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The Role of Cerebrovascular Disease on Cognitive and Functional Status and Psychosis in Severe Alzheimer's Disease

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Abstract.
Background: The pathophysiology behind psychosis in patients with Alzheimer's disease (AD) remains unknown. Recently, vascular risk factors have been recognized as important modifiers of the clinical presentation of AD.
Objective: The purpose of our study is to investigate the mechanism through which vascular risk factors mediate psychosis and whether or not it involves cerebrovascular lesions.
Methods: Data was provided by the National Alzheimer's Coordinating Centre. The Uniform Data Set was used to collect information on subject-reported history of vascular risk factors, clinician-reported state of cognitive performance, and presence of psychosis based on the Neuropsychiatric Inventory Questionnaire (NPI-Q). The Neuropathology Data Set was used to evaluate the presence of vascular lesions and the severity of AD pathology. Subjects with high probability of AD based on the NIA/AA Reagan criteria were included in the analysis.
Results: We identified 1,459 patients with high probability of AD and corresponding NPI-Q scores. We confirmed the association between hypertension and diabetes on psychosis, specifically in delusions and the co-occurrence of delusions and hallucinations. Furthermore, the presence of white matter rarefaction based on pathological evaluation was associated with hallucinations. A history of vascular risk factors was positively associated with vascular lesions. However, vascular lesions in the presence of vascular risk factors did not increase the likelihood of psychosis. Furthermore, vascular lesions were not associated with greater cognitive or functional impairments in this group with severe AD pathology.
Conclusion: Vascular risk factors and vascular lesions are independently associated with psychosis in patients with severe AD. However, vascular lesions are not the mechanism through which vascular risk factors mediate psychosis.

Keywords: Cerebrovascular diseases, delusions, dementia, hallucinations, infarction, neuropathology, pathology, risk factors, vascular

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INTRODUCTION

Psychosis is one of the common and disruptive conditions that occurs with Alzheimer's disease (AD). It is estimated that approximately 40% of patients with AD experience psychotic symptoms during the course of their illness [1]. Psychosis refers to a range of symptoms, generally categorized into delusions and hallucinations. Common delusional symptoms in AD include delusions of persecution, abandonment, infidelity, and misidentification. Hallucination symptoms are typically visual and auditory, but visual hallucinations are more common in AD [2]. Psychosis is often accompanied by behavioral disturbances [3–6] and a greater rate of cognitive decline [7–9], causing significant distress to both the patients and their caregivers [10, 11]. However, the pathophysiology behind psychosis in AD remains largely unknown, limiting the ability to properly manage and treat patients.

Increasingly, cerebrovascular disease has been recognized as an important risk factor for the clinical manifestations of AD [12–16]. Several studies have shown that vascular factors significantly increase the likelihood of dementia [17]. Only recently, the role of cerebrovascular disease on psychosis in AD has been investigated. A study by Fischer and colleagues showed that vascular risk factors, but not plaque or tangle burden, are associated with psychosis in AD [18]. Other studies suggest that the presence of vascular pathology in certain regions of the brain, such as lacunar infarcts in the basal ganglia, impose a higher risk of developing delusional symptoms [19]. In the present study, we investigate the association between vascular risk factors and vascular pathology on cognitive and functional status and psychosis in patients with high probability of AD, corresponding to severe pathology. Furthermore, we examine whether or not vascular pathology is the mechanism through which vascular risk factors mediate the development of psychosis.

MATERIALS AND METHODS

Data source and subject criteria

Data was obtained from the National Alzheimer's Coordinating Centre (NACC) encompassing records from approximately 30 Alzheimer's Disease Centers across the United States. The Uniform Data Set (UDS) and Neuropathology Data Set (NP) collected between September 2005 and December 2015 were analyzed.

The UDS was used to obtain demographical and clinical data. The demographic variables include age, sex, and education. The clinical variables comprise of informant-reported history of vascular risk factors, including hypertension, hypercholesterolemia, diabetes, and smoking (smoked more than 100 cigarettes in lifetime, total years smoked, and average number of packs per day). Clinician-reports for vascular risk factors were collected recently, and thus do not have corresponding neuropathology data. The duration of illness was calculated based on clinician's assessment on age at cognitive decline and age of death. The UDS was also used to collect clinician-reported scores on Mini-Mental State Examination (MMSE), Functional Activity Questionnaire (FAQ), and Global Clinical Dementia Rating (CDR). The presence and severity of psychotic symptoms (mild, moderate, severe), i.e., delusions or hallucinations in the month prior to the interview based on Neuropsychiatric Inventory Questionnaire, Quick version (NPI-Q) were also collected. The criteria for delusions on the NPI-Q are mainly persecutory delusions. The hallucinations symptoms include both visual and auditory hallucinations.

The NP was used to evaluate the severity of AD pathology, based on the density of neocortical neuritic plaque (CERAD score) and the Braak Stage for neurofibrillary degeneration. The NP was also used to collect data on the presence of vascular pathology, including microinfarcts (old microinfarcts not observed grossly), lacunae (small artery infarcts and/or hemorrhages less than 1 cm), cerebral amyloid angiopathy (CAA), arteriosclerosis, and white matter rarefaction (subcortical arteriosclerotic leukoencephalopathy). The severity of white matter rarefaction (none, mild, moderate, or severe), which was recorded beginning in January 2014, was further categorized into minor (if none or mild) or major (if moderate or severe) severity of white matter rarefaction. Lewy body pathology was categorized as absent (if no Lewy bodies were found) or present (if Lewy bodies were observed in the brainstem, limbic region or amygdala, neocortical, olfactory bulb, or regions unspecified) as determined by alpha-synuclein immunohistochemistry.

Patients with other primary etiological diagnosis, including brain injury, CNS neoplasm, Down's syndrome, and Huntington's disease on the UDS were excluded from the analysis. Subjects with high probability of AD based on the NIA/AA Reagan criteria,

with CERAD score of 'frequent neuritic plaque' and Braak stage of V or VI were included (thus corresponding to severe AD pathology) [20].

Any positive score for delusions or hallucinations at any visit during the course of a patient's illness was considered positive for psychosis. Patients were categorized into never psychotic (AD-P), psychotic (AD+P), delusions only (AD+D), hallucinations only (AD+H), or co-occurrence of delusions and hallucinations (AD+DH).

Statistical analysis

All the statistical analyses were done using the statistical software SPSS Statistics 23.0. Each of the categories of psychosis, AD+P, AD+D, AD+H, and AD+DH were independently analyzed against the AD-P group. The χ^2 test was used to analyze categorical data. The independent samples *t*-test was used for continuous data with normal distribution. The Mann-Whitney test was used for continuous data if Kolmogorov-Smirnov test of normality was statistically significant. The ordinal regression analysis was used for ordinal data. ANCOVA was used when accounting for variance in the demographic or clinical characteristics between the diagnostic groups. No correction was applied for multiple testing. Statistical significance was assessed using $\alpha = 0.05$.

RESULTS

The previous study by Fischer and colleagues using the NACC database collected between September 2005 and May 2012 identified 664 patients with high probability of AD using the NIA/AA Reagan criteria [18]. In our study, we identified 1459 patients with high probability of AD, which includes overlapping patients from the previous study. Within this group, we identified 734 AD-P, 326 AD+D, 170 AD+H, and 229 AD+DH.

Demographic and clinical characteristics

Subjects in the AD+P and AD+H were significantly younger at age of clinical visit compared to the AD-P counterparts. Subjects in the AD+H group were also younger at age at death. The age of onset of cognitive decline based on clinician's assessment was not statistically different between the diagnostic groups. The duration of illness was shorter in the AD+H group compared to the AD-P group. The interval between last clinical visit and death was significantly shorter in all categories of psychosis compared to the AD-P counterparts. The average interval between last clinical visit and death were under two years in all of the diagnostic categories. There were no statistical differences between psychotic status and sex (Table 1).

Vascular pathologies, Lewy bodies, and cognitive and functional status

Within our criteria of high probability of AD, there were no significant associations between vascular pathologies and cognitive or functional status, based on the MMSE, FAQ, and global CDR scores. The presence of Lewy body pathology was associated with lower MMSE scores, and higher FAQ scores, corresponding to greater cognitive and functional impairments (Table 2).

Vascular risk factors and vascular pathology

A history of vascular risk factors was positively associated with certain vascular pathologies. Patients

Table 1
The demographic and clinical distribution of subjects within each diagnostic categories (AD-P Never psychotic; AD+P Psychotic; AD+D Delusions only; AD+H Hallucinations only; AD+DH Co-occurrence of delusions and hallucinations). Each of the psychotic categories were independently analyzed against the non-psychotic group (AD-P)

	AD-P		AD+P		AD+D		AD+H		AD+DH	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/ean	%/SD
Age at clinical visit	734/77.09	10.58	725/76.02*	10.78	326/77.08	10.24	170/74.43**	10.84	229/75.68	11.35
Age at death	734/78.91	10.4	725/78.11	10.82	326/79.34	10.22	170/76.35**	10.99	229/77.66	11.35
Interval between last clinical visit and death in years	734/1.80	1.77	725/1.31**	1.35	326/1.45**	1.49	170/1.28**	1.32	229/1.14**	1.14
Age onset	714/69.13	10.59	720/68.20	10.75	324/69.43	10.33	168/66.52	10.52	228/67.68	11.34
Duration of Illness	714/9.56	3.93	720/9.95	3.97	324/9.90	3.84	168/9.93**	4.23	228/10.03	3.95
Sex										
Males	411	56%	383	53%	176	54%	92	54%	115	50%
Females	323	44%	342	47%	150	46%	78	46%	114	50%

*$p = 0.010$ to 0.050; **$p \leq 0.010$.

Table 2
The distribution of vascular lesions, Lewy bodies, and cognitive and functional impairments

	MMSE		FAQ		Global CDR	
	N/ Mean	SD	N/ Mean	SD	N/ Mean	SD
Microinfarcts						
Absent	888/12.73	8.47	1236/25.25	7.15	1253/2.15	0.88
Present	180/12.97	8.20	256/25.51	6.47	260/2.15	0.87
Lacunae						
Absent	728/12.40	8.45	999/25.57	6.87	1017/2.17	0.87
Present	128/12.40	9.07	181/25.49	7.22	183/2.22	0.88
White matter rarefaction						
Absent	837/12.61	8.46	1247/25.27	7.08	1164/2.15	0.88
Present	193/12.74	8.28	301/26.04	6.30	305/2.24	0.84
Lewy bodies	**		**			
Absent	622/13.45	8.50	900/24.98	7.44	915/2.13	0.90
Present	442/11.82	8.24	587/25.75	6.36	592/2.16	0.85

*$p = 0.010$ to 0.050; **$p \leq 0.010$.

with a history of hypertension were significantly more likely to have microinfarcts, lacunae, and white matter rarefaction on pathological examination. Patients with a history of hypercholesterolemia or diabetes were more likely to have lacunae. A history of smoking was significantly associated with presence of white matter rarefaction. Lewy body pathology was negatively associated with hypertension, and was not associated with other vascular risk factors analyzed in this study (Table 3).

Association of vascular risk factors, vascular pathologies, and Lewy bodies with psychosis

In accordance with the previous study by Fischer and colleagues, we found a significant association between presence of psychosis and hypertension or diabetes [18]. This association was specific to patients with delusions and co-occurrence of delusions and hallucinations (Table 4). We did not find any associations between the presence of microinfarcts, lacunae, CAA, and arteriosclerosis and psychosis. However, a significant association was found between white matter rarefaction and psychosis, specifically AD+H. The presence of Lewy body pathology was positively associated with the AD+P, AD+H, and AD+DH group compared to AD-P (Table 4).

Vascular pathology as mediator

Given that vascular risk factors and vascular pathologies are linked, and independently associated with psychosis, we then investigated whether vascular pathologies are the mediators through which vascular risk factors affect psychosis. However, in patients with a history of vascular risk factors, vascular pathologies, including white matter rarefaction, were not more common in any of the subgroups of psychosis compared to the AD-P group (Table 5). Lewy body pathology was not analyzed as a mediator because their only association with a vascular risk factor (hypertension) is negative. However, since Lewy bodies are positively associated with psychosis, their presence was used as a covariate in the analysis.

DISCUSSION

Several longitudinal studies in the elderly population have suggested that cerebrovascular disease is associated with increased likelihood of dementia [21–27]. However, an evidence-based review by Chui and colleagues show that there are no associations between vascular risk factors and AD pathology [28]. Studies with neuropathological confirmation have reported that the association between vascular pathology and dementia was observed only in patients with low to moderate, but not severe AD pathology [29, 30]. Consistent with these findings, the present study shows that vascular pathologies do not affect cognitive or functional performance in subjects with high severity of AD pathology.

Importantly, our study confirms the finding that vascular risk factors are associated with increased risk of psychosis, specifically delusions [18]. However, the mechanism through which vascular risk factors affect the onset of psychosis remains unknown. In our study, we examined the role of vascular pathology as an intermediate mechanism through which vascular risk factors affect the onset of psychosis. We confirmed that risk factors are positively associated with vascular pathology, including microinfarcts, lacunae, and white matter rarefaction. Only one type of

Table 3
The distribution of vascular risk factors, vascular pathologies, and Lewy bodies in subjects with severe Alzheimer's disease pathology

	Microinfarcts				Lacunae				White matter rarefaction				Lewy bodies			
	N/Mean	% /SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/ Mean	%/SD	N//Mean	%/SD	N/Mean	%/SD
	Absent		Present		Absent		Present		Absent		Present		Absent		Present	
Hypertension			**				**				*				*	
Absent	624	55%	99	40%	518	55%	62	38%	488	54%	87	45%	419	50%	301	55%
Present	516	45%	147	60%	420	45%	103	62%	413	46%	108	55%	418	50%	243	45%
Hypercholesterolemia							*									
Absent	593	53%	115	50%	511	56%	75	46%	486	55%	98	52%	439	54%	264	50%
Present	526	47%	117	50%	408	44%	87	54%	398	45%	92	48%	376	50%	266	50%
Diabetes							**									
Absent	1127	91%	228	88%	927	92%	150	84%	885	91%	187	93%	815	90%	535	91%
Present	109	9%	31	12%	77	8%	29	16%	89	9%	15	7%	87	10%	52	9%
Smoked more than 100 cigarettes in life											*					
No	666	54%	127	50%	520	52%	98	55%	522	54%	92	45%	504	56%	285	50%
Yes	560	46%	125	50%	472	48%	79	45%	436	46%	112	55%	393	44%	290	50%
Total years smoked cigarettes	1175/11.26	16.58	236/11.50	17.38	842/11.71	16.93	168/12.09	17.97	919/11.40	16.97	184/13.47	17.57	862 /10.77	16.64	544/12.10	16.66
Average number of packs smoked per day											*					
No Reported Cigarette	655	56%	126	54%	511	55%	96	56%	512	56%	91	49%	497	58%	280	52%
1 cigarette to less than 1/2 pack	152	13%	29	12%	117	13%	18	11%	113	12%	22	12%	102	12%	78	14%
1/2 pack to less than 1 pack	179	15%	36	15%	148	16%	27	16%	140	15%	35	19%	122	14%	92	17%
1 pack to 11/2 packs	105	9%	18	8%	91	10%	14	8%	84	9%	18	10%	74	9%	49	9%
11/2 packs to 2 packs	44	4%	9	4%	34	4%	8	5%	32	4%	10	5%	31	4%	22	4%
More than 2 Packs	33	3%	15	6%	34	4%	7	4%	32	4%	9	5%	31	4%	17	3%

*$p = 0.010$ to 0.050; **$p \leq 0.010$.

Table 4
The distribution of vascular risk factors, vascular pathologies, and degenerative pathology in each of the diagnostic categories of psychosis (AD-P Never psychotic; AD+P Psychotic; AD+D Delusions only AD+H Hallucinations only; AD+DH Co-occurrence of delusions and hallucinations). Each of the psychotic categories were independently analyzed against the non-psychotic group (AD-P)

	AD-P		AD+P		AD+D		AD+H		AD+DH	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
Vascular Risk Factors										
Hypertension			**		**				*	
Absent	369	56%	327	49%	145	47%	82	55%	100	47%
Present	292	44%	347	51%	165	53%	67	45%	115	53%
Hypercholesterolemia										
Absent	346	53%	328	50%	143	49%	83	56%	102	49%
Present	306	47%	322	50%	151	51%	66	44%	105	51%
Diabetes					*				*	
Absent	672	92%	639	89%	288	89%	155	95%	196	87%
Present	57	8%	75	11%	36	11%	9	5%	30	13%
Smoked more than 100 cigarettes in life										
No	371	51%	392	55%	371	51%	92	55%	126	56%
Yes	351	49%	319	45%	351	49%	75	45%	100	44%
Total years smoked cigarettes	692/11.78	16.93	675/11.00	16.62	303/11.22	16.63	158/9.49	14.66	214/11.79	17.91
Average number of packs smoked per day										
No Reported Cigarette	362	49%	389	54%	172	53%	91	54%	126	55%
1 cigarette to less than 1/2 pack	93	13%	86	11%	35	11%	22	13%	29	13%
1/2 pack to less than 1 pack	119	16%	90	12%	42	13%	1	11%	29	13%
1 pack to 11/2 packs	62	8%	55	8%	22	7%	12	7%	21	9%
11/2 packs to 2 packs	25	3%	28	4%	15	5%	4	2%	9	4%
More than 2 Packs	25	3%	23	3%	11	3%	9	5%	3	1%
Vascular Pathology										
Microinfarcts										
Absent	599	82%	608	84%	267	82%	149	88%	192	84%
Present	134	18%	117	16%	59	18%	21	12%	37	16%
Lacunae										
Absent	483	86%	487	85%	210	84%	131	91%	146	81%
Present	80	14%	87	15%	40	16%	13	9%	34	19%
Cerebral Amyloid Angiopathy (CAA)										
None	141	19%	128	18%	55	17%	31	18%	42	18%
Mild	252	34%	242	33%	104	32%	55	32%	83	36%
Moderate	199	27%	197	27%	94	29%	48	28.%	55	24%
Severe	129	18%	136	19%	69	21%	28	16%	39	17%
White matter rarefaction							*			
Absent	481	84%	454	80%	204	82%	111	78%	139	78%
Present	89	16%	116	20%	44	18%	32	22%	40	22%
Arteriolosclerosis										
None	134	18%	123	17%	54	17%	28	17%	41	18%
Mild	213	29%	219	30%	99	30%	48	28%	72	31%
Moderate	190	26%	187	26%	89	27%	47	28%	51	22%
Severe	90	12%	102	14%	45	14%	20	12%	37	16%
Degenerative Pathology										
Lewy bodies			**				**		**	
Absent	467	64%	402	56%	196	60%	87	51%	119	52%
Present	262	36%	322	44%	130	40%	83	49%	109	48%

*$p = 0.010$ to 0.050; **$p \leq 0.010$.

vascular pathology, specifically presence of white matter rarefaction, was related to a form of psychosis, hallucinations. Furthermore, vascular pathology in the presence of vascular risk factors did not increase the likelihood of psychosis, indicating that the contributions of hypertension or diabetes to the development of psychosis are mediated by mechanisms other than vascular lesions. Alternatively, the location, rather than the presence of vascular lesions, would be the critical factor, but this is not the case when the effects of vascular lesions on cognitive performance in subjects with moderate AD load are considered [29, 30]. Previous studies on white matter hyperintensities on psychosis have produced mixed results. Many studies show no correlation between periventricular and white matter hyperintensities

Table 5
The distribution of vascular lesions and psychosis each diagnostic categories of psychosis in presence of vascular risk factors in subjects with high probability of AD. (AD-P Never psychotic; AD+P Psychotic; AD+D Delusions only; AD+H Hallucinations only; AD+DH Co-occurrence of delusions and hallucinations). Each of the psychotic categories were independently analyzed against the non-psychotic group (AD-P)

	AD-P		AD+P		AD+D		AD+H		AD+DH	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%	N/Mean	%/SD	N/Mean	%/SD
History of Hypertension +,										
Microinfarcts										
Absent	223	77%	274	79%	127	77%	58	87%	89	77%
Present	68	23%	73	21%	38	23%	9	13%	26	23%
Lacunae										
Absent	183	81%	217	79%	97	78%	52	90%	68	75%
Present	43	19%	56	21%	27	22%	6	10%	23	25%
White matter rarefaction										
Absent	216	77%	258	76%	129	80%	49	74%	80	71%
Present	65	23%	82	24%	32	20%	17	26%	33	29%
History of Hypercholesterolemia +										
Microinfarcts										
Absent	244	80%	270	84%	127	84%	58	88%	85	81%
Present	62	20%	52	16%	24	16%	8	12%	20	19%
Lacunae										
Absent	194	84%	203	82%	87	78%	53	91%	63	79%
Present	37	16%	46	18%	24	22%	5	9%	17	21%
White matter rarefaction										
Absent	231	80%	246	78%	117	79%	53	82%	76	75%
Present	58	20%	68	22%	31	21%	12	18%	25	25%
History of Smoking +										
Microinfarcts										
Absent	282	80%	266	85%	117	81%	65	87%	84	88%
Present	69	20%	48	15%	27	19%	10	13%	11	12%
Lacunae										
Absent	241	85%	218	86%	99	86%	59	94%	60	79%
Present	41	15%	36	14%	16	14%	4	6%	16	21%
White matter rarefaction										
Absent	282	79%	302	79%	128	77%	73	80%	101	82%
Present	74	21%	79	21%	39	23%	18	20%	22	18%

*$p = 0.010$ to 0.050; **$p \leq 0.010$.

and psychosis [31–33]. Other studies indicate that regional white matter hyperintensities affect development of delusional symptoms [34, 35]. However, these findings on white matter hyperintensities are derived from imaging studies. The results from our study based on neuropathological data suggest that white matter rarefaction increases the likelihood of psychosis, specifically hallucinations.

There are some limitations to the present study. One of the limitations of the study is that multiple univariate tests were employed in the statistical analysis, which may inflate the rate of type I error. We, as others before us, have not corrected for multiple testing in this exploratory stage [36, 37]. Another limitation is the time gap between last clinical visit and the time of death. The average time interval between last clinical visit and death in years was within two years, but the progression of the illness possibly varied among the subject population.

Furthermore, vascular risk factors analyzed in this study are subject or caregiver reported historical data, and whether the condition is still active or has been treated is not available. The NACC database started to implement clinician-reported measures since 2015, which would provide a numerical evaluation for accessing vascular risk factors at time of the visit. With respect to our analysis on cognitive performance, the results may be reflective of a floor effect given that patients with severe AD have limited functional and cognitive capacity. The choice of high AD pathology load is inseparable from high probability that the dementia is due to AD, the rationale for our choice of inclusion criterion. The presentation of psychosis collected on the NPI-Q also introduces some limitations. First of all, NPI-Q records presentation of psychosis during the last month prior to clinical visit, and does not take into account the trajectory of psychotic symptoms over time. Secondly, the criteria

for delusions on NPI-Q are persecutory delusions. Therefore, the association between vascular risk factors and other types of delusions in AD remains to be further investigated.

In summary, we demonstrate the importance of cerebrovascular disease in the clinical manifestation of psychosis, but not in cognitive performance in subjects with severe AD pathology. However, the mechanism through which vascular risk factors affects psychosis is not mediated through just the presence of vascular pathology. It is possible that vascular risk factors and vascular lesions trigger widespread alterations in the brain, which in the presence of moderate AD load results in cognitive impairment, but in the presence of severe AD results in psychosis. Prospective studies investigating the trajectories of vascular pathology and clinical manifestation AD will help to better understand the pathophysiology of AD.

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REFERENCES

[1] Ropacki SA, Jeste DV (2005) Epidemiology of and risk factors for psychosis of Alzheimer's disease: A review of 55 studies published from 1990 to 2003. *Am J Psychiatry* **162**, 2022-2030.

[2] Murray PS, Kumar S, Demichele-Sweet M, Sweet RA (2014) Psychosis in Alzheimer's disease. *Biol Psychiatry* **75**, 542-552.

[3] Lopez OL, Wisniewski SR, Becker JT, Boller F, DeKosky ST (1999) Psychiatric medication and abnormal behavior as predictors of progression in probable Alzheimer disease. *Arch Neurol* **56**, 1266-1272.

[4] Gilley DW, Wilson RS, Beckett LA, Evans DA (1997) Psychotic symptoms and physically aggressive behavior in Alzheimer's disease. *J Am Geriatr Soc* **45**, 1074-1079.

[5] Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC, Breitner JC (2000) Mental and behavioral disturbances in dementia: Findings from the Cache County Study on Memory in Aging. *Am J Psychiatry* **157**, 708-714.

[6] Cummings JL, Brodaty H, Ballard CG, Lyketsos CG, Grossberg GT, Robert P, Gauthier S (2009) Management of agitation and aggression associated with Alzheimer disease. *Nat Rev Neurol* **5**, 245-255.

[7] Gilley DW, Whalen ME, Wilson RS, Bennett DA (1991) Hallucinations and associated factors in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* **3**, 371-376.

[8] Chui HC, Lyness SA, Sobel E, Schneider LS (1994) Extrapyramidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer's disease. *Arch Neurol* **51**, 676-681.

[9] Fischer CE, Ismail Z, Schweizer TA (2012) Delusions increase functional impairment in Alzheimer's disease. *Dement Geriatr Cogn Disord* **33**, 393-399.

[10] Everitt DE, Fields DR, Soumerai SS, Avorn J (1991) Resident behavior and staff distress in the nursing home. *J Am Geriatr Soc* **39**, 792-798.

[11] Kaufer DI, Cummings JL, Christine D, Bray T, Castellon S, Masterman D, MacMillan A, Ketchel P, DeKosky ST (1998) Assessing the impact of neuropsychiatric symptoms in Alzheimer's disease: The neuropsychiatric inventory caregiver distress scale. *J Am Geriatr Soc* **46**, 210-215.

[12] de Bruijn RF, Ikram MA (2014) Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Med* **12**, 130.

[13] Villeneuve S, Jagust W (2015) Imaging vascular disease and amyloid in the aging brain: Implications for treatment. *J Prev Alzheimers Dis* **1**, 64-70.

[14] Kalaria RN, Akinyemi R, Ihara M (2012) Does vascular pathology contribute to Alzheimer changes? *J Neurol Sci* **322**, 141-147.

[15] Qiu C, Xu W, Winblad B, Fratiglioni L (2010) Vascular risk profiles for dementia and Alzheimer's disease in very old people: A population-based longitudinal study. *J Alzheimers Dis* **20**, 293-300.

[16] Reitz C, Tang M, Schupf N, Manly JJ, Mayeux R, Luchsinger JA (2010) A summary risk score for the prediction of Alzheimer disease in elderly persons. *Arch Neurol* **67**, 835-841.

[17] Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, Launer LJ, Laurent S, Lopez OL, Nyenhuis D, Petersen RC, Schneider JA, Tzourio C, Arnett

DK, Bennett DA, Chui HC, Higashida RT, Lindquist R, Nilsson PM, Roman GC, Sellke FW, Seshadri S, American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery, and Anesthesia, on behalf of the American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery, and Anesthesia (2011) Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* **42**, 2672-2713.

[18] Fischer CE, Qian W, Schweizer TA, Millikin CP, Ismail Z, Smith EE, Lix LM, Shelton P, Munoz DG (2015) Lewy bodies, vascular risk factors, and subcortical arteriosclerotic leukoencephalopathy, but not Alzheimer pathology, are associated with development of psychosis in Alzheimer's disease. *J Alzheimers Dis* **50**, 283-295.

[19] Palmqvist S, Sarwari A, Wattmo C, Bronge L, Zhang Y, Wahlund LO, Nagga K (2011) Association between subcorticial lesions and behavioural and psychological symptoms in patients with Alzheimer's disease. *Dement Geriatr Cogn Disord* **32**, 417–423.

[20] Hyman BT, Trojanowski JQ (1997) Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *J Neuropathol Exp Neurol* **56**, 1095-1097.

[21] Arvanitakis Z, Leurgans SE, Barnes LL, Bennett DA, Schneider JA (2011) Microinfarct pathology, dementia, and cognitive systems. *Stroke* **42**, 722-727.

[22] Hughes TM, Sink KM (2016) Hypertension and its role in cognitive function: Current evidence and challenges for the future. *Am J Hypertens* **29**, 149-157.

[23] White L, Small BJ, Petrovitch H, Ross GW, Masaki K, Abbott RD, Hardman J, Davis D, Nelson J, Markesbery W (2005) Recent clinical-pathologic research on the causes of dementia in late life: Update from the Honolulu-Asia Aging Study. *J Geriatr Psychiatry Neurol* **18**, 224-227.

[24] Iadecola C (2013) The pathobiology of vascular dementia. *Neuron* **80**, 844-866.

[25] Petrovitch H, Ross GW, Steinhorn SC, Abbott RD, Markesbery W, Davis D, Nelson J, Hardman J, Masaki K, Vogt MR, Launer L, White LR (2005) AD lesions and infarcts in demented and non-demented Japanese-American men. *Ann Neurol* **57**, 98-103.

[26] Scarmeas N, Brandt J, Albert M, Hadjigeorgiou G, Papadimitriou A, Dubois B, Sarazin M, Devanand D, Honig L, Marder K, Bell K, Wegesin D, Blacker D, Stern Y (2005) Delusions and hallucinations are associated with worse outcome in Alzheimer disease. *Arch Neurol* **62**, 1601-1608.

[27] Qiu C, Winblad B, Fratiglioni L (2005) The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurol* **4**, 487-499.

[28] Chui HC, Zheng L, Reed BR, Vinters HV, Mack WJ (2012) Vascular risk factors and Alzheimer's disease: Are these risk factors for plaques and tangles or for concomitant vascular pathology that increases the likelihood of dementia? An evidence-based review. *Alzheimers Res Ther* **4**, 1-36.

[29] Snowdon DA (1997) Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA* **277**, 813-817.

[30] Esiri MM, Nagy Z, Smith MZ, Smith AD, Barnetson L (1999) Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *Lancet* **354**, 919-920.

[31] Harrell LE, Duvall E, Folks DG, Duke L, Bartolucci A, Conboy T, Callaway R, Kerns D (1991) The relationship of high-intensity signals on magnetic resonance images to cognitive and psychiatric state in Alzheimer's disease. *Arch Neurol* **48**, 1136-1140.

[32] Lopez OL, Becker JT, Rezek D, Wess J, Boiler F, Reynolds CF, Panisset M (1992) Neuropsychiatric correlates of cerebral white-matter radiolucencies in probable Alzheimer's disease. *Arch Neurol* **49**, 828-834.

[33] Zanetti MV, Schaufelberger MS, de Castro CC, Menezes PR, Scazufca M, McGuire PK, Murray RM, Busatto GF (2008) White-matter hyperintensities in first-episode psychosis. *Br J Psychiatry* **193**, 25-30.

[34] Binetti G, Padovani A, Magni E, Bianchetti A, Scuratti A, Lenzi GL, Trabucchi M (1995) Delusions and dementia: Clinical and CT correlates. *Acta Neurol Scand* **91**, 271-275.

[35] Lee DY, Choo IH, Kim KW, Jhoo JH, Youn JC, Lee UY, Woo JI (2006) White matter changes associated with psychotic symptoms in Alzheimer's disease patients. *J Neuropsychiatry Clin Neurosci* **18**, 191-198.

[36] Chung EJ, Babulal GM, Monsell SE, Cairns NJ, Roe CM, Morris JC (2015) Clinical features of Alzheimer disease with and without Lewy bodies. *JAMA Neurol* **72**, 789-796.

[37] Hsiao JJ, Lu PH, Grill JD, Teng E (2015) Longitudinal declines in instrumental activities of daily living in stable and progressive mild cognitive impairment. *Dement Geriatr Cogn Disord* **39**, 12-24.