsson PM: **Early vascular aging (EVA): consequences and prevention.** *Vasc Health Risk Manag* 2008, **4**:547-552.
- Jellinger KA: **Clinicopathological analysis of dementia disorders in the elderly—an update.** *J Alzheimers Dis* 2006, **9**:61-70.
- Rockwood K, Macknight C, Wentzel C, Black S, Bouchard R, Gauthier S, Feldman H, Hogan D, Kertesz A, Montgomery P: **The diagnosis of "mixed" dementia in the Consortium for the Investigation of Vascular Impairment of Cognition (CIVIC).** *Ann N Y Acad Sci* 2000, **903**:522-528.
- Matthews FE, Stephan BC, Bond J, McKeith I, Brayne C; Medical Research Council Cognitive Function and Ageing Study: **Operationalisation of mild cognitive impairment: a graphical approach.** *PLoS Med* 2007, **4**:1615-1619.
- Morris JC: **Mild cognitive impairment is early-stage Alzheimer disease: time to revise diagnostic criteria.** *Arch Neurol* 2006, **63**:15-16.
- Stephan BC, Matthews FE, McKeith IG, Bond J, Brayne C; Medical Research Council Cognitive Function and Ageing Study: **Early cognitive change in the general population: How do different definitions work?** *J Am Geriatr Soc* 2007, **55**:1534-1540.
- Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC: **Mild cognitive impairment - beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment.** *J Intern Med* 2004, **256**:240-246.
- Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L: **Introduction: mild cognitive impairment: beyond controversies, towards a consensus.** *J Intern Med* 2004, **256**:181-182.
- Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST: **Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology.** *Neurology* 2001, **56**:1133-1142.
- Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E: **Mild cognitive impairment: clinical characterization and outcome.** *Arch Neurol* 1999, **56**:303-308.
- Petersen RC, O'Brien J: **Mild cognitive impairment should be considered for DSM-V.** *J Geriatr Psychiatry Neurol* 2006, **19**: 147-154.
- Bruscoli M, Lovestone S: **Is MCI really just early dementia? A systematic review of conversion studies.** *Int Psychogeriatr* 2004, **16**:129-140.
- Matthews FE, Stephan BC, McKeith IG, Bond J, Brayne C; Medical Research Council Cognitive Function and Ageing Study: **Two-year progression from mild cognitive impairment to dementia: To what extent do different definitions agree?** *J Am Geriatr Soc* 2008, **56**:1424-1433.
- Stephan BC, Brayne C, McKeith IG, Bond J, Matthews FE; Medical Research Council Cognitive Function and Ageing Study: **Mild cognitive impairment in the older population: Who is missed in classifications and does it matter?** *Int J Geriatr Psychiatry* 2008, **23**:863-871.
- Tervo S, Kivipelto M, Hänninen T, Vanhanen M, Hallikainen M, Mannermaa A, Soininen H: **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* 2004, **17**:196-203.
- Collie A, Maruff P: **An analysis of systems of classifying mild cognitive impairment in older people.** *Aust N Z J Psychiatry* 2002, **36**:133-140.
- Kivipelto M, Helkala EL, Hänninen T, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A: **Midlife vascular risk factors and late-life mild cognitive impairment: a population-based study.** *Neurology* 2001, **56**:1683-1689.
- Selnes OA, Royall RM, Grega MA, Borowicz LM Jr., Quaskey S, McKhann GM: **Cognitive changes 5 years after coronary artery bypass grafting: Is there evidence of late decline?** *Arch Neurol* 2001, **58**:598-604.
- Gamaldo A, Moghekar A, Kilada S, Resnick SM, Zonderman AB, O'Brien R: **Effect of a clinical stroke on the risk of dementia in a prospective cohort.** *Neurology* 2006, **67**:1363-1369.
- Reitz C, Tang MX, Manly J, Schupf N, Mayeux R, Luchsinger JA: **Plasma lipid levels in the elderly are not associated with the risk of mild cognitive impairment.** *Dement Geriatr Cogn Disord* 2008, **25**:232-237.
- Ravaglia G, Forti P, Maioli F, Martelli M, Servadei L, Brunetti N, Pantieri G, Mariani E: **Conversion of mild cognitive impairment to dementia: predictive role of mild cognitive impairment subtypes and vascular risk factors.** *Dement Geriatr Cogn Disord* 2006, **21**:51-58.
- Bowler JV: **Modern concept of vascular cognitive impairment.** *Br Med Bull* 2007, **83**:291-305.
- Román GC, Sachdev P, Royall DR, Bullock RA, Orgogozo JM, López-Pousa S, Arizaga R, Wallin A: **Vascular cognitive disorder: a new diagnostic category updating vascular cognitive impairment and vascular dementia.** *J Neurol Sc* 2004, **226**:81-87.
- Bowler JV, Hachinski V: **Vascular cognitive impairment: a new approach to vascular dementia.** *Baillieres Clin Neurol* 1995, **4**: 357-376.
- Hachinski V: **Vascular cognitive impairment: a unified approach to cognitive disorders.** *Brain Cogn* 2007, **63**:196-255.
- Selnes OA, Vinters HV: **Vascular cognitive impairment.** *Nature* 2006, **2**:538-547.
- Rockwood K, Moorhouse PK, Song X, MacKnight C, Gauthier S, Kertesz A, Montgomery P, Black S, Hogan DB, Guzman A, Bouchard R, Feldman H; Consortium to Investigate Vascular Impairment of Cognition (CIVIC) Cohort: **Disease progression in vascular cognitive impairment: Cognitive, functional and behavioural outcomes in the Consortium to Investigate Vascular Impairment of Cognition (CIVIC) cohort study.** *J Neurol Sci* 2007, **252**:106-112.
- Hsiung GY, Donald A, Grand J, Black SE, Bouchard RW, Gau-

- thier SG, Loy-English I, Hogan DB, Kertesz A, Rockwood K, Feldman HH: **Outcomes of cognitively impaired not demented at 2 years in the Canadian Cohort Study of Cognitive Impairment and Related Dementias.** *Dement Geriatr Cogn Disord* 2006, **22**:413-420.
35. Wentzel C, Rockwood K, MacKnight C, Hachinski V, Hogan DB, Feldman H, Østbye T, Wolfson C, Gauthier S, Verreault R, McDowell I: **Progression of impairment in patients with vascular cognitive impairment without dementia.** *Neurology* 2001, **57**:714-716.
 36. Ebly EM, Hogan DB, Parhad IM: **Cognitive impairment in the nondemented elderly. Results from the Canadian Study of Health and Aging.** *Arch Neurol* 1995, **52**:612-619.
 37. American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders, Text Revision.* Washington, DC: American Psychiatric Association; 2000.
 38. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van Belle G, Berg L: **The Consortium to Establish a Registry for Alzheimer's Disease (CERAD): Part II. Standardization of the neuropathologic assessment of Alzheimer's disease.** *Neurology* 1991, **41**:479-486.
 39. Mirra SS: **The CERAD neuropathology protocol and consensus recommendations for the postmortem diagnosis of Alzheimer's disease: a commentary.** *Neurobiol Aging* 1997, **18**:S91-94.
 40. Grudzien A, Shaw P, Weintraub S, Bigio E, Mash DC, Mesulam MM: **Locus coeruleus neurofibrillary degeneration in aging, mild cognitive impairment and early Alzheimer's disease.** *Neurobiol Aging* 2007, **28**:327-335.
 41. Rice KL: **Vascular dementia: distinguishing characteristics, treatment, and prevention.** *J Vasc Nurs* 2004, **22**:59.
 42. Sachdev PS, Brodat H, Looi JCL: **Vascular dementia: diagnosis, management and possible prevention.** *Med J Aust* 1999, **170**: 81-85.
 43. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study MC: **Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales.** *Lancet* 2001, **357**:169-175.
 44. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR: **Brain infarction and the clinical expression of Alzheimer disease. The Nun Study.** *JAMA* 1997, **277**:813-817.
 45. Passmore AP, Bayer AJ, Steinhagen-Thiessen E: **Cognitive, global, and functional benefits of donepezil in Alzheimer's disease and vascular dementia: results from large-scale clinical trials.** *J Neurol Sci* 2005, **229-230**:141-146.
 46. Small GW: **The role of neuroimaging in the diagnosis of vascular dementia.** *Acta Neurol Scand Suppl* 2002, **106**:10-14.
 47. Nyenhuis DL, Gorelick PB: **Diagnosis and management of vascular cognitive impairment.** *Curr Atheroscler Rep* 2007, **9**:326-332.
 48. Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, Powers WJ, DeCarli C, Merino JG, Kalra RN, Vinters HV, Holtzman DM, Rosenberg GA, Wallin A, Dichgans M, Marler JR, Leblanc GG: **National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards.** *Stroke* 2006, **37**:2220-2241.
 49. Graham NL, Emery T, Hodges JR: **Distinctive cognitive profiles in Alzheimer's disease and subcortical vascular dementia.** *J Neurol Neurosurg Psychiatry* 2004, **75**:61-71.
 50. McPherson SE, Cummings JL: **Neuropsychological aspects of vascular dementia.** *Brain Cogn* 1996, **31**:269-282.
 51. Paul RH, Cohen RA, Ott BR, Zawacki T, Moser DJ, Davis J, Gordon N, Stone W: **Cognitive and functional status in two subtypes of vascular dementia.** *NeuroRehabilitation* 2000, **15**: 199-205.
 52. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, Salmon DP, Lowe J, Mirra SS, Byrne EJ, Lennox G, Quinn NP, Edwardson JA, Ince PG, Bergeron C, Burns A, Miller BL, Lovestone S, Collerton D, Jansen EN, Ballard C, de Vos RA, Wilcock GK, Jellinger KA, Perry RH: **Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop.** *Neurology* 1996, **47**:1113-1124.
 53. Walker AJ, Meares S, Sachdev PS, Brodaty H: **The differentiation of mild frontotemporal dementia from Alzheimer's disease and healthy aging by neuropsychological tests.** *Int Psychogeriatr* 2005, **17**:57-68.
 54. Ingles JL, Wentzel C, Fisk JD, Rockwood K: **Neuropsychological predictors of incident dementia in patients with vascular cognitive impairment, without dementia.** *Stroke* 2002, **33**:1999-2002.
 55. Ribeiro F, de Mendonca A, Guerreiro M: **Mild cognitive impairment: deficits in cognitive domains other than memory.** *Dement Geriatr Cogn Disord* 2006, **21**:284-290.
 56. Petersen RPD: **Mild cognitive impairment: current research and clinical implications.** *Semin Neurol* 2007, **27**:22-31.
 57. Rasquin SM, Lodder J, Visser PJ, Lousberg R, Verhey FR: **Predictive accuracy of MCI subtypes for Alzheimer's disease and vascular dementia in subjects with mild cognitive impairment: a 2-year follow-up study.** *Dement Geriatr Cogn Disord* 2005, **19**:113-119.
 58. Nordlund A, Rolstad S, Klang O, Lind K, Hansen S, Wallin A: **Cognitive profiles of mild cognitive impairment with and without vascular disease.** *Neuropsychology* 2007, **21**:706-712.
 59. Hayden KM, Warren LH, Pieper CF, Ostbye T, Tschanz JT, Norton MC, Breitner JCS, Welsh-Bohmer KA: **Identification of VaD and AD prodromes: the Cache County Study.** *Alzheimers Dement* 2005, **1**:19-29.
 60. Loewenstein DA, Acevedo A, Agron J, Issacson R, Strauman S, Crocco E, Barker WW, Duara R: **Cognitive profiles in Alzheimer's disease and in mild cognitive impairment of different etiologies.** *Dement Geriatr Cogn Disord* 2006, **21**:309-315.
 61. DeCarli C, Mungas D, Harvey D, Reed B, Weiner M, Chui H, Jagust W: **Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia.** *Neurology* 2004, **63**:220-227.
 62. Maruyama M, Matsui T, Tanji H, Nemoto M, Tomita N, Otsuki M, Arai H, Sasaki H: **Cerebrospinal fluid tau protein and periventricular white matter lesions in patients with mild cognitive impairment: implications for 2 major pathways.** *Arch Neurol* 2004, **61**:716-720.
 63. Koppel J: **Memory impairment, but not cerebrovascular disease, predicts progression of MCI to dementia.** *Neurology* 2005, **64**:766.
 64. Meyer JS, Huang J, Chowdhury MH: **MRI confirms mild cognitive impairments prodromal for Alzheimer's, vascular and Parkinson-Lewy body dementias.** *J Neurol Sci* 2007, **257**:97-104.
 65. Vermeer SE, Longstreth WT Jr., Koudstaal PJ: **Silent brain infarcts: a systematic review.** *Lancet Neurol* 2007, **6**:611-619.
 66. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, Fitzpatrick A, Fried L, Haan MN: **Risk factors for dementia in the cardiovascular health cognition study.** *Neuro-epidemiology* 2003, **22**:13-22.
 67. Backman L, Jones S, Berger AK, Laukka EJ, Small BJ: **Multiple cognitive deficits during the transition to Alzheimer's disease.** *J Intern Med* 2004, **256**:195-204.
 68. Johnson SC, Schmitz TW, Moritz CH, Meyerand ME, Rowley HA, Alexander AL, Hansen KW, Gleason CE, Carlsson CM, Ries ML, Asthana S, Chen K, Reiman EM, Alexander GE: **Activation of brain regions vulnerable to Alzheimer's disease: the effect of mild cognitive impairment.** *Neurobiol Aging* 2006, **27**:1604-1612.
 69. Devanand DP, Pradhaban G, Liu X, Khandji A, De Santi S, Segal S, Rusinek H, Pelton GH, Honig LS, Mayeux R, Stern Y, Tabert MH, de Leon MJ: **Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease.** *Neurology* 2007, **68**:828-836.
 70. Zhang Y, Schuff N, Jahng GH, Bayne W, Mori S, Schad L, Mueller S, Du AT, Kramer JH, Yaffe K, Chui H, Jagust WJ, Miller BL, Weiner MW: **Diffusion tensor imaging of cingulum fibers in mild cognitive impairment and Alzheimer disease.** *Neurology* 2007, **68**:13-19.
 71. Assaf Y, Pasternak O: **Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review.** *J Mol Neurosci* 2008, **34**:51-61.
 72. Rose SE, McMahon KL, Janke AL, O'Dowd B, de Zubicaray G, Strudwick MW, Chalk JB: **Diffusion indices on magnetic resonance imaging and neuropsychological performance in amnesic mild cognitive impairment.** *J Neurol Neurosurg Psychiatry* 2006, **77**:1122-1128.
 73. Chua TC, Wen W, Slavin MJ, Sachdev PS: **Diffusion tensor**

- imaging in mild cognitive impairment and Alzheimer's disease: a review. *Curr Opin Neurol* 2008, **21**:83-92.
74. Schuff N, Zhu XP: **Imaging of mild cognitive impairment and early dementia.** *Br J Radiol* 2007, **80**:S109-114.
 75. Jack CR Jr., Shiung MM, Weigand SD, O'Brien PC, Gunter JL, Boeve BF, Knopman DS, Smith GE, Ivnik RJ, Tangalos EG, Petersen RC: **Brain atrophy rates predict subsequent clinical conversion in normal elderly and amnesic MCI.** *Neurology* 2005, **65**:1227-1231.
 76. Jack CR Jr., Petersen RC, Xu YC, O'Brien PC, Smith GE, Ivnik RJ, Boeve BF, Waring SC, Tangalos EG, Kokmen E: **Prediction of AD with MRI-based hippocampal volume in mild cognitive impairment.** *Neurology* 1999, **52**:1397-1403.
 77. Apostolova LG, Dutton RA, Dinov ID, Hayashi KM, Toga AW, Cummings JL, Thompson PM: **Conversion of mild cognitive impairment to Alzheimer disease predicted by hippocampal atrophy maps.** *Arch Neurol* 2006, **63**:693-699.
 78. Scheff SW, Price DA, Schmitt FA, Mufson EJ: **Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment.** *Neurobiol Aging* 2006, **27**:1372-1384.
 79. Miller SL, Fenstermacher E, Bates J, Blacker D, Sperling RA, Dickerson BC: **Hippocampal activation in adults with mild cognitive impairment predicts subsequent cognitive decline.** *J Neurol Neurosurg Psychiatry* 2008, **79**:630-635.
 80. Geroldi C, Rossi R, Calvagna C, Testa C, Bresciani L, Binetti G, Zanetti O, Frisoni GB: **Medial temporal atrophy but not memory deficit predicts progression to dementia in patients with mild cognitive impairment.** *J Neurol Neurosurg Psychiatry* 2006, **77**:1219-1222.
 81. Metastasio A, Rinaldi P, Tarducci R, Mariani E, Feliziani FT, Cherubini A, Pelliccioli GP, Gobbi G, Senin U, Mecocci P: **Conversion of MCI to dementia: role of proton magnetic resonance spectroscopy.** *Neurobiol Aging* 2006, **27**:926-932.
 82. Tomaszewski Farias S, Jagust WJ: **Neuroimaging in non-Alzheimer dementias.** *Clin Neurosci Res* 2004, **3**:383-395.
 83. Sinha S, Misra A, Bal CS, Gouda NK, Pandey RM, Tiwari S: **Evaluation of cerebral blood flow by single-photon emission computed tomography in young Asian Indians with hypertension.** *J Hum Hypertens* 2005, **20**:143-148.
 84. van Dijk EJ, Breteler MM, Schmidt R, Berger K, Nilsson LG, Oudkerk M, Pajak A, Sans S, de Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Launer LJ, Hofman A; CASCADE Consortium: **The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study.** *Hypertension* 2004, **44**:625-630.
 85. Murray AD, Staff RT, Shenkin SD, Deary IJ, Starr JM, Whalley LJ: **Brain white matter hyperintensities: relative importance of vascular risk factors in nondemented elderly people.** *Radiology* 2005, **237**:251-257.
 86. van Dijk EJ, Vermeer SE, de Groot JC, van de Minkels J, Prins ND, Oudkerk M, Hofman A, Koudstaal PJ, Breteler MM: **Arterial oxygen saturation, COPD, and cerebral small vessel disease.** *J Neurol Neurosurg Psychiatry* 2004, **75**:733-736.
 87. Schmidt R, Launer LJ, Nilsson LG, Pajak A, Sans S, Berger K, Breteler MM, de Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Hofman A; CASCADE Consortium: **Magnetic resonance imaging of the brain in diabetes: the Cardiovascular Determinants of Dementia (CASCADE) study.** *Diabetes* 2004, **53**:687-692.
 88. den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, Hofman A, Breteler MM: **Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI.** *Diabetologia* 2003, **46**:1604-1610.
 89. van Harten B, de Leeuw F-E, Weinstein HC, Scheltens P, Biesels GJ: **Brain imaging in patients with diabetes: a systematic review.** *Diabetes Care* 2006, **29**:2539-2548.
 90. Ikram MA, Vrooman HA, Vernooij MW, van der Lijn F, Hofman A, van der Lugt A, Niessen WJ, Breteler MM: **Brain tissue volumes in the general elderly population. The Rotterdam Scan Study.** *Neurobiol Aging* 2008, **29**:882-890.
 91. Guillozet AL, Weintraub S, Mash DC, Mesulam MM: **Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment.** *Arch Neurol* 2003, **60**:729-736.
 92. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE: **Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function.** *Arch Neurol* 2004, **61**:378-384.
 93. Bennett DA, Schneider JA, Bienias JL, Evans DA, Wilson RS: **Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions.** *Neurology* 2005, **64**:834-841.
 94. Morris JC, Price AL: **Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease.** *J Mol Neurosci* 2001, **17**:101-118.
 95. Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L: **Mild cognitive impairment represents early-stage Alzheimer disease.** *Arch Neurol* 2001, **58**:397-405.
 96. Saito Y, Murayama S: **Neuropathology of mild cognitive impairment.** *Neuropathology* 2007, **27**:578-584.
 97. Jicha GA, Parisi JE, Dickson DW, Johnson K, Cha R, Ivnik RJ, Tangalos EG, Boeve BF, Knopman DS, Braak H, Petersen RC: **Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia.** *Arch Neurol* 2006, **63**:674-681.
 98. Garcia JH: **The neuropathology of stroke.** *Hum Path* 1975, **6**:583-598.
 99. Arvanitakis Z, Schneider JA, Wilson RS, Li Y, Arnold SE, Wang Z, Bennett DA: **Diabetes is related to cerebral infarction but not to AD pathology in older persons.** *Neurology* 2006, **67**:1960-1965.
 100. Nelson PT, Smith CD, Abner EA, Schmitt FA, Scheff SW, Davis GJ, Keller JN, Jicha GA, Davis D, Wang-Xia W, Hartman A, Katz DG, Markesbery WR: **Human cerebral neuropathology of Type 2 diabetes mellitus.** *Biochim Biophys Acta* 2009, **1792**:454-469.
 101. Andin U, Gustafson L, Passant U, Brun A: **A clinico-pathological study of heart and brain lesions in vascular dementia.** *Dement Geriatr Cogn Disord* 2005, **19**:222-228.
 102. Andin U, Passant U, Gustafson L, Englund E: **Alzheimer's disease (AD) with and without white matter pathology-clinical identification of concurrent cardiovascular disorders.** *Arch Gerontol Geriatr* 2007, **44**:277-286.
 103. Petrovitch H, White LR, Izmirlian G, Ross GW, Havlik RJ, Markesbery W, Nelson J, Davis DG, Hardman J, Foley DJ, Launer LJ: **Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS.** *Neurobiol Aging* 2000, **21**:57-62.
 104. Kalara RN, Kenny RA, Ballard CG, Perry R, Ince P, Polvikoski T: **Towards defining the neuropathological substrates of vascular dementia.** *J Neurol Sci* 2004, **226**:75-80.
 105. Sparks DL, Scheff SW, Liu H, Landers TM, Coyne CM, Hunsaker JC 3rd: **Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension.** *J Neurol Sci* 1995, **131**:162-169.
 106. Sparks DL: **Coronary artery disease, hypertension, ApoE, and cholesterol: a link to Alzheimer's disease?** *Ann N Y Acad Sci* 1997, **826**:128-146.
 107. Beeri MS, Rapp M, Silverman JM, Schmeidler J, Grossman HT, Fallon JT, Purohit DP, Perl DP, Siddiqui A, Lesser G, Rosendorff C, Haroutunian V: **Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers.** *Neurology* 2006, **66**:1399-1404.
 108. Irina A, Seppo H, Arto M, Paavo R Sr., Hilkka S: **β -Amyloid load is not influenced by the severity of cardiovascular disease in aged and demented patients.** *Stroke* 1999, **30**:613-618.
 109. Alafuzoff I, Helisalmi S, Mannermaa A, Soininen H: **Severity of cardiovascular disease, apolipoprotein E genotype, and brain pathology in aging and dementia.** *Ann N Y Acad Sci* 2000, **903**:244-251.
 110. Jagust W: **Untangling vascular dementia.** *Lancet* 2001, **358**:2097-2098.
 111. Jagust WJ, Zheng L, Harvey DJ, Mack WJ, Vinters HV, Weiner MW, Ellis WG, Zarow C, Mungas D, Reed BR, Kramer JH, Schuff N, DeCarli C, Chui HC: **Neuropathological basis of magnetic resonance images in aging and dementia.** *Ann Neurol* 2008, **63**:72-80.
 112. Brayne C: **Clinicopathological studies of the dementias from an epidemiological viewpoint.** *Br J Psychiatry* 1993, **162**:439-446.
 113. Stephan BCM, Brayne C: **Vascular factors and prevention of dementia.** *Int Rev Psychiatry* 2008, **20**:344-356.
 114. Grodstein F: **Cardiovascular risk factors and cognitive function.** *Alzheimers Dement* 2007, **3**:S16-S22.
 115. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA: **Mediterranean diet and mild cognitive impairment.** *Arch*

Neurol 2009, **66**:216-225.

116. Kirshner HS: **Mild cognitive impairment: to treat or not to treat.** *Curr Neurol Neurosci Rep* 2005, **5**:455-457.
117. Jelic V, Kivipelto M, Winblad B: **Clinical trials in mild cognitive impairment: lessons for the future.** *J Neurol Neurosurg Psychiatry* 2006, **77**:429-438.
118. Middleton L, Kirkland S, Rockwood K: **Prevention of CIND by physical activity: different impact on VCI-ND compared with MCI.** *J Neurol Sci* 2008, **269**:80-84.
119. Skoog I: **Antihypertensive treatment and dementia prevention.** *Lancet Neurol* 2008, **7**:664-665.