Vascular factors and risk for neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study

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ABSTRACT

Objective: To examine, in an exploratory analysis, the association between vascular conditions and the occurrence of neuropsychiatric symptoms (NPS) in a population-based sample of incident Alzheimer's disease (AD).

Methods: The sample consisted of 254 participants, identified through two waves of assessment. NPS were assessed using the Neuropsychiatric Inventory. Prior to the onset of AD, data regarding a history of stroke, hypertension, hyperlipidemia, heart attack or coronary artery bypass graft (CABG), and diabetes were recorded. Logistic regression procedures were used to examine the relationship of each vascular condition to individual neuropsychiatric symptoms. Covariates considered were age, gender, education, APOE genotype, dementia severity, and overall health status.

Results: One or more NPS were observed in 51% of participants. Depression was most common (25.8%), followed by apathy (18.6%), and irritability (17.7%). Least common were elation (0.8%), hallucinations (5.6%), and disinhibition (6.0%). Stroke prior to the onset of AD was associated with increased risk of delusions (OR = 4.76, p = 0.02), depression (OR = 3.87, p = 0.03), and apathy (OR = 4.48, p = 0.02). Hypertension was associated with increased risk of

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delusions (OR = 2.34, p = 0.02), anxiety (OR = 4.10, p = 0.002), and agitation/aggression (OR = 2.82, p = 0.01). No associations were observed between NPS and diabetes, hyperlipidemia, heart attack or CABG, or overall health.

Conclusions: Results suggest that a history of stroke and hypertension increase the risk of specific NPS in patients with AD. These conditions may disrupt neural circuitry in brain areas involved in NPS. Findings may provide an avenue for reduction in occurrence of NPS through the treatment or prevention of vascular risk conditions.

Key words: dementia, Alzheimer's disease, neuropsychiatric, disturbance, risk factors, vascular

Introduction

Neuropsychiatric symptoms (NPS) such as depression, anxiety, delusions and hallucinations commonly occur in Alzheimer's disease (AD), the most common form of dementia in late life. Evidence suggests that between 60% and 90% of individuals with AD experience at least one disturbance during the course of their illness (e.g. Brodaty *et al.*, 2001; Ikeda *et al.*, 2004; Steinberg *et al.*, 2006). They contribute to greater caregiver and patient distress (e.g. Danhauer *et al.*, 2004; Craig *et al.*, 2005), more costly interventions (e.g. Finkel, 2000; Beeri *et al.*, 2002), and accelerated cognitive and functional decline (e.g. Boyle *et al.*, 2003; Copeland *et al.*, 2003; Holtzer *et al.*, 2003). Given such high rates of occurrence and their serious impact, it is important to understand what contributes to the development of NPS.

Previous studies have identified a number of factors that increase the risk and modify the rate of NPS among individuals with AD. Increasing the risk for depression are older age, female gender (e.g. Gilley *et al.*, 2004), and less education (e.g. Harwood *et al.*, 2000). Increasing the risk for apathy is greater severity of cognitive and functional impairment (e.g. Starkstein *et al.*, 2001; Boyle *et al.*, 2003) and older age (e.g. Starkstein *et al.*, 2006). Higher risk of agitation and aggression in AD are also associated with increasing cognitive and functional impairment (e.g. Holtzer *et al.*, 2003; Copeland *et al.*, 2003), older age (e.g. Tsai *et al.*, 1996), and less education (e.g. Gabryelewicz *et al.*, 2002). Psychotic symptoms, such as delusions or hallucinations, have been associated with more severe cognitive and functional impairment (e.g. Harwood *et al.*, 2000; Paulsen *et al.*, 2000), female gender (e.g. Leroi *et al.*, 2003), and older age (e.g. Bassiony *et al.*, 2000). Some studies have reported that genetic factors, specifically the $\varepsilon4$ allele of the Apolipoprotein E (APOE), confer an increased risk for NPS in AD, including aggression, depression and psychosis (e.g. Craig *et al.*, 2004; van der Flier *et al.*, 2007). However, the majority of studies have reported no relationship between APOE genotype and neuropsychiatric disturbances (e.g. Hirono *et al.*, 1999; Levy *et al.*, 1999).

Little is known about the relationship between modifiable risk factors, such as medical and health-related condition and NPS in AD. Vascular conditions, such

as hypertension, hyperlipidemia and stroke, are of particular interest because they are common in the elderly and have been found to be risk factors for NPS among individuals *without* AD. Few studies have examined the association between vascular conditions and NPS among individuals with AD, but a limited number of studies suggests that cerebrovascular factors, such as white matter lesions, confer an increased risk for depression (O'Brien *et al.*, 2000) and apathy (Starkstein *et al.*, 1997). In support of the link between depression and cerebrovascular disease are studies reporting depressive symptoms to be 1.5 to 2.5 times more prevalent in vascular dementia (VaD) than AD (e.g. Ballard *et al.*, 2000; Lyketsos *et al.*, 2000; Alexopoulos, 2003). Poor overall health has also been associated with NPS in AD, including depression (Chan *et al.*, 2003), irritability, agitation, aggression, and disinhibition (Steinberg *et al.*, 2006).

Most studies examining vascular conditions as risk factors for NPS in AD have relied on clinic-based samples, an approach that limits generalizability. Furthermore, only a small number have controlled for dementia severity. This is an important factor to consider, as some disturbances vary in prevalence by stage of disease (e.g. Ferretti *et al.*, 2001; Lopez *et al.*, 2003). The purpose of the current investigation was to examine whether the presence of vascular conditions or risk factors prior to dementia onset predicts the development of NPS in a population-based sample of individuals with *incident* AD. This is among the first studies to examine the *vascular antecedents* of NPS among individuals with AD in a population. Previous investigations with the Cache County cohort have reported prevalence rates, clustering and risk factors for NPS in AD (Lyketsos *et al.*, 2000; 2001; Steinberg *et al.*, 2006). These studies utilized the *prevalence* dementia sample from the Cache County Study, and the present investigation is restricted to incident AD.

Methods

Participant screening

The Cache County Study on Memory, Health, and Aging (CCMS) is a longitudinal cohort study of AD and other dementias. Selection methods for participants in the CCMS have been reported in detail elsewhere (Breitner *et al.*, 1999; Lyketsos *et al.*, 2000; Miech *et al.*, 2002). Briefly, eligible members of the population, defined as all permanent residents of Cache County, Utah aged 65 or older on 1 January 1995, underwent a multistage screening and assessment protocol. Individuals with prevalent dementia were identified in the initial study wave (1995) and those with incident dementia were identified in two follow-up waves (1998–1999 and 2002–2004). The average duration between the first and second waves was 3.20 (SD = 0.21) years, while the average duration between the second and third waves was 4.33 (SD = 0.23). At each wave, participants were screened for dementia using a revision of the 100-point modified Mini-mental State Examination (3MS; Tschanz *et al.*, 2002). Further cognitive screening was conducted using the Informant Questionnaire for Cognitive Decline in the Elderly (IQCODE; Jorm and Jacomb, 1989) for individuals who were unable to

complete the 3MS or obtained a score below 60. In waves 1 and 2, individuals whose sensory- and education-adjusted screening scores fell below 87 (in wave 2, 84 for those over age 80; Breitner *et al.*, 1999; Miech *et al.*, 2002;) or IQCODE scores ≥ 3.27 were studied further using the Dementia Questionnaire (DQ; Silverman *et al.*, 1986). Based on the results of the DQ, participants with suspected dementia or a dementia prodrome, as well as a designated subsample of individuals, were selected for a comprehensive clinical assessment conducted by a registered nurse and psychometric technician in the presence of a reliable informant. The designated subsample consisted of 19% of the participants and was drawn without replacement from the entire cohort, stratified by age and sex, and enriched for APOE ε4 genotype (Khachaturian *et al.*, 2000; Hayden *et al.*, 2006). The procedures for wave 3 were similar to those of the first two waves, except that all participants with 3MS scores below 91, members of the designated subsample, and individuals over the age of 84 underwent a clinical assessment. Informants were available at the clinical assessment for all study participants in the present sample.

During the clinical assessment, the nurse administered an interview with the informant to ascertain medical, cognitive, and demographic history and a brief medical and neurological examination. The psychometric technician administered a neuropsychological test battery to the participant. All clinical assessment data were reviewed in initial diagnostic conferences by a geriatric psychiatrist, neuropsychologist, and the examining clinical team. Individuals with suspected dementia underwent follow-up laboratory testing and neuroimaging, in addition to an examination by a geriatric psychiatrist.

Assessment of dementia and dementia severity

Dementia diagnoses for CCMS participants were assigned after review of all available information at consensus conferences comprised of experienced clinicians in geropsychiatry, neurology and neuropsychology. Age at onset of incident dementia was estimated based on a review of a chronology of symptoms systematically obtained from the informant interview at the clinical assessment. The team of diagnosticians estimated onset age as the age at which the participant met DSM-IIIR criteria for dementia (American Psychiatric Association, 1987). The present investigation includes only individuals with possible or probable AD. Individuals with other dementias or mixed AD and VaD were excluded from these analyses. The diagnoses of possible or probable AD followed the criteria of the National Institute of Neurological and Communicative Disorders and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann *et al.*, 1984). There were 101 individuals diagnosed with AD at the first incidence wave, and 153 at the second. Dementia severity was assigned using the Clinical Dementia Rating Scale (CDR; Hughes *et al.*, 1982; Morris *et al.*, 1997), considering six domains of cognitive and functional performance: memory, orientation, judgment, community, hobbies, and personal care. For the purpose of this investigation, global CDR ratings (ranging from 0 to 5) were

grouped into three stages of severity: mild ($CDR \leq 1$), moderate ($CDR = 2$), and severe ($CDR \geq 3$).

Assessment of neuropsychiatric symptoms

At the clinical assessment visit, NPS were assessed using the Neuropsychiatric Inventory (NPI; Cummings *et al.*, 1994). The NPI is a structured informant interview conducted with the dementia participant's caregiver, which is used to rate the participant on each of 10 domains of NPS during the previous month: delusions, hallucinations, agitation/aggression, depression/dysphoria, apathy/indifference, elation/euphoria, anxiety, disinhibition, irritability/lability, and aberrant motor behavior. For each symptom endorsed, the interviewer follows up with a series of questions to rate the frequency and severity of the disturbance (Cummings *et al.*, 1994). For descriptive purposes, symptom severity was estimated by multiplying scores for frequency and severity within each NPI domain (e.g. Cummings *et al.*, 1994; Iverson *et al.*, 2002).

Assessment of vascular conditions, demographics and APOE genotype

Lifetime medical health data were obtained from participants in wave 1, and updated at each subsequent wave so that risk factor information was available antecedent to the age of dementia onset. Information about cerebrovascular disease and other vascular conditions was obtained through questions such as: *"Has a doctor or nurse told you that you had a stroke?"* For individuals who responded yes, follow-up questions regarding stroke severity and sequelae were then asked, including *"Did one side of your body or one arm or leg become weaker than the other?"* and *"Did you lose the ability to speak or understand what was said to you for more than one day?"* Cardiovascular conditions that preceded the onset of dementia were ascertained through direct questions for heart attack/CABG or chronic conditions such as diabetes, hypertension and hyperlipidemia (elevated serum cholesterol). History of each condition was coded as a binary variable and the number of each type of event (e.g. heart attack, stroke) was also recorded. The onset age of chronic vascular conditions and dates of acute events were also queried and updated at each wave, so that it could be determined whether the condition occurred antecedent to dementia. The mean (SD) number of years between the last update of vascular conditions and dementia diagnosis was 0.72 ($SD = 0.57$).

Using data regarding medical history, medications, blood pressure measurements and clinical exam obtained from the clinical assessment in each wave, an indication of each subject's overall health was rated in a consensus between the research nurse, neuropsychologist and geropsychiatrist using the General Medical Health Rating (GMHR; Lyketsos *et al.*, 1999). The GMHR is a measure of general medical comorbidity developed specifically for use with dementia patients, and results in a rating on an ordinal scale of 1 (poor), 2 (fair), 3 (good), and 4 (excellent). It has been used successfully in the Cache County Study to rate seriousness of comorbidity, and has been associated with greater cognitive and functional impairment in people with dementia (Lyketsos *et al.*,

2005). Buccal scrapings were collected from 4932 participants (97%) for APOE genotyping at the initial wave.

Analyses

In exploratory analyses, two-way associations in the form of χ^2 tests of independence and bivariate logistic regression procedures were examined between vascular conditions (independent variables) assessed prior to the onset of dementia and individual NPS (dependent variables) ascertained at the time of AD diagnosis. For those NPS found to be significantly associated with vascular risk factors in exploratory analyses, multivariate logistic regression models were used to examine the relationship of each vascular condition (stroke, hypertension, hyperlipidemia, heart attack or CABG, and diabetes) to the occurrence of the NPS, while adjusting for other vascular variables. Overall health, age, gender, education level, presence of the APOE $\varepsilon4$ allele, and dementia severity (CDR score) were selected as covariates based on previous literature suggesting their association with NPS. Dementia severity was coded as an ordinal variable with three levels: mild (CDR ≤ 1), moderate (CDR $= 2$), and severe (CDR ≥ 3). The regression models were developed in the following manner. For each vascular condition and NPS found to be significantly associated in the bivariate analyses, a logistic regression model that included the independent variable (e.g. stroke) and the outcome of interest (e.g. depression) was estimated. Age, gender, education level, APOE, and dementia severity were then sequentially entered, followed by other vascular risk factors (e.g. hypertension, hyperlipidemia) theoretically linked to cerebrovascular disease. Finally, GMHR was entered in order to control for overall health status. Each covariate was retained if its associated wald statistic was p ≤ 0.05. The final model was compared with the saturated model using the likelihood ratio test.

Results

Demographic characteristics for the sample are shown in Table 1. The sample was predominantly female (68.1% versus 31.9% male). The mean age was 85.68 (SD $= 6.62$), and participants ranged in age (68 to > 89) at the time of

Table 1. Summary of demographic characteristics

AGE		EDUCATION (YEARS)		GENDER				DEMENTIA SEVERITY (CDR)					
				FEMALE		MALE		MILD		MODERATE		SEVERE	
MEAN	SD	MEAN	SD	n	%	n	%	n	%	n	%	n	%
85.7	6.6	13.3	2.9	173	68.1	81	31.9	206	84.1	30	12.2	9	3.7

N = 254.

Table 2. Frequency and severity of neuropsychiatric symptoms (NPS)

NEUROPSYCHIATRIC SYMPTOMS	PRESENT		SEVERITY		
	n	%	MEAN	SD	RANGE* (MIN/MAX)
Delusions	43	17.3	3.05	2.42	1/12
Hallucinations	14	5.6	2.00	1.80	1/6
Agitation/aggression	26	10.5	2.88	2.09	1/9
Depression/dysphoria	64	25.8	3.53	3.03	1/12
Apathy/indifference	46	18.6	4.52	3.44	1/12
Anxiety	29	11.7	3.41	2.63	1/12
Disinhibition	15	6.0	3.00	2.93	1/12
Irritability/lability	44	17.7	3.55	2.81	1/12
Aberrant motor behavior	20	8.1	4.10	2.88	1/12

*Range of severity includes only subjects for whom the particular NPS was present.
Note that 4–7 cases were lacking information regarding presence/absence of NPS.

dementia diagnosis. Specifically, 20.5% were under the age of 80, 49.2% were between 80 and 89, and 30.3% were over the age of 89. The mean educational attainment for the total sample was 13.27 (SD = 2.92) years and ranged from three years of formal education to doctoral level study, with over half (52.0%) having completed high school. The majority of participants (84.1%) were in the mild stage, 12.2% in the moderate stage, and 3.7% in the severe stage of dementia severity on the CDR. Mean duration of dementia at the time of assessment was 1.94 (SD = 1.31) years and ranged from less than one year to eight years.

Table 2 shows the frequency and severity of behavioral disturbances observed. Over half (51.0%) of participants exhibited at least one NPS, the most common being depression (25.8%). Apathy (18.6%), irritability (17.7%), and delusions (17.3%) were also common. Elation was the least common, reported in fewer than 1% of participants; for this reason it was and excluded from later analyses. Also depicted in Table 2 are mean severity ratings. Severity of NPS was generally mild, with scores on the 12-point NPI domain scales ranging from 2.00 for hallucinations to 4.52 for apathy.

Among vascular conditions, hypertension was most common, present in 31.3%. A history of hyperlipidemia was reported by 13% of participants, while 12.7% reported a history of either heart attack or CABG. Stroke and diabetes were uncommon, with only 10.2% of participants reporting diabetes and 4.5% reporting a history of stroke. With respect to overall health status, 56.9% of individuals were rated in fair to poor health and 43.1% in good to excellent health.

Significant associations between several vascular variables and individual behavioral disturbances were revealed in χ^2 tests. Stroke was associated with delusions ($\chi^2 = 6.29$, df = 1, p = 0.01), depression ($\chi^2 = 5.01$, df = 1, p = 0.03), and apathy ($\chi^2 = 5.94$, df = 1, p = 0.02). Hypertension was associated with delusions ($\chi^2 = 7.66$, df = 1, p = 0.006), agitation/aggression ($\chi^2 = 6.45$, df = 1,

Table 3. Relationship of vascular risk factors to neuropsychiatric symptoms (NPS) in participants with AD

NEUROPSYCHIATRIC SYMPTOM	NPS PRESENT/ ABSENT	BEST FITTING MODEL	χ^2	df	p	OR	95% CI FOR OR	
							LOWER	UPPER
Apathy	46/201	Stroke	5.53	1	0.02	4.48	1.28	15.61
		Age*	5.42	1	0.02	.94	.89	.99
Depression	64/184	Stroke	4.64	1	0.03	3.87	1.13	13.23
		Age*	4.00	1	0.05	.96	.92	1.00
Agitation/aggression	26/222	Hypertension	6.06	1	0.01	2.82	1.24	6.45
Anxiety	29/219	Hypertension	9.63	1	0.002	4.10	1.68	10.00
		Age*	7.36	1	0.007	.91	.86	.98
		Dementia severity+	6.75	1	0.009	2.50	1.25	5.01
Delusions	43/205	Hypertension	5.60	1	0.02	2.34	1.16	4.75
		Stroke	5.75	1	0.02	4.76	1.33	17.01
		Dementia severity+	6.72	1	0.01	2.21	1.21	4.02

Absent from the table are the other NPS for which vascular factors showed no significant associations.
*Odds ratios (OR) represent change in odds per one-year increase in age.
+Odds ratios represent change in odds per unit change in dementia severity (mild, moderate, severe).

Table 4. Odds ratios and 95% confidence intervals for non-significant relationships between vascular conditions and NPS

	CHOLESTEROL	DIABETES	HEART ATTACK/ CABG	HYPERTENSION	STROKE
Delusions	1.48 (0.59, 3.72)	1.21 (0.43, 3.43)	0.66 (0.22, 2.01)	*N/A*	*N/A*
Hallucinations	2.35 (0.60, 9.21)	*	1.24 (0.26, 5.86)	1.36 (0.43, 4.29)	*
Agitation/aggression	2.01 (0.69, 5.90)	0.70 (0.15, 3.14)	1.25 (0.40, 3.91)	*N/A*	0.85 (0.10, 6.90)
Depression	1.35 (0.58, 3.14)	0.70 (0.25, 1.95)	1.43 (0.63, 3.23)	0.92 (0.49, 1.72)	*N/A*
Apathy	1.58 (0.63, 4.00)	0.86 (0.28, 2.65)	2.09 (0.88, 4.91)	1.03 (0.51, 2.08)	*N/A*
Anxiety	1.18 (0.38, 3.68)	0.64 (0.14, 2.85)	0.22 (0.03, 1.71)	*N/A*	1.73 (0.36, 8.42)
Disinhibition	3.83 (0.75, 19.56)	1.36 (0.29, 6.40)	0.50 (0.06, 3.96)	2.61 (0.91, 7.47)	3.83 (0.75, 19.56)
Irritability	1.90 (0.78, 4.64)	0.36 (0.08, 1.59)	1.67 (0.69, 4.01)	1.04 (0.51, 2.10)	1.79 (0.46, 7.05)
Aberrant motor behavior	1.89 (0.58, 6.12)	0.96 (0.21, 4.39)	0.73 (0.16, 3.30)	0.91 (0.33, 2.46)	*

*Cell counts were too low to conduct logistic regression analyses. Results of Fisher's Exact Tests for these relationships yielded p > 0.05.
CABG = coronary artery bypass graft.

p = 0.01), and anxiety ($\chi^2 = 12.09$, df = 1, p = 0.001). The remaining vascular conditions (diabetes, hyperlipidemia, and heart attack or CABG) were not significantly associated with any NPS. Overall health rating was not significantly associated with any of the behavioral disturbances.

In the logistic models, adjusting for other vascular variables, overall health, dementia severity and demographic covariates (age, gender, education and APOE), these associations remained significant. Stroke was associated with a higher risk of apathy (OR = 4.48, CI(95) = 1.28, 15.61, p = 0.02), delusions (OR = 4.76, CI(95) = 1.33, 17.01, p = 0.02) and depression (OR = 3.87, CI(95) = 1.13, 13.23, p = 0.03). Hypertension was associated with greater odds of delusions (OR = 2.34, CI(95) = 1.16, 4.75, p = 0.02), agitation/aggression (OR = 2.82, CI(95) = 1.24, 6.45, p = 0.01), and anxiety (OR = 4.10, CI(95) = 1.58, 10.00, p = 0.002).

Other factors associated with increased risk of NPS were age and dementia severity. Younger age was associated with an increase of 4–9% in risk for anxiety, apathy and depression. More severe dementia was associated with delusions (OR = 2.21, CI(95) = 1.21, 4.02, p = 0.01), anxiety (OR = 2.50, CI(95) = 1.25, 5.01, p = 0.008) and disinhibition (OR = 3.44, CI(95) = 1.56, 7.57, p = 0.002). Note, however, that the latter are based on a small number of cases, as the majority of subjects were in the mild stage of dementia severity. Additionally, men were significantly more likely than women to experience disinhibition (OR = 2.79, CI(95) = 1.29, 13.66, p = 0.02). Table 3 displays the results of the final regression models for the above relationships. Each behavioral disturbance was more likely to occur in the presence of the vascular condition. Presence of APOE ε4 allele and education was not associated with any neuropsychiatric symptom. Results of the bivariate regression analyses for relationships that were not significant are depicted in Table 4. Note that due to small cell counts, logistic regression procedures could not be performed in such cases, and Fisher's Exact tests were conducted.

Discussion

In this population-based study of AD, we found evidence to suggest that a history of stroke was associated with a three- to four-fold increased risk of apathy, depression and delusions, while hypertension was associated with a two- to three-fold increased risk of anxiety, agitation/aggression and delusions. Diabetes, hyperlipidemia, heart attack or CABG, and overall health rating were not significantly associated with any NPS. The odds of anxiety, depression and apathy decreased with age, and odds of delusions were greater with increasing dementia severity.

The association of stroke with apathy is consistent with the results of previous studies (e.g. Okada *et al.*, 1997; Starkstein *et al.*, 1997; Angelelli *et al.*, 2004) and may reflect stroke-related damage to areas of the prefrontal cortex or related neural pathways, involved in the planning and execution of goal-directed behavior. This conclusion is supported by previous associations between apathy and dysfunction in prefrontal and anterior temporal brain regions (Okada *et al.*,

1997; Craig *et al.*, 1996). Cerebrovascular disease has previously been linked to depression in several studies of individuals with dementia (e.g. O'Brien *et al.*, 2000; Hargrave *et al.*, 2000). Studies reporting depressive symptoms to be 1.5 to 2.5 times more prevalent in VaD than AD (e.g. Ballard *et al.*, 2000; Lyketsos *et al.*, 2000; Alexopoulos, 2003) also suggest a vascular role in the development of depression.

Few studies have examined the relationship between stroke or hypertension and psychotic symptoms in dementia. One might speculate that vascular conditions lead to dysfunction in brain regions involved in psychotic symptoms. Hypertension is a known risk factor for stroke, which may result in lesions or affect the neural circuitry in the temporal lobe, thought to be involved in the production of delusions (Geroldi *et al.*, 2000; Lopez *et al.*, 2001). Alternatively, psychotic symptoms may occur as a side effect of antihypertensive medications (e.g. Ahmad, 1996). Bassiony *et al.* (2000) reported that delusions and hallucinations in AD were associated with the use of antihypertensive medications. It is possible that the side effects of antihypertensive medications become more salient in these patients due to reduced neural reserves associated with dementia. However, in the Cache County population, there was no relationship between antihypertensive use and psychotic symptoms (data not shown).

The observed relationship between hypertension and anxiety is consistent with previous research among individuals *without* dementia (e.g. McLaughlin *et al.*, 2003; Mehta *et al.*, 2003). The association between hypertension and agitation/aggression has not been studied previously, however. It may be that agitation is simply an expression of anxiety in persons with dementia.

Overall health was not associated with any NPS, in contrast to previous studies supporting a relationship between poor general health and various NPS (Chan *et al.*, 2003; Tran *et al.*, 2006). However, these studies did not differentiate between dementia subtypes, and dementias due to vascular pathology generally carry greater medical burden than AD. Our sample of *incident AD cases* exhibited low levels of medical comorbidity, with fewer than 40% reporting more than one physical illness. The finding that physical health is associated with depression in VaD but not in AD (Ballard *et al.*, 1996) supports this conclusion. A previous study of *prevalent* dementia from this population (Steinberg *et al.*, 2006) found worse general health to be associated with agitation, irritability, disinhibition and aberrant motor behavior. In contrast to the present focus on incident AD cases, differences in results may reflect the inclusion of other forms of dementia as well as greater disease severity and longer dementia duration associated with prevalent samples in the previous study.

Various limitations merit discussion. First, in order to capture risk factors antecedent to dementia onset, the vascular conditions and risk factor information of some participants were based on reports from up to two years before the dementia diagnosis. Specifically, the presence of a risk factor was only taken into account if it was present at the interview session prior to the assessment at which dementia was diagnosed. Although this interval was under two years for all but four participants (98%), this conservative approach may have led to the omission

of some emergent conditions and biased the results toward the null. Second, the statistical analyses involved multiple comparisons, raising the possibility of Type I error rates. As this study was exploratory in nature, the findings require replication in other populations. Third, given that this study was cross-sectional with retrospective examination of vascular risk factors, we did not examine losses to follow-up. Our results are conditioned upon people with dementia who lived and were therefore able to participate in the study. Since dementia was only ascertained every three years, it is possible that individuals with a more virulent form of dementia who died prior to being assessed for NPS may be missing from the analyses. Fourth, each NPS was examined in terms of its presence or absence; severity or intensity of individual symptoms was not considered. Thus a "dose response" relationship could not be established. However, since most NPI disturbances in this sample were in the mild range, an examination of the relationship of vascular conditions to the severity of NPS was not possible. Fifth, there was a certain degree of overlap among NPS, with approximately 30% of individuals suffering from two or more NPS. A previous study with this population underscored the presence of clusters of NPS or syndromes (Lyketsos *et al.*, 2001), providing a compelling argument for the need to study psychiatric symptoms in the context of other disturbances. Future research should therefore consider how vascular conditions are related to neuropsychiatric syndromes as opposed to individual disturbances. Finally, some caution should be taken when attempting to generalize the results to other populations, particularly those with different ethnic backgrounds and different prevalence of vascular risk factors.

Despite these limitations, this study has several advantages, including the population-based sample, which limits concerns about referral bias, the thorough assessment and diagnosis of dementia, high participation rates among participants and informants, and the availability of data on vascular risk factors and conditions that preceded the onset of dementia.

In sum, several vascular conditions appear to confer an increased risk for NPS in AD. Knowledge gained from this investigation may assist clinicians in preparing patients and caregivers for the occurrence of psychiatric symptoms in the presence of multiple vascular conditions and in minimizing associated health risks.

Conflict of interest

None.

Description of authors' roles

K. Treiber and J. Tschanz were responsible for formulating research questions, designing the study, conducting data analyses, and drafting and revising the article. C. Corcoran assisted with study design and provided expertise in statistical analyses. C. Lyketsos, M. Norton, and P. Rabins provided input in formulating research questions and study design, and critically reviewed

the article for intellectual content. D. Stein assisted with study design and offered critical input. M. Steinberg, R. Green, K. Welsh-Bohmer, and J. Breitner were involved in the study design and in identifying cases of dementia. Neuropsychological testing and clinical assessment procedures were developed by Drs. Welsh-Bohmer and Breitner. Dr. Tschanz provided training and oversight of all field staff and reviewed all individual neuropsychological test results to render professional diagnoses.

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