Gruppo di ricerca geriatrica

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UNIVERSITY & RESEARCH HOSPITALS

La componente vascolare nella malattia di Alzheimer

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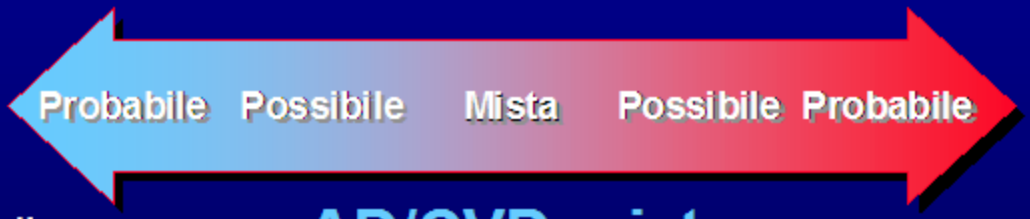
Sovrapposizione della malattia di Alzheimer con la demenza vascolare



AD

Placche amiloidi
Fattori genetici
Deg. neurofibrillare

AD/CVD mista

Placche amiloidi
Fattori genetici
Deg. neurofibrillare
Stroke/TIA
Ipertensione
Diabete
Ipercolesterolemia
Cardiopatia

VaD

Stroke/TIA
Ipertensione
Diabete
Ipercolesterolemia
Cardiopatia

Kalaria & Ballard, 1999

Demenza vascolare: evoluzione concettuale

- 1974 – Multi-infarct dementia (MID) coined (Hachinski). ICD and DSM based on this
- 1980's/90's – MID just one of many causes of Vascular dementia (e.g. subcortical disease)
- 1992/3 – Consensus criteria for VaD published
- 1990's – Considerable overlap between risk factors for AD and Vascular dementia
- 1990's – Considerable overlap between AD and vascular pathology, recognition mixed cases most common in community samples (MRC/CFAS 2001)
- Dementia not appropriate term (requires memory deficit)
- 2003 - Vascular Cognitive Impairment (IPA)(O'Brien et al, 2003)

NINDS-AIREN criteria for probable vascular dementia

The criteria for the clinical diagnosis of probable vascular dementia include all of the following:
Dementia
Defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.
Exclusion criteria: Cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.
Cerebrovascular disease
Defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of relevant CVD by brain imaging (CT or MRI) including multiple large vessel infarcts or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as multiple basal ganglia and white matter lacunes, or extensive periventricular white matter lesions, or combinations thereof.
A relationship between the above two disorders
Manifested or inferred by the presence of one or more of the following:
(a) Onset of dementia within three months following a recognized stroke;
(b) Abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

AD: Alzheimer disease; CVD: cerebrovascular disease; CT: computed tomography; MRI: magnetic resonance imaging.

Roman G et al. Neurology 1993 Feb;43(2):250-60.

DSM-5 criteria for major vascular neurocognitive disorder

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains:

Learning and memory.

Language.

Executive function.

Complex attention.

Perceptual-motor.

Social cognition.

B. The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia).

E. The clinical features are consistent with a vascular etiology, as suggested by either of the following:

Onset of the cognitive deficits is temporally related to one or more cerebrovascular events.

Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function.

F. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.

G. The deficits are not better explained by another brain disease or systemic disorder.

DSM: diagnostic and statistical manual.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington, VA 2013.

UpToDate®

Vascular Contributions to Cognitive Impairment and Dementia

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

(*Stroke*. 2011;42:2672-2713.)

Table 2. Vascular Cognitive Impairment

1. The term *VCI* characterizes all forms of cognitive deficits from VaD to MCI of vascular origin.
2. These criteria cannot be used for subjects who have an active diagnosis of drug or alcohol abuse/dependence. Subjects must be free of any type of substance for at least 3 months.
3. These criteria cannot be used for subjects with delirium.

Dementia

1. The diagnosis of dementia should be based on a decline in cognitive function from a prior baseline and a deficit in performance in ≥2 cognitive domains that are of sufficient severity to affect the subject's activities of daily living.
2. The diagnosis of dementia must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions.
3. The deficits in activities of daily living are independent of the motor/sensory sequelae of the vascular event.

Probable VaD

1. There is cognitive impairment and imaging evidence of cerebrovascular disease and
   a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or
   b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL).
2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

Possible VaD

There is cognitive impairment and imaging evidence of cerebrovascular disease but

1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and the cognitive impairment.
2. There is insufficient information for the diagnosis of VaD (eg, clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia *could* be classified as having probable VaD.
4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as
   a. A history of other neurodegenerative disorders (eg, Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies);
   b. The presence of Alzheimer disease biology is confirmed by biomarkers (eg, PET, CSF, amyloid ligands) or genetic studies (eg, *PS1* mutation); or
   c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.

Vascular Contributions to Cognitive Impairment and Dementia

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

(*Stroke*. 2011;42:2672-2713.)

VaMCI

1. VaMCI includes the 4 subtypes proposed for the classification of MCI: amnestic, amnestic plus other domains, nonamnestic single domain, and nonamnestic multiple domain.
2. The classification of VaMCI must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions. The classification should be based on an assumption of decline in cognitive function from a prior baseline and impairment in at least 1 cognitive domain.
3. Instrumental activities of daily living could be normal or mildly impaired, independent of the presence of motor/sensory symptoms.

Probable VaMCI

1. There is cognitive impairment and imaging evidence of cerebrovascular disease and
   a. There is a clear temporal relationship between a vascular event (eg, clinical stroke) and onset of cognitive deficits, or
   b. There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (eg, as in CADASIL).
2. There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

Possible VaMCI

There is cognitive impairment and imaging evidence of cerebrovascular disease but

1. There is no clear relationship (temporal, severity, or cognitive pattern) between the vascular disease (eg, silent infarcts, subcortical small-vessel disease) and onset of cognitive deficits.
2. There is insufficient information for the diagnosis of VaMCI (eg, clinical symptoms suggest the presence of vascular disease, but no CT/MRI studies are available).
3. Severity of aphasia precludes proper cognitive assessment. However, patients with documented evidence of normal cognitive function (eg, annual cognitive evaluations) before the clinical event that caused aphasia *could* be classified as having probable VaMCI.
4. There is evidence of other neurodegenerative diseases or conditions in addition to cerebrovascular disease that may affect cognition, such as
   a. A history of other neurodegenerative disorders (eg, Parkinson disease, progressive supranuclear palsy, dementia with Lewy bodies);
   b. The presence of Alzheimer disease biology is confirmed by biomarkers (eg, PET, CSF, amyloid ligands) or genetic studies (eg, *PS1* mutation); or
   c. A history of active cancer or psychiatric or metabolic disorders that may affect cognitive function.

Unstable VaMCI

Subjects with the diagnosis of probable or possible VaMCI whose symptoms revert to normal should be classified as having "unstable VaMCI."

VCI indicates vascular cognitive impairment; VaD, vascular dementia; MCI, mild cognitive impairment; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CT/MRI, computed tomography/magnetic resonance imaging; PET, positron emission tomography; CSF, cerebrospinal fluid; and VaMCI, vascular mild cognitive impairment.

Interaction of vascular dementia and Alzheimer's disease: the Nun study

	Percentage with dementia	Adjusted odds ratio
No brain infarct (reference)	57	1.0
1 - 2 lacunar infarcts	75	6.7
large infarcts	93	20.7

D. Snowdon, JAMA 277: 813-.817, 1997

Brain infarction and the clinical expression of Alzheimer disease. The Nun Study.

Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR.
JAMA. 1997 Mar 12;277(10):813-7.

These findings suggest that cerebrovascular disease may play an important role in determining the presence and severity of the clinical symptoms of AD.

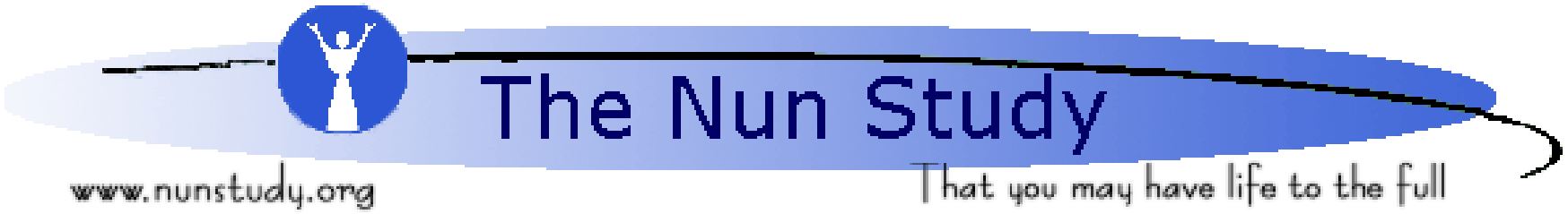


TABLE 1

ALZHEIMER'S DISEASE: *RISK FACTORS*

Age
Female gender
ApoE-4 genotype
Family history of dementia
Hypercholesterolemia
Hyper-homocysteinemia
Diabetes
Head injury
Psychological stress
Hypertension
Smoking

Cummings JL. *Primary Psychiatry.* Vol 15, No 2. 2008.

TABLE 2

ALZHEIMER'S DISEASE: *PROTECTIVE FACTORS*

Education
Active cognitive involvement/leisure activity
Physical activity/exercise
Diet with high antioxidant content • Omega-3 fatty acids • Vitamins E, C
Dietry vitamins • B_6, B_{12}, folate
Alcohol (modest use)
Statins
Nonsteroidal anti-inflammatory agents

Cummings JL. *Primary Psychiatry.* Vol 15, No 2. 2008.

Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease

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ABSTRACT

Objective: Growing evidence suggests that vascular risk factors (VRF) contribute to cognitive decline. The aim of this study was to investigate the impact of VRF on the conversion from mild cognitive impairment (MCI) to Alzheimer disease (AD) dementia.

Methods: A total of 837 subjects with MCI were enrolled at baseline and followed up annually for 5 years. The incidence of AD dementia was investigated. A mixed random effects regression model was used to analyze the association between VRF and the progression of MCI assessed with Mini-Mental State Examination and instrumental Activities of Daily Living. Cox proportional hazard models were used to identify the association between VRF and dementia conversion, and to examine whether treatment of VRF can prevent dementia conversion.

Results: At the end of the follow-up, 298 subjects converted to AD dementia, while 352 remained MCI. Subjects with VRF had a faster progression in cognition and function relative to subjects without. VRF including hypertension, diabetes, cerebrovascular diseases, and hypercholesterolemia increased the risk of dementia conversion. Those subjects with MCI in whom all VRF were treated had a lower risk of dementia than those who had some VRF treated. Treatment of individual VRF including hypertension, diabetes, and hypercholesterolemia was associated with the reduced risk of AD conversion.

Conclusion: VRF increased the risk of incident AD dementia. Treatment of VRF was associated with a reduced risk of incident AD dementia. Although our findings are observational, they suggest active intervention for VRF might reduce progression in MCI to AD dementia. *Neurology*® 2011;76:1485–1491

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

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Summary

Background Modifiable vascular and lifestyle-related risk factors have been associated with dementia risk in observational studies. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a proof-of-concept randomised controlled trial, we aimed to assess a multidomain approach to prevent cognitive decline in at-risk elderly people from the general population.

Methods In a double-blind randomised controlled trial we enrolled individuals aged 60–77 years recruited from previous national surveys. Inclusion criteria were CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age. We randomly assigned participants in a 1:1 ratio to a 2 year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site. Group allocation was not actively disclosed to participants and outcome assessors were masked to group allocation. The primary outcome was change in cognition as measured through comprehensive neuropsychological test battery (NTB) *Z* score. Analysis was by modified intention to treat (all participants with at least one post-baseline observation). This trial is registered at ClinicalTrials.gov, number NCT01041989.

Findings Between Sept 7, 2009, and Nov 24, 2011, we screened 2654 individuals and randomly assigned 1260 to the intervention group (n=631) or control group (n=629). 591 (94%) participants in the intervention group and 599 (95%) in the control group had at least one post-baseline assessment and were included in the modified intention-to-treat analysis. Estimated mean change in NTB total *Z* score at 2 years was 0·20 (SE 0·02, SD 0·51) in the intervention group and 0·16 (0·01, 0·51) in the control group. Between-group difference in the change of NTB total score per year was 0·022 (95% CI 0·002–0·042, p=0·030). 153 (12%) individuals dropped out overall. Adverse events occurred in 46 (7%) participants in the intervention group compared with six (1%) participants in the control group; the most common adverse event was musculoskeletal pain (32 [5%] individuals for intervention *vs* no individuals for control).

Interpretation Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population.

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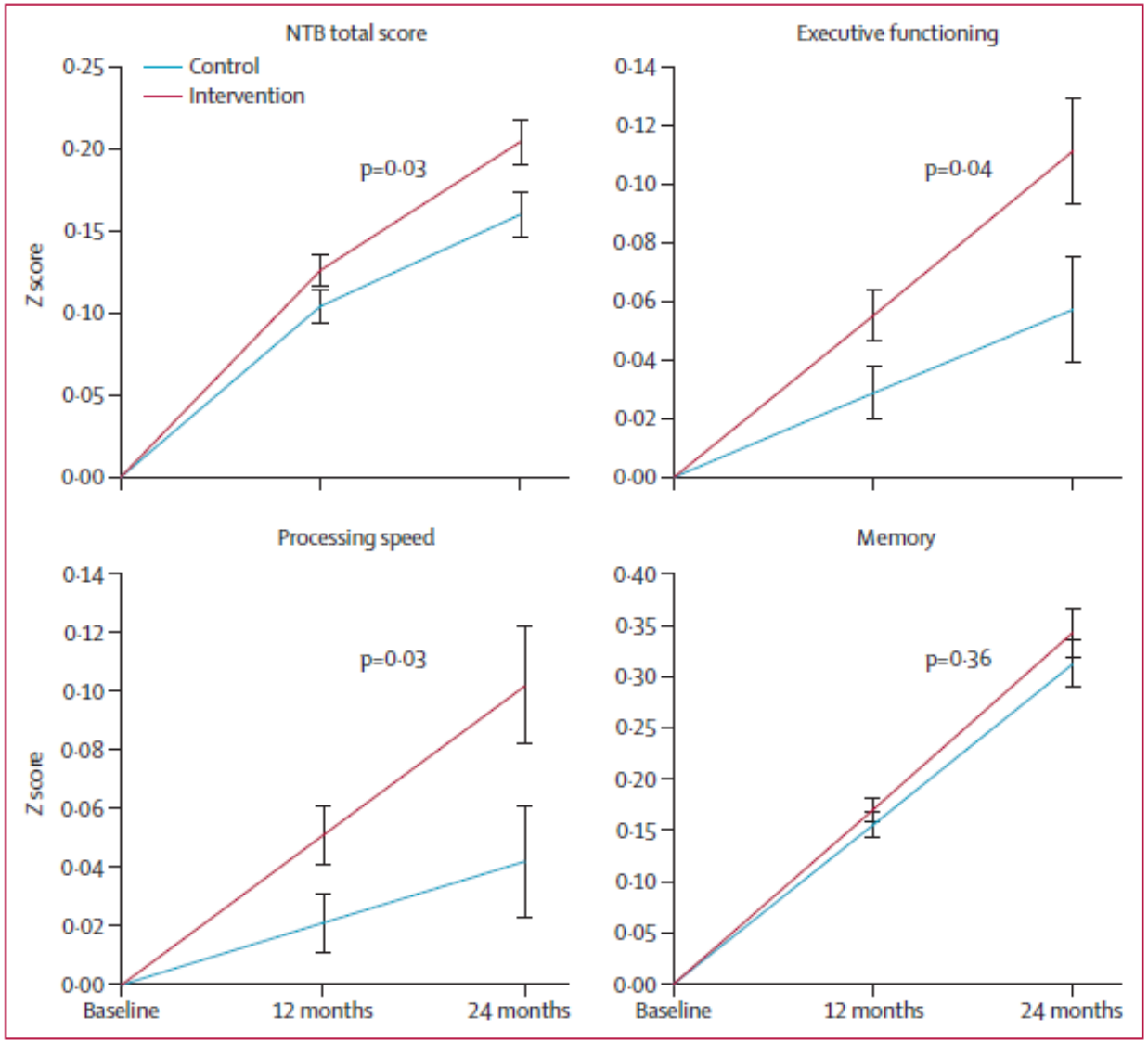


Figure 2: **Change in cognitive performance during the 2 year intervention**
Figure shows estimated mean change in cognitive performance from baseline until 12 and 24 months (higher scores suggest better performance) in the modified intention-to-treat population. Error bars are SEs. Mixed-model repeated-measures analyses were used to assess between-group differences (group x time interaction) in changes from baseline to 24 months based on data from all participants with at least one post-baseline measurement. NTB=neuropsychiatric test battery.

	Low education	Smoking	Physical inactivity	Depression	Mid-life hypertension	Diabetes	Mid-life obesity	Combined
10% Reduction	533,884	411,842	380,022	325,198	166,434	80,740	66,552	1,146,082
25% Reduction	1,374,855	1,051,872	968,709	826,297	419,340	202,592	166,880	3,047,536

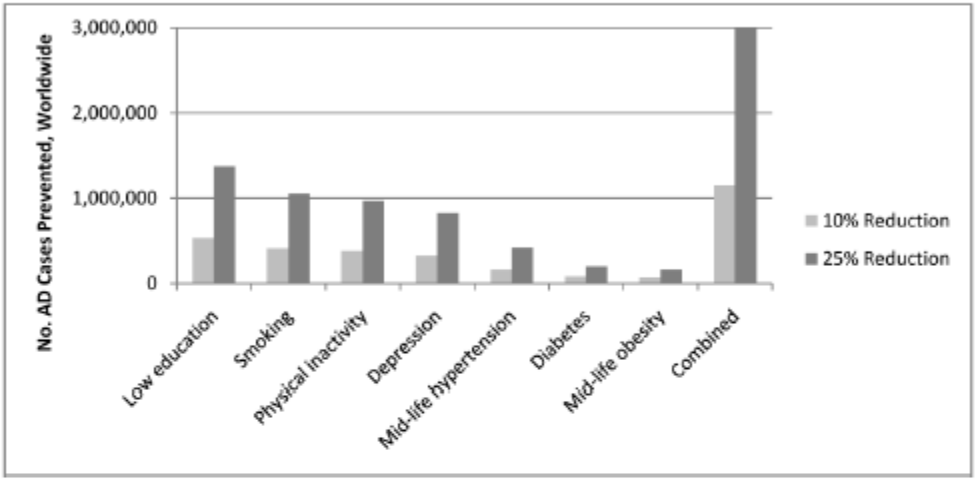


Figure 1.

The number of Alzheimer's disease (AD) cases that could potentially be prevented through risk factor reductions of 10% or 25% worldwide (Figure 1a) and in the US (Figure 1b) was estimated by multiplying current prevalence estimates by 0.90 and 0.75, respectively, and subtracting the revised number of attributable cases from the original number. These estimates assume that a causal relationship exists between the risk factor and AD and that the relative risk estimate is a good approximation of the impact of risk factor reduction. Therefore, the actual number of cases prevented could be higher or lower depending on the extent to which these assumptions are valid. In addition, the combined estimate assumes that the individual risk factors are independent and have an additive relationship. Because several of the risk factors examined are inter-related, the combined PAR estimates should be considered as maximums.

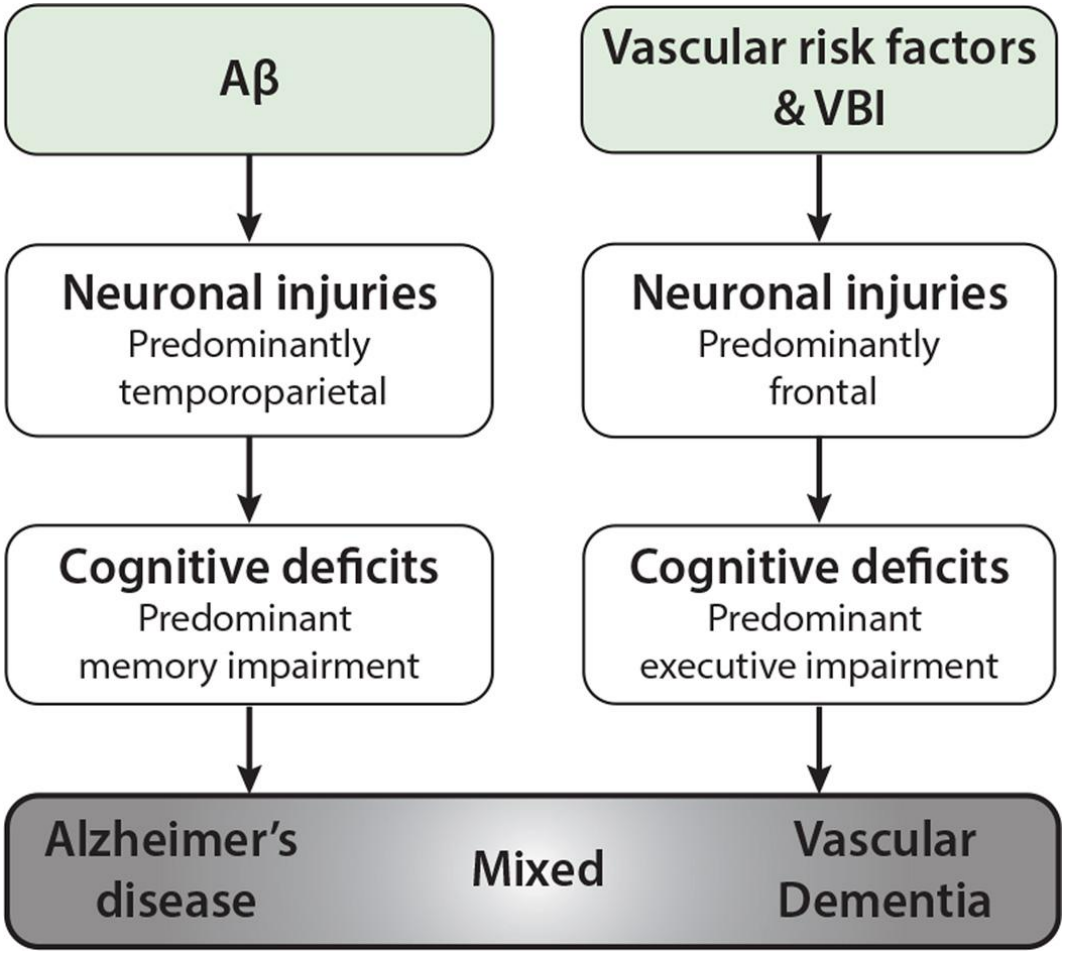
Lancet Neurol. 2011 September ; 10(9): 819–828.

Table 3. Pharmacological Treatments for VCI

Treatment	Recommendation (Class/Level of Evidence)	Comments
Donepezil[396–400]	Class IIa, Level A, for "pure" VaD	Study 307, 308 (n=1219): modest benefit for cognitive and global, less robust for function; Study 319 (n=974): only cognitive benefit
Galantamine[401–403]	Class IIa, Level A, for mixed Alzheimer disease–cerebrovascular disease; Class IIb for "pure" VaD	Pure and mixed VaD Gal-Int-6 (n=592): benefit in all primary outcomes overall; only cognitive benefit in pure disease; "Pure" VaD (Gal-Int-26; n=788): modest benefit in cognitive/executive measures
Rivastigmine[404,405]	Class IIb, Level C	VCIND study (n=50): modest benefit in some executive functions
Memantine[406,407]	Class IIb, Level A	n=900: Modest cognitive benefits only

VCI indicates vascular cognitive impairment; VaD, vascular dementia; and VCIND, vascular cognitive impairment, no dementia. Study 307, 308, and 319 and "Gal-Int-6" and "Gal-Int-26" are names of the studies.

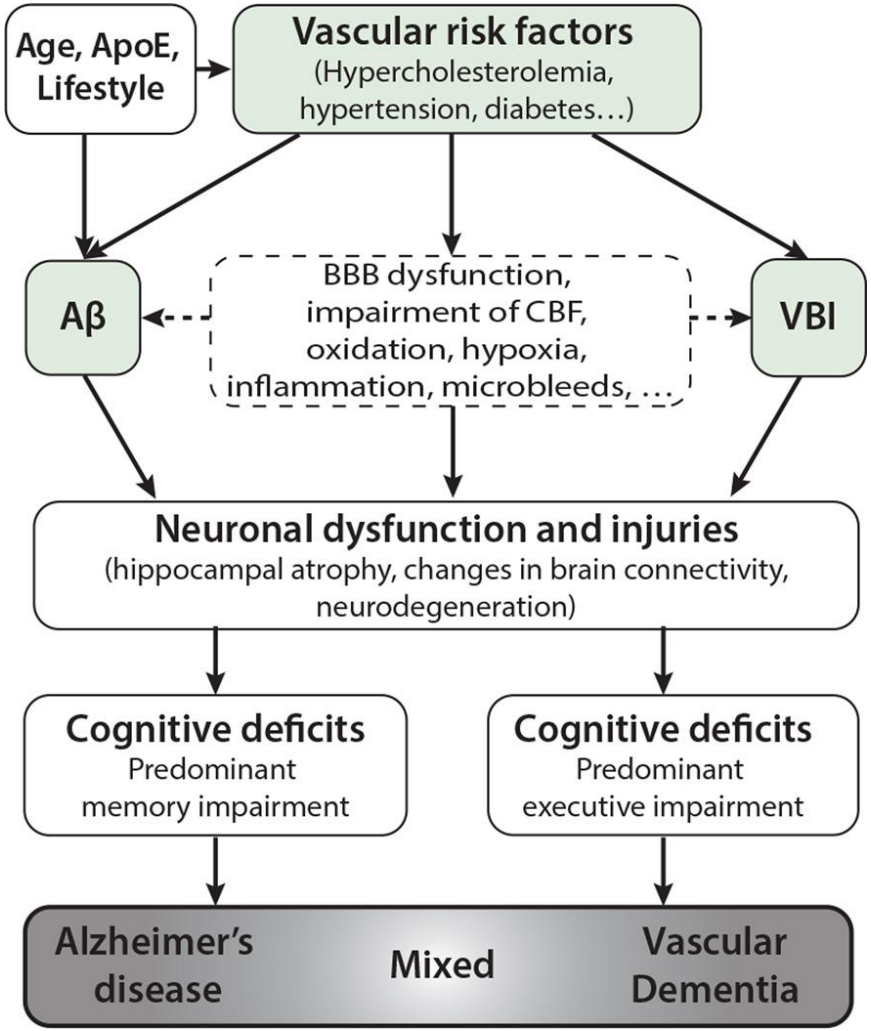
(*Stroke*. 2011;42:2672-2713.)



Independent Alzheimer and vascular pathways: an autopsy based model

Autopsy studies suggest that Alzheimer and vascular pathologies increase the risk of AD via independent and additive pathways. Because both pathologies frequently co-occur and because vascular risk factors such as hypertension and diabetes are well known risk factors for AD, mixed dementia is often considered the most frequent type of dementia.

J Prev Alzheimers Dis. 2015



Alzheimer and vascular independent and shared pathways : an in-vivo based model

Proposed conception of the relationship between AD and vascular factors. While Aβ burden and vascular brain injuries (VBI, white matter lesions and infarcts) still have distinct pathways, vascular risk factors are associated with both Aβ burden and VBI. Vascular risk factors are also associated with brain integrity via a pathway that is independent from Aβ and VBI. Accordingly, vascular risk factors should be a particular target for prevention.

J Prev Alzheimers Dis. 2015

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White matter changes and diabetes predict cognitive decline in the elderly

The LADIS Study

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ABSTRACT

Objective: We aimed to study if age-related white matter changes (WMC) and vascular risk factors were predictors of cognitive decline in elderly subjects with WMC living independently.

Methods: The Leukoaraiosis and Disability prospective multinational European study (LADIS) evaluates the impact of WMC on the transition of independent elderly subjects into disability. Independent elderly were enrolled due to the presence of WMC. Subjects were evaluated yearly during 3 years with a comprehensive clinical protocol and a neuropsychological battery. Additionally, dementia, subtypes of dementia, and cognitive decline without dementia were classified according to usual clinical criteria. MRI was performed at entry and at the end of the study.

Results: A total of 639 subjects were included (74.1 ± 5 years, 55% women, 9.6 ± 3.8 years of schooling). At end of follow-up, 90 patients had dementia and 147 had cognitive impairment no dementia. Using Cox regression analysis, WMC severity independently predicted cognitive decline (dementia and not dementia), independently of age, education, and medial temporal atrophy (MTA). Diabetes at baseline was the only vascular risk factor that independently predicted cognitive decline during follow-up, controlling for age, education, WMC severity, and temporal atrophy. Considering subtypes of dementia, Alzheimer disease (AD) was predicted only by MTA, while vascular dementia was predicted by previous stroke, WMC severity, and MTA.

Conclusion: WMC severity and diabetes are independent predictors of cognitive decline in an initially nondisabled elderly population. Vascular dementia is predicted by previous stroke and WMC, while AD is predicted only by MTA. *Neurology*® 2010;75:160–167

The Aging Brain and Cognition

Contribution of Vascular Injury and Aβ to Mild Cognitive Dysfunction

Natalie L. Marchant, PhD; Bruce R. Reed, PhD; Nerses Sanossian, MD; Cindee M. Madison, MA; Stephen Kriger, BS; Roxana Dhada, BA; Wendy J. Mack, PhD; Charles DeCarli, MD; Michael W. Weiner, MD; Dan M. Mungas, PhD; Helena C. Chui, MD; William J. Jagust, MD

Importance: β-Amyloid (Aβ) deposition and vascular brain injury (VBI) frequently co-occur and are both associated with cognitive decline in aging. Determining whether a direct relationship exists between them has been challenging. We sought to understand VBI's influence on cognition and clinical impairment, separate from and in conjunction with pathologic changes associated with Alzheimer disease (AD).

Objective: To examine the relationship between neuroimaging measures of VBI and brain Aβ deposition and their associations with cognition.

Design and Setting: A cross-sectional study in a community- and clinic-based sample recruited for elevated vascular disease risk factors.

Participants: Clinically normal (mean age, 77.1 years [N=30]), cognitively impaired (mean age, 78.0 years [N=24]), and mildly demented (mean age, 79.8 years [N=7]) participants.

Interventions: Magnetic resonance imaging, Aβ (Pittsburgh Compound B–positron emission tomographic [PiB-PET]) imaging, and cognitive testing.

Main Outcome Measures: Magnetic resonance images were rated for the presence and location of infarct (34 infarct-positive participants, 27 infarct-negative participants) and were used to quantify white matter lesion volume. The PiB-PET uptake ratios were used to create a PiB index by averaging uptake across regions vulnerable to early Aβ deposition; PiB positivity (29 PiB-positive participants, 32 PiB-negative participants) was determined from a data-derived threshold. Standardized composite cognitive measures included executive function and verbal and nonverbal memory.

Results: Vascular brain injury and Aβ were independent in both cognitively normal and impaired participants. Infarction, particularly in cortical and subcortical gray matter, was associated with lower cognitive performance in all domains ($P<.05$ for all comparisons). Pittsburgh Compound B positivity was neither a significant predictor of cognition nor interacted with VBI.

Conclusions and Relevance: In this elderly sample with normal cognition to mild dementia, enriched for vascular disease, VBI was more influential than Aβ in contemporaneous cognitive function and remained predictive after including the possible influence of Aβ. There was no evidence that VBI increases the likelihood of Aβ deposition. This finding highlights the importance of VBI in mild cognitive impairment and suggests that the impact of cerebrovascular disease should be considered with respect to defining the etiology of mild cognitive impairment.

JAMA Neurol. 2013;70(4):488-495. Published online February 11, 2013. doi:10.1001/2013.jamaneurol.405

White Matter Hyperintensities and Cerebral Amyloidosis

Necessary and Sufficient for Clinical Expression of Alzheimer Disease?

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Importance: Current hypothetical models emphasize the importance of β-amyloid in Alzheimer disease (AD) pathogenesis, although amyloid alone is not sufficient to account for the dementia syndrome. The impact of small-vessel cerebrovascular disease, visualized as white matter hyperintensities (WMHs) on magnetic resonance imaging scans, may be a key factor that contributes independently to AD presentation.

Objective: To determine the impact of WMHs and Pittsburgh Compound B (PIB) positron-emission tomography–derived amyloid positivity on the clinical expression of AD.

Design: Baseline PIB–positron-emission tomography values were downloaded from the Alzheimer's Disease Neuroimaging Initiative database. Total WMH volume was derived on accompanying structural magnetic resonance imaging data. We examined whether PIB positivity and total WMHs predicted diagnostic classification of patients with AD (n = 20) and control subjects (n = 21). A second analysis determined whether WMHs discriminated between those with and without the clinical diagnosis of AD among those who were classified as PIB positive (n = 28). A third analysis examined whether WMHs, in addition to PIB status, could be used to predict future risk for AD among subjects with mild cognitive impairment (n = 59).

Setting: The Alzheimer's Disease Neuroimaging Initiative public database.

Participants: The study involved data from 21 normal control subjects, 59 subjects with mild cognitive impairment, and 20 participants with clinically defined AD from the Alzheimer Disease's Neuroimaging Initiative database.

Main Outcome Measures: Clinical AD diagnosis and WMH volume.

Results: Pittsburgh Compound B positivity and increased total WMH volume independently predicted AD diagnosis. Among PIB-positive subjects, those diagnosed as having AD had greater WMH volume than normal control subjects. Among subjects with mild cognitive impairment, both WMH and PIB status at baseline conferred risk for future diagnosis of AD.

Conclusions and Relevance: White matter hyperintensities contribute to the presentation of AD and, in the context of significant amyloid deposition, may provide a second hit necessary for the clinical manifestation of the disease. As risk factors for the development of WMHs are modifiable, these findings suggest intervention and prevention strategies for the clinical syndrome of AD.

JAMA Neurol. 2013;70(4):455-461. Published online February 18, 2013. doi:10.1001/jamaneurol.2013.1321

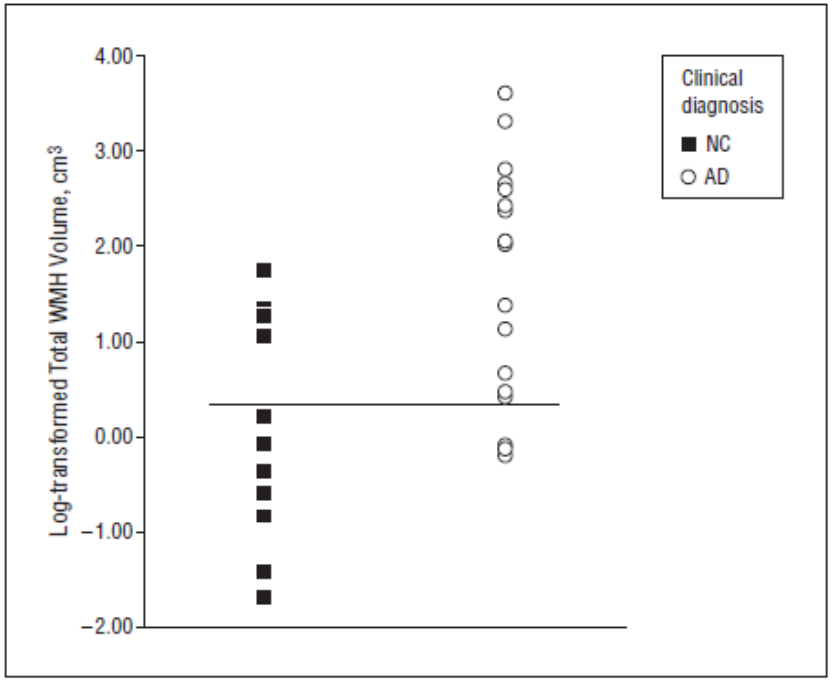

Figure 3. Distribution of white matter hyperintensity (WMH) volume among Pittsburgh Compound B–positive participants as a function of clinical diagnosis. For illustration, data are presented in log-transformed units. At a cutoff score of 0.22 log-transformed units (approximately 1.25 cm^3 raw units) of WMH volume (solid line), there is 83% sensitivity and 64% specificity for diagnostic classification. AD indicates Alzheimer disease; NC, normal control.

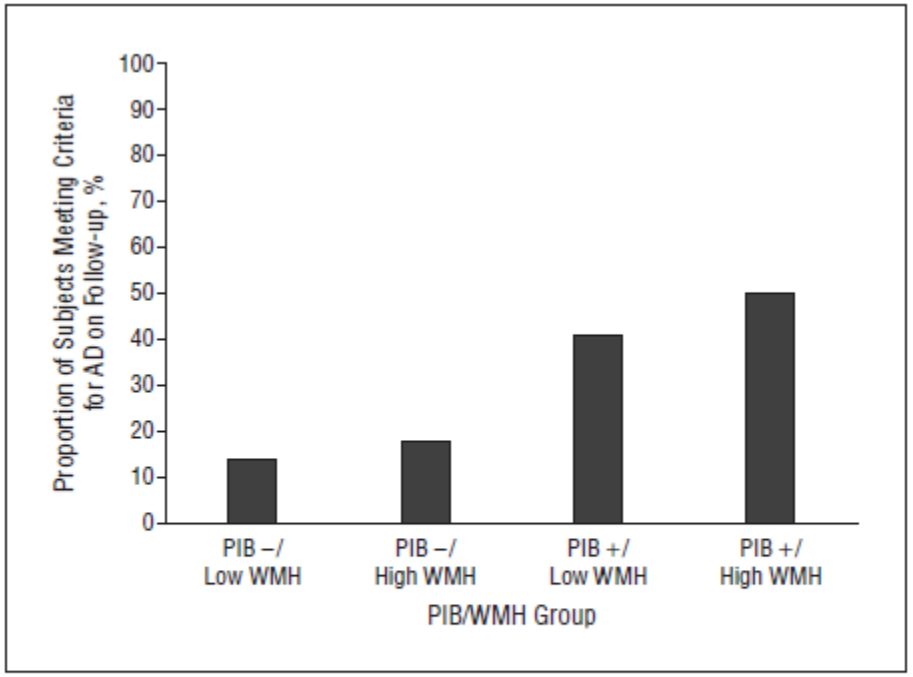

Figure 4. Proportion of subjects with mild cognitive impairment who converted to Alzheimer disease (AD) during the follow-up period as a function of the Pittsburgh Compound B (PIB)/white matter hyperintensity (WMH) group.

ONLINE FIRST

Dissociable Effects of Alzheimer Disease and White Matter Hyperintensities on Brain Metabolism

Thaddeus J. Haight, PhD; Susan M. Landau, PhD; Owen Carmichael, PhD; Christopher Schwarz, PhD; Charles DeCarli, MD; William J. Jagust, MD; for the Alzheimer's Disease Neuroimaging Initiative

Importance: Cerebrovascular disease and Alzheimer disease (AD) frequently co-occur and seem to act through different pathways in producing dementia.

Objective: To examine cerebrovascular disease and AD markers in relation to brain glucose metabolism in patients with mild cognitive impairment.

Design and Setting: Cohort study among the Alzheimer Disease Neuroimaging Initiative clinical sites in the United States and Canada.

Participants: Two hundred three patients having amnestic mild cognitive impairment (74 of whom converted to AD) with serial imaging during a 3-year follow-up period.

Main Outcomes and Measures: Quantified white matter hyperintensities (WMHs) represented cerebrovascular disease, and cerebrospinal fluid β-amyloid represented AD pathology. Brain glucose metabolism in temporoparietal and frontal brain regions was measured using positron emission tomography with fluorodeoxyglucose F18.

Results: In converters, greater WMHs were associated with decreased frontal metabolism (−0.048; 95% CI, −0.067 to −0.029) but not temporoparietal metabolism (0.010; 95% CI, −0.010 to 0.030). Greater cerebrospinal fluid β-amyloid (per 10-pg/mL increase) was associated with increased temporoparietal metabolism (0.005; 95% CI, 0.000-0.010) but not frontal metabolism (0.002; 95% CI, −0.004 to 0.007) in the same patients. In nonconverters, similar relationships were observed except for a positive association of greater WMHs with increased temporoparietal metabolism (0.051; 95% CI, 0.027-0.076).

Conclusions and Relevance: The dissociation of WMHs and cerebrospinal fluid β-amyloid in relation to regional glucose metabolism suggests that these pathologic conditions operate through different and independent pathways in AD that reflect dysfunction in different brain systems. The positive association of greater WMHs with temporoparietal metabolism suggests that these pathologic processes do not co-occur in nonconverters.

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Cerebrovascular Effects of Apolipoprotein E

Implications for Alzheimer Disease

Berislav V. Zlokovic, MD, PhD

Human apolipoprotein E (apoE) has 3 isoforms: apoE2, apoE3, and apoE4. *APOE4* is a major genetic risk factor for Alzheimer disease and is associated with dementia in Down syndrome and poor neurological outcome after traumatic brain injury, cerebral hemorrhage, and other neuropathological disorders. While apoE4 can induce neuropathology by participating in various cellular and molecular pathways, herein I review data supporting the hypothesis that apoE4 has direct toxic effects on the cerebrovascular system that in turn can lead to secondary neuronal dysfunction and degeneration as well as accumulation of neurotoxins in brain such as β-amyloid (Aβ) in Alzheimer disease. I review Aβ-independent cerebrovascular effects of apoE, particularly activation of a proinflammatory cyclophilin A–mediated pathway in brain vascular pericytes by apoE4 that has recently been shown to lead to a loss of cerebrovascular integrity and blood-brain barrier breakdown causing neuronal injury. I also review Aβ-dependent cerebrovascular effects of apoE such as faulty Aβ clearance from brain to circulation by apoE4. Finally, I discuss isoform-specific interactions of apoE with low-density lipoprotein receptor-related protein 1 on brain vascular cells (ie, endothelial cells, pericytes), which play an important role in Aβ-independent and Aβ-dependent effects of apoE on cerebral vasculature.

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Vascular risk factors and Alzheimer's Disease

BMC Medicine

REVIEW **Open Access**

The overlap between vascular disease and Alzheimer's disease – lessons from pathology

Johannes Attems[1*] and Kurt A Jellinger[2]

Abstract

Recent epidemiological and clinico-pathological data indicate considerable overlap between cerebrovascular disease (CVD) and Alzheimer's disease (AD) and suggest additive or synergistic effects of both pathologies on cognitive decline. The most frequent vascular pathologies in the aging brain and in AD are cerebral amyloid angiopathy and small vessel disease. Up to 84% of aged subjects show morphological substrates of CVD in addition to AD pathology. AD brains with minor CVD, similar to pure vascular dementia, show subcortical vascular lesions in about two-thirds, while in mixed type dementia (AD plus vascular dementia), multiple larger infarcts are more frequent. Small infarcts in patients with full-blown AD have no impact on cognitive decline but are overwhelmed by the severity of Alzheimer pathology, while in early stages of AD, cerebrovascular lesions may influence and promote cognitive impairment, lowering the threshold for clinically overt dementia. Further studies are warranted to elucidate the many hitherto unanswered questions regarding the overlap between CVD and AD as well as the impact of both CVD and AD pathologies on the development and progression of dementia.

Keywords: Alzheimer's disease, Cerebrovascular lesions, Cerebral amyloid angiopathy, Cognitive impairment, Lacunes, Microinfarcts, Small vessel disease, White matter lesions

Vascular pathology in aging and Alzheimer's disease

The types of vascular pathology in the aged human brain include:

- Cerebral amyloid angiopathy (CAA);
- Cerebral atherosclerosis, SVD (in most cases caused by hypertension, i.e., hypertensive vasculopathy), or microvascular degeneration (tortuosity, fibro- and lipohyalinosis,);
- Blood–brain barrier (BBB) dysfunction causing white matter lesions (WMLs), microinfarctions, lacunes or lacunar infarcts, and microbleeds [17,87].

Table 1 Types and location of cerebrovascular lesions in vascular dementia (total 188)

Multiple infarcts (61 = 32.5%)	
MCA bilateral	4
MCA left/right	9
MCA bilat. + PCAS/PCAD	2/1
MCA bilat. + PCA bilat.	2
MCAS + PCAS	4
MCAD + PCAD	4
PCA bilateral	3
PCA left/right	5/7
ACAS + MCAS	2
ACAD	1
Multiple cortico-subcortico bilateral	12
Multiple cortico-subcortico left hem.	2
SAE (subcortical) (108 = 57.4%)	
Basal ganglia	21
Basal ganglia + white matter	31
Basal ganglia + thalamus (+white matter)	33
Basal ganglia brainstem (+thalamus)	23
SID/strategic infarcts (19 = 10.1%)	
Thalamus bilateral	9
Thalamus left	2
Thalamus + hippocampus	8

Abbreviations: ACAD, Anterior cerebral artery dexter; ACAS, Anterior cerebral artery sinister; MCA, Middle cerebral artery; MCAD, Middle cerebral artery dexter; MCAS, Middle cerebral artery sinister; PCA, Posterior cerebral artery; PCAD, Posterior cerebral artery dexter; PCAS, Posterior cerebral artery sinister; SAE, Subcortical arteriosclerotic encephalopathy; SID, strategic infarct dementia.

Table 2 Types and location of cerebrovascular lesions in mixed dementia (n = 83)

1) AD + Multiple infarcts (47 = 56.6%)	
MCA bilateral	7
MCA left	6
MCA right (+ lacunes basal ganglia)	3/1
MCA + ACA bilat.	1
MCA + PCA left	2
MCA + PCA right	1
MCA + PCA left/right	3/3
MCA bilat. +PCAD	1
PCA bilateral	2
Multiple cort. and subcort. bilateral	13
Multiple left hemisphere	4
2) AD + SAE (subcortical) (33 = 39.8%)	
Lacunes basal ganglia	15
Lacunes basal ganglia + white matter	8
Lacunes basal ganglia + thalamus	10
3) AD + SID/strategic infarcts (3 = 3.6%)	
Thalamus bilateral	2
Thalamus + hippocampus	1

Abbreviations: ACA, Anterior cerebral artery; AD, Alzheimer's disease; MCA, Middle cerebral artery; PCA, Posterior cerebral artery; SAE, Subcortical arteriosclerotic encephalopathy; SID, strategic infarct dementia.

Table 3 Common lesions in AD, VaD, MIX, and aged controls (from [130])

Pathological feature	AD [%]	VaD [%]	MIX [%]	Aged controls [%]
Cerebral amyloid angiopathy	98	30	~90	23–45
Small vessel disease/MVD	~50	>50	>50	~20
Total infarctions	10–20	100	30–40	>10
Microinfarcts/lacunes	30–46	70	60–70	17–21
Intracerebral hemorrhage	10–15	15	10	1–2
White matter pathology	40	80	70–80	<20
Loss of cholinergic markers	75	40	~70	
CVD/atherosclerosis	45–60	60	~60	30–53

Abbreviations: AD, Alzheimer's disease; CVD, Cerebrovascular disease; MIX, mixed type dementia (AD plus vascular dementia); MVD, Microvascular disease; VaD, Vascular dementia.

Contribution of Cerebrovascular Health to the Diagnosis of Alzheimer Disease

Whether the contribution of vascular health to AD is entirely independent of its basic neuropathology (amyloid deposition and tauopathy), merely concomitant with it, or sometimes a trigger for its expression, the presence of vascular risk exacerbates cognitive aging and better and earlier control of its manifestations (eg, hypertension, diabetes) will make a positive contribution to public health, both cardiovascular and cognitive. Longitudinal studies that carefully track vascular health risk factors and measure the development of key biomarkers for AD within individuals over time are essential to understanding the nature of the interaction between vascular disease and cognitive aging and the conversion from MCI to AD diagnosis.

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