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# Frequency of Subclinical Heart Disease in Elderly Persons with Dementia

**Christiane Reitz, MD PhD**[*,1], **Adam M. Brickman, PhD**[*,2], **José A. Luchsinger, MD, MPH**[1,2,3], **William E. Wu**[2], **Scott A. Small, MD**[1,2,4], **Ming-Xin Tang, PhD**[1,6], and **Richard Mayeux, MD, MSc**[1,2,4,5,7]

1*The Gertrude H. Sergievsky Center (Reitz, Luchsinger, Small, Tang, Mayeux) Columbia University College of Physicians and Surgeons, New York, NY, USA*

2*The Taub Institute for Research on Alzheimer's Disease and the Aging Brain (Brickman, Wu, Small, Luchsinger, Mayeux) Columbia University College of Physicians and Surgeons, New York, NY, USA*

3*The Department of Medicine (Luchsinger) Columbia University College of Physicians and Surgeons, New York, NY, USA*

4*The Department of Neurology (Small and Mayeux) Columbia University College of Physicians and Surgeons, New York, NY, USA*

5*The Department of Psychiatry (Mayeux) Columbia University College of Physicians and Surgeons, New York, NY, USA*

6*The Department of Biostatistics in the Mailman School of Public Health (Tang) Columbia University College of Physicians and Surgeons, New York, NY, USA*

7*The Department of Epidemiology in the Mailman School of Public Health (Mayeux) Columbia University College of Physicians and Surgeons, New York, NY, USA*

## Abstract

We compared the frequency of structural and functional heart abnormalities, assessed using transthoracic echocardiography, among persons with Alzheimer's disease (AD), vascular dementia (VaD), stroke and healthy control subjects. Compared with controls, patients with AD were more likely to have aortic valve thickening, aortic valve regurgitation, left ventricular wall motion abnormalities, left ventricular hypertrophy and a reduced ejection fraction. Persons with VaD were more likely to have aortic valve regurgitation, but mitral valve thickening and triscuspid valve regurgitation were also more frequent. In the absence of dementia, persons with stroke differed from controls by more frequent mitral valve calcifications. With the increasing prevalence of AD and VaD, clinicians have to be more attentive to the presence of structural heart disease and its complications in persons with these conditions.

**Correspondence** Richard Mayeux at the Gertrude H. Sergievsky Center, 630 West 168th Street, Columbia University, New York, NY 10032. Phone: 212-305-3192, Fax: 212-305-2518, email: E-mail: rpm2@columbia.edu.
*authors contributed equally to this work

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### Keywords

Heart disease; echocardiography; dementia; Alzheimer's disease; vascular dementia

## INTRODUCTION

The prevalence of dementia is increasing in elderly populations and is expected to quadruple by the year 2047.[1] The most common form of dementia is Alzheimer's disease (AD), representing about 70% of cases, followed by vascular dementia.[2]

There is growing evidence that heart disease and its antecedents are associated with an increased risk of subsequent dementia, including AD and dementia related to cerebrovascular disease (VaD). Different studies reported associations between atrial fibrillation or lower systolic left ventricular function with cognitive impairment or dementia,[3,4] and there is evidence that middle or end-stage heart failure and cardiac transplantation are associated with subsequent worsening in cognitive performance.[3] Several cardiovascular risk factors and systemic atherosclerosis, which in turn are associated with cardiac disease, are related to a higher risk of cognitive impairment and dementia.[5,6] We previously observed associations between diabetes mellitus,[7] hyperinsulinemia,[8] smoking,[9,10] and stroke[11,12] with AD or cognitive decline.

The evidence relating cardiac disease with dementia has been mostly derived from epidemiological or clinical studies aiming to assess the effect of heart disease or vascular risk factors on the risk of subsequent dementia or AD. Whether persons with AD are, from a clinical point of view, more likely to suffer from subclinical structural or functional heart disease than persons without dementia remains unclear, may have an important public health impact, and needs to be answered. In this study, we compared the frequencies of subclinical measures of structural and functional heart disease, assessed by echocardiography, among persons with AD, VaD, stroke without dementia, and elderly without dementia or stroke of the same age. We also compared the prevalence of cardiac disease among persons with and without dementia.

## METHODS

### Subjects and Setting

Participants were part of a longitudinal study of Medicare recipients 65 years or older residing in northern Manhattan (Washington Heights, Hamilton Heights, Inwood) that has been described elsewhere.[13] Each person underwent an in-person interview of general health and function at the time of study entry followed by a standard assessment, including medical history, physical and neurological examination, and a neuropsychological battery.[14] Baseline data were collected from 1992 through 1994. Follow-up data were collected during evaluations at sequential intervals of approximately 18 months, performed from 1994 to 1996, 1996 to 1997, and 1997 to 1999. This study was approved by the institutional review board of the Columbia University Medical Center.

For this study we recruited in a random fashion participants who underwent clinical assessment at baseline to form four groups: probable AD, vascular dementia, stroke without dementia, and persons without dementia or stroke to conduct a cross-sectional study of subclinical cardiac disease. The final sample undergoing echocardiography comprised 75 persons. From the original 160 individuals approached, those who did not participate in the study were more often demented (61.3 vs. 36.0%), slightly older (78.2 vs. 75.9 years), less educated (6.9 vs. 8.7 years) and more likely to have diabetes (45.2 vs. 9.3%), heart disease (28.3 vs. 21.4%) and hypertension (61.2 vs. 53.4%) than persons who completed the study.

### Diagnosis of Dementia

Diagnoses of dementia had been previously established from information gathered from the initial and follow-up assessments and medical records. None of the data collected for the present study were used for diagnosis. The diagnosis of dementia was based on standard research criteria and required evidence of cognitive decline, including memory impairment on the neuropsychological test battery as well as evidence of impairment in social or occupational function (Clinical Dementia Rating[15]> 0.5).

A diagnosis of VaD was considered for individuals with dementia combined with a history or clinical evidence of stroke[16] and was classified as follows: (1) stroke related dementia (i.e., new onset of dementia within 3 months of a stroke), (2) dementia due to focal effects of a stroke (i.e., dementia resulting from stroke(s) in strategic area(s) whose singular or additive effects accounted for the cognitive impairment), and (3) possible AD with concomitant stroke (i.e., progressive dementia associated with a clinical history of stroke in which the temporal relationship could not be established).

The diagnosis of AD was based on the National Institute of Neurological and Cognitive Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.[17] For this study only patients with *probable* AD were recruited to represent this diagnosis.

### Diagnosis of Stroke

Stroke was defined according to the WHO criteria.[18] We ascertained a history of stroke from an interview with the participants and their informants. Persons with stroke were confirmed through a review of their medical records, 85% of which included results of brain imaging. The remainder were confirmed by direct examination.

### Other covariates

A history of either diabetes mellitus or hypertension was based on self report. Body mass index (BMI) was calculated by the formula BMI = weight (Kg)/height $(m)^2$. APOE genotypes were determined as described by Hixson and Vernier with slight modification.[19] We classified persons as homozygeous or heterozygeous for the APOE ε4 allele or not having any ε4 allele.

### Noninvasive Cardiac Imaging

Two-dimensional and color-flow Doppler transthoracic echocardiography (ECHO) were performed using Hewlett-Packard Sonos 2500 equipment (Andover, Mass.), with a 2.5 Mhz transducer. We imaged the heart in all standard views from parasternal and apical windows by trained technicians, with image interpretation performed by board-certified cardiologists experienced in cardiac imaging and blinded to all clinical information on the participants. Assessment of ECHO-defined structural or functional heart abnormalities included: valvular vegetations; prosthetic valves; valve regurgitation; left ventricular regional wall abnormalities (LVWMA), resulting in hypokinetic or akinetic segments; left ventricular aneurysm; reduced left ventricular ejection fraction (LVEF); left ventricular hypertrophy (LVH), abnormal left ventricular wall or septum thickness; impaired function of the right ventricle (RV), abnormal RV pressure; abnormal RV size; and abnormal TR jet velocity.

### Statistical Methods

We compared the demographics and other potentially relevant factors among individuals with VaD, AD, stroke without dementia and control subjects without dementia and stroke. We used chi square tests for categorical data and analysis of variance for continuous variables. We then used regression analyses to estimate the association of dementia (AD or VaD) or stroke with the individual echocardiographic outcome measures. In these analyses, valvular vegetations,

prosthetic valves, valve regurgitation, LVWMA, impairment of LVEF, LVH, impaired RV function, abnormal RV pressure and abnormal RV size were used as dichotomized variable (no/any). LA size, LVED, LV posterior wall thickness, LV septum thickness, RV pressure and TR jet velocity were used as continuous variables. After performing crude models, we repeated the analyses adjusting the models for age and sex.

## RESULTS

The mean age was 75.9 ± 6.9 years, and 60.0% were women, 29.3% Hispanic, 22.7% non-Hispanic White and 48.0% non-Hispanic Black. The mean years of education were 8.8 ± 5.2, and 12.0% were homo- or heterozygeous for the APOE-ε4 allele. Compared with controls without dementia and stroke, persons with AD or VaD were older and less educated (Table 1).

Overall, 12% of the participants had a moderately or severely impaired ejection fraction (EF), 64% left ventricular hypertrophy (LVH), and 5% signs of left ventricular dilatation (LVD). Patients with AD were more likely to have aortic valve thickening (AVT), aortic valve regurgitation (AVR), left ventricular wall motion abnormalities (LVWMA), left ventricular hypertrophy (LVH), and a reduced EF compared with controls (Table 2). Persons with VaD were more likely to have AVR than controls, but mitral valve thickening (MVT) and triscuspid valve regurgitation (TVR) were also more frequent. These differences remained stable in multivariate regression analyses adjusting for age and sex, but were slightly attenuated in models additionally controlling for education, ethnicity, APOEε4 allele and potential vascular risk factors (Table 3).

## DISCUSSION

The existence of a link between cardiovascular disease and dementia has been suggested because both diseases share common risk factors[20] including markers of inflammation[21,22] and genetic risk factors.[23] The clinical relevance of this biologic link would reside in the demonstration of an excess burden of clinical cardiovascular disease among subjects with dementia. In the present study, compared to elderly controls, patients with AD had a higher frequency of aortic valve regurgitation and left ventricular hypertrophy, and they showed a trend to reduced ejection fraction and left ventricular wall motion abnormalities. VaD was associated with a trend towards an increased frequency of aortic valve regurgitation and mitral valve thickening. Non-demented patients with stroke had more mitral annular calcifications than controls. Thus, persons with AD were more likely to have structural and functional heart abnormalities compared to controls of similar age and gender, and these abnormalities were similar to those of individuals with stroke or VaD.

The mechanisms through which subclinical cardiac disease may be linked to impaired cognitive function in the absence of manifest cerebrovascular disease remain unclear. The relation between left ventricular dysfunction, left ventricular hypertrophy, impaired ejection fraction or atrial fibrillation and manifest stroke is well established,[24] and it is reasonable to postulate that cardiac disease exerts its effect on the risk of dementia through effects on the cerebral vessels. Left ventricular dysfunction and atrial fibrillation have also been associated with silent lacunar infarcts,[25,26] and they may be a more common cause of silent cerebrovascular lesions than previously assumed. Myocardial dysfunction may also cause periodic disability in maintaining cerebral blood flow, leading to subsequent impairment of cognitive function.[27] There is also evidence for reverse causation. APOEε4, a major risk factor for both sporadic and late-onset Alzheimer's disease as well as dementia with stroke, is also associated with the risk of left ventricular dysfunction,[28] and there are indications that the APOEε4 allele is associated with an increased risk of (a)symptomatic left ventricular dysfunction in patients

with Alzheimer's disease.[29] Thus, persons with AD who have a higher frequency of the APOEε4 genotype may be more vulnerable to subsequent cardiac disease.

Alternative explanations for our findings have to be addressed. One is that heart disease is more prevalent in VaD, and that our results are explained by misclassification of AD as VaD. We addressed this issue by including only persons with *probable* AD in the AD group, making misclassification less likely. Another potential explanation is chance. However, given the statistical robustness of our findings, it is unlikely that they were spurious or due to Type I statistical error. Rather, the results are in line with the *a priori* hypothesis of a higher burden of cardiac disease among persons with dementia. The results were not unexpected and were consistent with previous studies,[3,4,29] limiting the possibility of a chance association.

Our results may have been biased as more than half of the participants originally recruited were excluded from the study because of incomplete echocardiographic assessments. These were more often persons with AD, VaD or stroke than controls. However, it seems unlikely that the association between heart disease and dementia among these persons would change our observation. Because our analyses were cross-sectional, there is a potential for survival effects. If coexisting heart disease and dementia reduce survival, the combination of these disorders would be observed less, and the association would be underestimated. The number of persons with AD and VaD was small. This could have led to a lack of power to detect small effect sizes. Another limitation of our study is that it lacked information on clinical correlates of the subclinical abnormalities that were found.

Our study has important strengths. It is a population-based study nested in a prospective cohort study designed for the diagnosis of cognitive impairment and dementia with standard criteria. Assessment of subclinical structural and functional heart disease was performed using standardized echocardiography.

From a clinical standpoint, our findings suggest that persons with AD, the most common form of dementia, are more likely to have structural and functional heart abnormalities compared to controls of similar age and gender, and that these abnormalities are similar to those of individuals with stroke or VaD. With the increasing prevalence of AD and VaD, clinicians have to be more attentive to the presence of structural heart disease and its complications in persons with AD. Persons with dementia tend to be undertreated for their medical problems. This in turn can lead to progressive heart disease, hospitalizations, and increased health care costs. Standard of care, as for example in the case of systolic dysfunction ACE inhibitors or beta blockers, could reduce this risk.

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**Table 1**

Comparison of Characteristics among Study Groups

| | Vascular dementia (n=9) | Alzheimer's disease (n=18) | Stroke without dementia (n=16)† | Control subjects (n=32) |
|---|---|---|---|---|
| Women | 7 (77.8) | 9 (50.0) | 9 (56.3) | 20 (66.7) |
| Education in years, mean (SD) | 7.6 (5.6) | 4.3 (3.2)* | 10.8 (4.6) | 11.2 (4.6) |
| Age in years, mean (SD) | 77.6 (7.4) | 78.2 (7.1) | 73.8 (5.1) | 75.3 (7.4) |
| Body mass index in $kg/m^2$ | 26.5 (5.3) | 28.3 (4.9) | 29.2 (6.9) | 28.8 (5.4) |
| Ethnic group‡ | | | | |
| White/Non-Hispanic | -- | 2 (11.1) | 5 (31.3) | 6 (20.0) |
| Black/Non-Hispanic | 4 (44.4) | 9 (50.0) | 7 (43.8) | 16 (53.3) |
| Hispanic | 5 (55.5) | 6 (33.3) | 4 (25.0) | 7 (23.3) |
| other | -- | 1 (5.6) | -- | 1 (3.3) |
| Hypertension | 7 (77.8) | 12 (66.7) | 7 (43.8) | 14 (46.9) |
| Diabetes | -- | 3 (6.3) | 1 (6.3) | 3 (10.0) |
| Heart disease | 2 (22.2) | 5 (27.8) | 6 (37.5) | 3 (10.0) |
| Current or Past Smoking | 4 (44.4) | 9 (50.0) | 11 (68.8) | 14 (43.8) |
| Total Cholesterol, mean (SD) | 199.78 (30.2) | 178.4 (16.8) | 211.25 (43.2) | 194.52 (34.9) |

Values are expressed as number (percentage) unless otherwise indicated. Some percentages are based on an incomplete sample due to small amounts of missing data

*Significant at a 0.05 level versus control group, based on analysis of variance for continuous data and $\chi^2$ test for categorical data.

†defined according to World Health Organization Criteria.[18]

‡Classified by self-report using the format of the 1990 US census.[30]

**Table 2**

Comparison of Echocardiographic Characteristics among Dementia Group

| | Vascular dementia (n=9) | Alzheimer's disease (n=18) | Stroke without dementia (n=16)† | Control subjects (n=32) |
|---|---|---|---|---|
| **Aortic Valve** | | | | |
| Thickening | 6 (66.7) | 14 (77.8)* | 13 (81.3) | 19 (59.4) |
| Regurgitation | 6 (66.7)* | 12 (66.7)* | 9 (56.3) | 10 (31.3) |
| **Mitral Valve** | | | | |
| Thickening | 6 (66.7)* | 9 (50.0) | 7 (43.8) | 11 (34.4) |
| Regurgitation | 8 (88.9) | 13 (72.2) | 14 (87.5) | 28 (87.5) |
| Mitral Annular Calcifications | 5 (55.6) | 6 (33.3) | 9 (56.3) | 10 (31.3) |
| **Tricuspid Valve** | | | | |
| Thickening | 1 (11.1) | 3 (16.7) | 4 (25.0) | 5 (15.6) |
| Regurgitation | 9 (100.0)* | 15 (83.3) | 13 (81.3) | 22 (68.8) |
| **Pulmonal Valve** | | | | |
| Thickening | -- | -- | 1 (6.3) | -- |
| Regurgitation | 5 (55.6) | 9 (50.0) | 9 (56.3) | 21 (65.6) |
| **Left Heart** | | | | |
| LA Size (mm) | 36.2 (5.8) | 38.7 (6.5) | 35.6 (10.9) | 36.9 (4.2) |
| LV Dilatation | -- | 1 (5.9) | 2 (13.3) | 1 (3.1) |
| LVED (mm) | 42.9 (5.9) | 44.4 (7.1) | 41.3 (6.8) | 43.2 (5.1) |
| reduced LVEF†† | 1 (11.1) | 4 (23.5)* | 2 (12.5) | 2 (6.3) |
| Wall motion abnormalities | 1 (11.1) | 5 (29.4)* | 3 (18.8) | 2 (6.3) |
| LV Hypertrophy | 5 (62.5) | 15 (83.3)* | 12 (80.0) | 16 (50.0) |
| LV posterior wall thickness (mm) | 11.0 (1.5) | 13.0 (2.0) | 12.3 (1.4) | 12.0 (2.3) |
| LV septum thickness (mm) | 11.4 (2.5) | 13.0 (1.6) | 12.1 (4.0) | 12.0 (2.2) |
| Apex (%) | 8.1 (3.7) | 8.8 (2.8) | 8.2 (3.7) | 8.8 (3.3) |
| **Right Heart** | | | | |
| Increased RA size | 1 (11.1) | 3 (16.7) | 1 (6.3) | 1 (3.1) |
| Increased RV size | -- | -- | 1 (6.3) | 1 (3.1) |
| Impaired RV function | -- | -- | 1 (6.3) | 1 (3.1) |
| TR jet velocity (m/sec) | 2.3 (0.7) | 2.7 (0.5) | 2.9 (0.6) | 2.6 (0.6) |
| RV pressure (mmHg) | 34.0 (14.1) | 40.1 (10.3) | 44.9 (17.9) | 38.6 (13.5) |

Values are expressed as number (percentage) unless otherwise indicated.

*Significant at a 0.05 level versus control group, based on analysis of variance for continuous data and $\chi^2$ test for categorical data.

†defined according to World Health Organization Criteria.[18]

††categorized as none, mild, moderate or severe reduced ejection fraction

**Table 3**

OR and 95 % Confidence Intervals relating the Dementia Diagnosis to the Presence of Heart Abnormalities, adjusted for Age, Gender, Education, Ethnicity, APOE and Potential Vascular Risk Factors, using Controls without Dementia or Stroke as the Reference. There is One Model per Heart Abnormality.

| | Vascular dementia (n=9) | Alzheimer's disease (n=18) | Stroke without dementia (n=16)† |
|---|---|---|---|
| **Aortic Valve** | | | |
| Thickening | 0.8 (0.12-5.61) | 1.4 (0.29-7.14) | 1.3 (0.35-4.57) |
| Regurgitation | 4.2 (0.74-13.29) | 3.3 (1.01-11.88)* | 1.3 (0.31-4.36) |
| **Mitral Valve** | | | |
| Thickening | 4.4 (0.96-18.23) | 3.0 (0.71-12.58) | 0.9 (0.28-3.35) |
| Regurgitation | 0.6 (0.03-10.31) | 0.5 (0.08-3.32) | 1.2 (0.19-6.87) |
| Mitral Annular Calcifications | 2.7 (0.44-16.06) | 1.3 (0.29-5.44) | 3.5 (1.01-9.83)* |
| **Tricuspid Valve** | | | |
| Thickening | 0.5 (0.02-9.06) | 1.3 (0.18-8.51) | 0.9 (0.19-3.99) |
| Regurgitation | -- | 1.4 (0.27-6.78) | 1.4 (0.29-6.56) |
| **Pulmonal Valve** | | | |
| Regurgitation | 1.1 (0.19-6.43) | 0.7 (0.17-2.68) | 0.4 (0.11-1.36) |
| **Left Heart** | | | |
| LV Dilatation | -- | 1.3 (0.06-19.98) | 2.6 (0.31-21.42) |
| reduced LVEF | 3.1 (0.34-39.42) | 4.1 (0.44-9.86) | 4.9 (0.52-33.32) |
| Wall motion abnormalities | 3.3 (0.26-28.57) | 3.6 (0.98-20.35) | 4.6 (0.83-32.42) |
| LV Hypertrophy | 1.3 (0.20-8.11) | 4.5 (1.02-1.99)* | 2.2 (0.56-8.54) |

-- numbers too small for analysis

† defined according to World Health Organization Criteria.[18]