Evaluation of Selection Bias in an Incident-Based Dementia Autopsy Case Series

Debby Tsuang, MD, MSc,†‡ Kate L. Simpson, MPH,* Gail Li, MD, PhD,*‡ Ross L. Barnhart, Med,‡§‖ Steven D. Edland, PhD,¶ James Bowen, MD,‖ Wayne McCormick, MD,# Linda Teri, PhD,** David Nochlin, MD,†† Eric B. Larson, MD, MPH,# Mary Lou Thompson, PhD,‡‡ and James B. Leverenz, MD*‡‖§§*

Abstract: Neuropathological (np) relative frequency estimates of dementia may be biased if the autopsied subjects are not representative of all dementia subjects within a target population. We identified characteristics that differed between autopsied and non-autopsied subjects from an incident-based dementia case series and compared autopsy-based estimates of the relative frequency of np diagnoses before and after adjusting for potential selection bias. Clinically demented subjects who were autopsied (n = 206), had died but were not autopsied (n = 271), were still alive (n = 71), or had dropped out of the study (n = 82) were included. Compared with non-autopsied subjects, autopsied subjects were more likely to be Caucasian, educated beyond high school, and married. They also tended to have a lower baseline Mini-Mental State Examination score and were more likely to have a clinical diagnosis of Alzheimer disease (AD) than non-autopsied subjects. Neuropathological AD with Lewy bodies (LB) had the largest crude relative frequency estimate at 38% of the autopsy sample, followed by 25% for AD with vascular lesions, 13% for pure AD, 13% for LB (with or without vascular lesions), and 8% for pure vascular pathologies. Adjustment for potential sources of selection bias had little effect on relative frequency estimates, suggesting that np diagnoses in the autopsied subjects provide reasonable dementia relative frequency estimates among all clinically demented cases in this series.

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From the *Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington; †Department of Epidemiology, University of Washington, Seattle, Washington; ‡Mental Illness Research, Education, and Clinical Center, Seattle, Washington; §Department of Environmental Health, University of Washington, Seattle, Washington; ‖Department of Neurology, University of Washington, Seattle, Washington; ¶Division of Clinical Epidemiology, Mayo Clinic and Foundation, Rochester, Minnesota; #Department of Internal Medicine, University of Washington, Seattle, Washington; **School of Nursing, University of Washington, Seattle, Washington; ††Department of Pathology, University of Washington, Seattle, Washington; and ††Department of Biostatistics, University of Washington, Seattle, Washington; §§Parkinson's Disease Research, Education, and Clinical Center, VA Puget Sound Health Care System, Seattle, Washington.

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Reprints: Debby Tsuang, MD, MSc, VAPSHCS (116), 1660 South Columbian Way, Seattle, WA 98108 USA (e-mail: dwt1@u.washington.edu).

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INTRODUCTION

Accurate clinical diagnosis in incident-based studies of dementia can be challenging, particularly given the frequent presence of mixed etiologies.[1] Neuropathological (np) examination is critical for accurate diagnosis of dementia subtypes as well as of coexisting conditions. However, np findings (eg, relative frequency of a specific dementia diagnosis) in a study case series are likely biased if the autopsied sample differs from the rest of the study sample. For example, if autopsies are more likely to be obtained in subjects with a diagnosis of clinical Alzheimer disease (AD), and if neuropathological AD diagnosis is more likely for subjects with clinical AD, using autopsy data will overestimate the relative frequency of AD in the initial sample. This type of bias is called "selection bias," and statistical techniques exist to adjust for it.[2]

Previous studies have reported differences in demographic and clinical characteristics between autopsied and non-autopsied samples. Harrell and colleagues[3] found that autopsied patients were more likely to be Caucasian and were younger at age of onset and at age of death than non-autopsied patients. In the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), those who underwent autopsy were more likely to be Caucasian, were more highly educated, and had a longer duration of AD than those who did not undergo autopsy.[4] Furthermore, Bowler and colleagues[5] found that autopsy subjects were more likely to have received a clinical diagnosis of AD than subjects who did not undergo autopsy. How these differences between autopsied and non-autopsied subjects might affect the generalizability of np estimates to the entire sample remains unexplored.

An additional bias in the majority of autopsy studies examining the relative frequency of dementia subtypes is that the subjects are drawn from dementia specialty clinics or AD research centers. We have previously demonstrated that demographic and clinical characteristics of patients enrolled in specialized clinics and research centers differ from those of patients enrolled in incident-based samples.[6,7] Therefore, we

might expect dementia estimates from these autopsy samples to be even less representative of the true relative frequencies of dementia in the general medical community.

The present study used a large incident-based dementia case series to examine the effects of selection bias on autopsy-based dementia relative frequency estimates. This sample was assembled through efforts to identify and enroll all persons with incident dementia from a well-established health maintenance organization (HMO). Subjects are older and less demented than subjects recruited into specialty research registries, and the demographic characteristics (eg, sex, ethnicity, and education) of this sample resemble those of the individuals aged 65 and older in the Puget Sound region more closely than the demographic characteristics of specialty samples.[6] To explore the potential biases in the autopsy subjects of this sample, demographic and clinical characteristics were compared between subjects who did and did not undergo autopsy. Based on np findings in the autopsy sample, the relative frequencies of several np diagnoses were calculated and then adjusted for potential selection bias in this setting, providing estimates of the np dementia relative frequencies in the entire sample.

METHODS

Sample

Subjects in this study were drawn from the University of Washington (UW) Alzheimer's Disease Patient Registry (ADPR). The ADPR enrolled subjects from Group Health Cooperative, the largest and oldest HMO in the Puget Sound area. The purpose of this registry was to identify and enroll new cases of dementia that required medical attention among persons enrolled in the central Seattle region of the HMO. The eligibility of persons arriving at clinics with symptoms potentially consistent with previously undiagnosed dementia was determined through the review of specialty and primary care clinic logs, hospital records, head CT scans, and referrals from primary care practitioners and neurologists. The majority of referred cases, 48.8%, were from the subject's primary care physician.[8] In addition, 19.8% of the referrals were based on a subject's CT scan of the brain and 10% were referred from hospital admission records. Other sources for subjects included ER logs and mental health specialists. Persons with symptoms of memory loss suggestive of dementia were enrolled into the ADPR, where they were given a full workup for possible dementia which was followed by differential diagnosis. Those persons who previously had been diagnosed with dementia for more than one year (prevalent cases) were excluded from the study. In addition, approximately 20% of persons initially identified as having cognitive impairment declined to participate in the ADPR and an additional 14% declined to give informed consent.[9] Subjects underwent detailed clinical and neuropsychological assessments, and the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, (DSM-III-R) and the National Institute of Neurologic and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for dementia were applied.[10] This sample closely resembles the demographics of the general elderly population in the region and has been described in greater detail elsewhere.[1,6–8]

Nine hundred eighty-seven individuals were initially evaluated between 1987 and 1996 (Fig. 1); 58 subjects who were missing intake clinical diagnosis or who were deceased but for whom no date of death was available were excluded from the study. Of the remaining 929 subjects, another 277 who were evaluated but did not meet DSM-III-R criteria for dementia at intake were excluded. All subjects were approached regarding

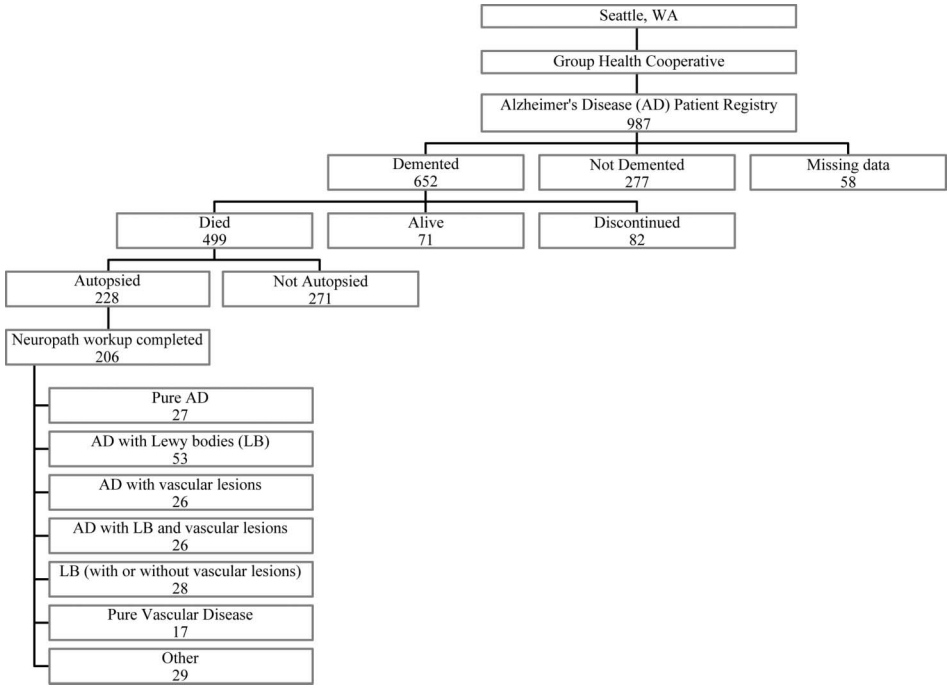

FIGURE 1. Case selection from the Seattle area into the present study.

autopsy at the first annual follow-up and annually thereafter until they decided whether or not to provide consent. By October 2003, 499 of the 652 subjects had died; 256 of the subjects who had died had consented to autopsy; 226 of these had autopsies completed, while 30 did not. These 30 individuals did not have autopsies performed for various reasons, such as relocation to another state or withdrawal of consent by family members at the time of death. Of the 243 who did not consent, 96 refused, 91 were undecided, and 56 were missing consent status. One who refused and one who was undecided eventually came to autopsy, however, for a total of 228 autopsy subjects. In summary, of subjects who had died by October 2003, 228 underwent an autopsy, and 271 were not autopsied. In October 2003, another 71 subjects were still alive, and 82 had dropped out of the ADPR.

Clinical and Neuropathological Assessments

DSM-III-R criteria for the clinical diagnoses of Alzheimer disease and multi-infarct dementia (MID) were used throughout the entire duration of the current study; 206 of the 228 autopsy subjects had received a standard neuropathological workup, including hematoxylin-eosin (H&E), modified Bielschowsky, and thioflavine S staining. In addition, alpha-synuclein immunostaining (antibody LB509, dilution, 1:400; Zymol, San Francisco, CA) and extranigral sampling were performed to fully characterize Lewy body (LB) pathologic features. The substantia nigra (SN), hippocampus, parahippocampal gyrus, amygdala, and cingulated gyrus were reviewed for the presence of LBs. An LB "positive" case was defined as having either H&E positive LB inclusions in the SN or greater than five alpha-synuclein–positive LB inclusions in an extra brainstem region. In the absence of LB inclusions in the SN, cases with six or more alpha-synuclein–positive cytoplasmic inclusions in the amygdala also were considered as positive for LB pathologic features.[11,12] Vascular lesions were identified and characterized for age and location using clinical records and neuropathological assessments. Recent infarcts (acute/subacute, ie, less than 1 year of age) were presumed to be terminal events that occurred after clinical assessments and therefore unlikely to contribute substantially to any clinical dementia during the study. These lesions were excluded from analyses. Vascular lesions, including lacunar infarcts, occurring more than one year prior to death and located above the tentorium, were considered to be significant regardless of volume. Such lesions were considered to be potentially contributory to the development of dementia and were considered significant in this study. All neuropathological records and assessments were systematically reviewed by JBL and DWT and classified into np categories. Autopsied subjects with Braak staging of IVB and above were considered to have neuropathological AD. Subjects with np AD who were positive for LB were classified as "AD/LB," while those with AD and concomitant vascular lesions were considered to have "AD/vascular lesions (AD/V)."[12] Vascular pathologies included infarcts and/or lacunes. Twenty-six individuals had AD, LB, and vascular pathologies and so were included in both the AD/LB and AD/V groups. Subjects with AD and no other clinically significant concomitant pathologies were considered to have "pure AD." Subjects without AD who were positive for LB, with or without vascular pathology, were classified as "LB (with or without vascular lesions)." Subjects with significant vascular lesions and AD-negative, LB-negative findings were considered to have "pure vascular disease." Subjects with np findings that did not correspond to any of the above categories were considered to have "other" pathology.

Statistical Methods

Demographic and clinical characteristics among autopsied, died-not-autopsied, alive, and discontinued subjects were compared using χ^2 statistics for categorical variables and ANOVA F-tests for continuous variables. Differences were further explored between autopsy subjects and the combined non-autopsied group (died-not-autopsied, alive, and discontinued) using χ^2 statistics for categorical variables and two-sample Student t tests for continuous variables. Variables with parameters that differed between the autopsied and non-autopsied groups were then examined for associations with each of the np outcomes: pure AD, AD/LB, LB (with or without vascular lesions), AD/V, pure vascular disease, and other pathologies via backward stepwise logistic regression models (significance level for removal from the model at 0.20 and significance level for entry at 0.15). The 26 individuals with three neuropathological findings (AD, LB, and vascular) were included in both the AD/LB and AD/V groups. Otherwise all groups were mutually exclusive. Within each stratum of the variables that were identified as being associated with both likelihood of autopsy and likelihood of the np outcome, it was assumed that np status was missing at random (ie, that there was no further selection bias). The *adjusted* relative frequency of the np outcome (adjusted for selection bias) was the weighted average of the relative frequencies across the covariate strata, weighted by the frequency of each stratum in the enrollment population.[2] Clearly, if a np diagnosis is unrelated to a covariate, or if the distribution of the covariate is the same in the autopsied and non-autopsied subjects, no adjustment for that covariate is necessary. All analyses were conducted using STATA version 7.0 (Stata Corp. 2001, College Station, TX) and Excel (Microsoft Corp. 2002, Redmond, WA).

RESULTS

A comparison of demographic and clinical characteristics among autopsied, dead-not-autopsied, alive, and discontinued subjects is shown in Table 1. Significant differences were observed in the distributions of gender ($P < 0.001$, with a greater percentage of females in the alive group); ethnic distribution ($P < 0.001$, with a greater percentage of Caucasians and a lower percentage of African Americans in the autopsy group); and marital status ($P = 0.04$, with a greater frequency of married subjects in the autopsied group). Mean age at intake also was significantly different among groups ($P < 0.001$), as was mean age at onset of symptoms ($P < 0.01$), although these differences were quite small (resulting P values from the 4 group comparisons are not shown in Table 1). While the amount of time spent in the study did not differ significantly between autopsied subjects and subjects who had died but were not autopsied, autopsied subjects tended to die at a younger age (83.6 [SD = 6.3] versus 84.9 [6.8] years for

TABLE 1. Comparisons of Demographic and Clinical Characteristics among Subjects Who Were Autopsied, Who Had Died but Were Not Autopsied, Who Were Still Alive, and Who Had Discontinued

	Died, Not Autopsied	Alive	Discont.	Non-Autopsied	Autopsied	P value (aut vs. non-aut)
Total	271	71	82	424	206	
	N (%)	N (%)	N (%)	N (%)	N (%)	
Gender						
Male	111 (41.0)	12 (16.9)	37 (45.1)	160 (37.7)	92 (44.7)	0.10
Female	160 (59.0)	59 (83.1)	45 (54.9)	264 (62.3)	114 (55.3)	
Ethnicity						
Caucasian	237 (87.5)	60 (84.5)	64 (78.1)	361 (85.1)	198 (96.1)	<0.001
African-American	24 (8.9)	9 (12.7)	11 (13.4)	44 (10.4)	3 (1.5)	
Other	10 (3.7)	2 (2.8)	7 (8.5)	19 (4.5)	5 (2.4)	
Education						
≤High school graduate	182 (67.2)	49 (69.0)	58 (70.7)	289 (68.2)	119 (57.8)	0.01
>High school graduate	89 (32.8)	22 (31.0)	24 (29.3)	135 (31.8)	87 (42.2)	
Married						
Yes	122 (45.0)	30 (42.3)	42 (51.2)	194 (45.8)	117 (56.8)	0.01
No	149 (55.0)	41 (57.8)	40 (48.8)	230 (54.3)	89 (43.2)	
DSM-III-R* diagnosis						
AD†	171 (63.1)	45 (63.4)	50 (61.0)	266 (62.7)	147 (71.4)	0.02
MID‡	38 (14.0)	5 (7.0)	10 (12.2)	53 (12.5)	12 (5.8)	
Others	62 (22.9)	21 (29.6)	22 (26.8)	105 (24.8)	47 (22.8)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age at intake (yrs)	80.6 (6.9)	77.3 (6.8)	77.7 (6.7)	79.5 (7.0)	79.1 (6.7)	0.52
Age at symptom onset (yrs)	77.7 (6.8)§	75.1 (6.7)	75.2 (7.1)	76.8 (6.9)‖	76.3 (6.8)	0.41
Age at death (yrs)	84.9 (6.8)	—	—	—	83.6 (6.3)	—
Time in study (intake-death)	4.3 (3.0)	—	—	—	4.5 (2.6)	—
Baseline MMSE¶	19.6 (4.7)#	22.5 (3.4)	21.8 (3.5)	20.5 (4.5)**	19.4 (5.3)††	0.01

*Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.
†Alzheimer's disease.
‡Multi-infarct dementia.
§N = 270: 1 subject missing age at onset.
‖N = 423: 1 subject missing age at onset.
¶Mini-Mental State Examination.
#N = 270: 1 subject missing baseline MMSE.
**N = 423: 1 subject missing baseline MMSE.
††N = 203: 3 subjects missing baseline MMSE.

died-not-autopsied subjects, $P = 0.03$). The groups further demonstrated different mean baseline Mini-Mental State Examination (MMSE) scores ($P < 0.001$); subjects who died tended to have lower initial MMSE scores.

Combining the died-not-autopsied, alive, and discontinued groups and comparing the demographic and clinical characteristics of this collective non-autopsied group to those of the autopsied group, ages at intake and at onset no longer differed significantly; however, distributions of ethnicity, marital status, and baseline MMSE remained significantly different (Table 1). In addition, the distribution of subjects' level of education was significantly different among groups ($P = 0.01$), with subjects in the autopsy group being more likely to have had education beyond high school. The distribution of clinical diagnosis also differed significantly between autopsied and non-autopsied subjects ($P = 0.02$), with a greater relative frequency of clinical AD in the autopsied group (71.4% versus 62.7% of non-autopsied subjects). Non-autopsied subjects were more likely to be female, although this difference was not significant (62.3% of non-autopsied versus 55.3% of autopsied subjects, $P = 0.10$).

Given their association with autopsy status, gender, ethnicity, education, marital status, baseline MMSE score, and initial clinical diagnosis were included as independent variables in stepwise logistic regression models for the autopsied subjects for each of the np outcomes of pure AD, AD/LB, LB (with or without vascular lesions), AD/V, and pure vascular dementia. Table 2 shows the distribution of these variables within each pathologic subgroup. In the logistic models, education and clinical diagnosis were found to be associated with np diagnosis of pure AD, and gender, marital status, education, and clinical diagnosis were associated with AD/LB. Gender,

TABLE 2. Neuropathological Findings by Variables Associated with Selection into Autopsy

	Pure Alzheimer Disease (AD)	AD with Lewy Bodies (LB)	LB (with or without vascular lesions)	AD with Vascular Lesions	Pure Vascular Disease	Other
Total*	27	79	28	52	17	29
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Gender						
Male	9 (33.3)	28 (35.4)	17 (60.7)	22 (42.3)	11 (64.7)	15 (51.7)
Female	18 (66.7)	51 (64.6)	11 (39.3)	30 (57.7)	6 (35.3)	14 (48.3)
Ethnicity						
Caucasian	25 (92.6)	77 (97.5)	28 (100.0)	50 (96.2)	16 (94.1)	27 (93.1)
African-American	0	1 (1.3)	0	1 (1.9)	1 (5.9)	1 (3.5)
Other	2 (7.4)	1 (1.3)	0	1 (1.9)	0	1 (3.5)
Education						
≤High school graduate	12 (44.4)	51 (64.6)	14 (50.0)	28 (53.9)	9 (52.9)	21 (72.4)
>High school graduate	15 (55.6)	28 (35.4)	14 (50.0)	24 (46.2)	8 (47.1)	8 (27.6)
Married						
Yes	14 (51.9)	49 (62.0)	19 (67.9)	31 (59.6)	11 (64.7)	11 (37.9)
No	13 (48.2)	30 (38.0)	9 (32.1)	21 (40.4)	6 (35.3)	18 (62.1)
DSM-III-R† diagnosis						
AD	23 (85.2)	64 (81.0)	15 (53.6)	40 (76.9)	8 (47.1)	17 (58.6)
MID	0	2 (2.5)	3 (10.7)	0	6 (35.3)	1 (3.5)
Others	4 (14.8)	13 (16.5)	10 (35.7)	12 (23.1)	3 (17.7)	11 (37.9)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Baseline MMSE‡	18.1 (5.8)	18.8 (5.4)	18.7 (6.0)§	20.1 (5.5)	21.0 (3.2)‖	21.6 (4.5)

*232 total subjects because 26 AD/DLB+Vasc subjects included in both AD with LB and AD with vascular lesions.
†Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.
‡Mini-Mental State Examination.
§N = 27: 1 subject missing baseline MMSE.
‖N = 15: 2 subjects missing baseline MMSE.

education, initial MMSE score, and clinical diagnosis were associated with an np diagnosis of LB (with or without vascular lesions). Gender and clinical diagnosis were predictive of pure vascular disease. None of the independent variables in the logistic model were associated with AD/V.

After adjustment for selection bias, the estimated relative frequency of AD/LB remained 38% (Table 3). Selection bias adjustments slightly decreased the estimated relative frequencies of both np pure AD and np LB (with or without vascular lesions) from 13% to 12%. The estimated relative frequency of pure vascular disease, 8%, increased to 10% after selection bias adjustments.

DISCUSSION

The objectives of this study were to elucidate the demographic and clinical differences between autopsied and non-autopsied subjects and to compare np dementia relative

TABLE 3. Estimated Relative Frequency (95% CI) of Neuropathological Pure Alzheimer Disease (AD), AD with Lewy Bodies (LB), LB (With or Without Vascular Lesions), AD with Vascular Lesions, and Pure Vascular Disease, Based on Autopsy Data Alone and With Adjustment for Selection Bias (Zhou et al. 1999).

Diagnosis	Crude Relative Frequency	Adjusted Relative Frequency
Pure AD*	0.13 (0.09, 0.18)	0.12 (0.08, 0.17)
AD with LB† (AD/LB)	0.38 (0.32, 0.45)	0.38 (0.31, 0.44)
LB (with or without vascular lesions)‡	0.13 (0.09, 0.19)	0.12 (0.08, 0.17)
AD with vascular lesions (AD/V)	0.25 (0.19, 0.32)	0.25 (0.19, 0.32)‖
Pure vascular disease§	0.08 (0.05, 0.13)	0.10 (0.06, 0.14)

Adjusted for differential selection according to the following:
*Education (≤HS, >HS) and DSM-III-R diagnosis at intake (AD, MID/other).
†Gender, marital status, education (≤HS, >HS), and DSM-III-R diagnosis at intake (AD, MID/other).
‡Gender, education (≤HS, >HS), MMSE score (<20, ≥20), and DSM-III-R diagnosis at intake (AD, MID/other).
§Gender and DSM-III-R diagnosis at intake (AD, MID, other).
‖No adjustment indicated for AD with vascular lesions group.
From reference 2.

frequency estimates before and after adjusting for this potential selection bias. The autopsied and non-autopsied subjects in our series differed in several demographic and clinical characteristics. Subjects who underwent autopsy were more likely to be Caucasian, to be educated beyond high school, to be married, and to receive a clinical diagnosis of AD than non-autopsied subjects. Autopsied subjects also had a lower baseline MMSE score than non-autopsied subjects. Autopsied subjects were much more likely to be male than living subjects, although the overall difference in gender between autopsied and non-autopsied subjects was not significant. Subjects demonstrated little difference in age at intake and age at onset of symptoms.

Comparability of these findings with past studies is limited by the fact that previous samples were comprised of recruits from specialty memory disorder clinics or AD research centers that included mostly prevalent cases.[3–5,13] In addition, at least two of these previous studies limited their non-autopsied sample to patients who had died.[3,4] This said, while Fillenbaum and colleagues[4] found that autopsied subjects had a significantly higher mean educational level than non-autopsied subjects, they did not find any significant differences between the two groups in marital status.

In our study, regardless of clinical diagnosis, Caucasian subjects were more likely to undergo autopsy than African-American subjects (data not shown). One limitation of these findings is that the number of non-Caucasian subjects in this sample was small, reflecting the ethnic distribution of the underlying population in this age group in King County.[6] However, this selection phenomenon of an overrepresentation of Caucasian subjects in autopsy samples is consistently observed in autopsy series.[3,4] Bonner and colleagues[14] found that pre-existing attitudes toward autopsy have a significant impact on autopsy consent rates in an urban African-American sample. Implementation of culturally sensitive recruitment increased autopsy rates from 2% to 29% in African-American patients with dementia or stroke.[14]

The relationship between autopsy status and clinical diagnosis remains unclear. Our study found that autopsied subjects were more likely to have a clinical diagnosis of AD than died-not-autopsied, alive, and discontinued subjects. Similarly, Bowler and colleagues[5] previously reported that subjects who underwent autopsy were more likely to have a clinical diagnosis of AD than subjects who had died but were not autopsied and who were still alive.[5] Studies by Harrell et al and by Nolan et al, however, found no difference in clinical diagnosis between autopsied and non-autopsied patients.[3,13] Besides the comparability limitations cited earlier, the study by Harrell and colleagues also included a much smaller sample size, with only 30 autopsied subjects and 39 died-not-autopsied comparison subjects.[3] The strength of the current study is the sample size and that only 11% of the subjects are still living; therefore, the ascertainment in this sample is almost complete. This limits the potential bias that only subjects with severe dementia would have died and come to autopsy.

It is not entirely clear why autopsy samples might contain a greater percentage of clinical AD subjects than the rest of the sample. Previous studies have reported that African Americans, Asians, and Hispanics are more likely to be clinically diagnosed with MID and other dementias than Caucasians,[16–19] and as noted earlier, African Americans are less likely to undergo autopsy. We might therefore expect that the greater percentage of clinical AD cases in autopsied samples is a reflection of the greater relative frequency of Caucasians who come to autopsy. However, we found a greater relative frequency of clinical AD subjects among the autopsied even when restricting our sample to Caucasians only (data not shown). Further studies are needed to validate these findings and to help explicate this relationship.

The estimate of np pure vascular disease in our sample (8%) is higher than that reported from specialty clinic samples (range 0%–4%).[3–5,13] This discrepancy can be accounted for by differences in the sample source. Specialty clinics are more likely to enroll younger and healthier subjects, while our incident-based case series is more likely to include older patients who have other comorbid conditions that might make them more prone to vascular-related changes in neuropathology. In addition, few incident-based studies are available to provide np relative frequency estimates for AD/LB, AD/V, pure AD, and LB (with or without vascular lesions). Furthermore, few available studies use the most up-to-date LB staining methods (eg, alpha-synuclein immunohistochemistry and amygdala sampling). Therefore, our estimates of AD/LB, AD/V, pure AD, and LB (with or without vascular lesions) cannot be compared with prior estimates.

For the neuropathological diagnoses considered in this study, the impact of selection bias of those autopsied relative to all enrolled is modest. Our assessment of selection bias, however, is limited to the demographic and clinical variables measured by the ADPR study. Other unmeasured factors also might influence selection to autopsy and therefore np relative frequency estimates. For example, subjects with a clinical diagnosis of MID might be more likely to undergo autopsy if their presentation is atypical. If these atypical subjects are also more likely to demonstrate pure vascular pathology upon autopsy, pure vascular dementia would be over-represented in the autopsy series. As the original clinical consensus diagnosis did not subdivide MID by specific clinical signs and symptoms at presentation, we could not assess this as a potential selection factor. However, since MID subjects comprised only 10% of our sample, this is unlikely to have had an appreciable effect on autopsy estimates overall.

Furthermore, it is important to note that our sample consisted entirely of individuals who presented with memory problems and not those who presented with other neurologic signs and symptoms, such as hemiparesis or parkinsonian signs and symptoms. Therefore, dementia attributable primarily to cerebrovascular or Parkinson's disease may not accurately be represented in our study sample. Finally, some of the neuropathological entities (eg, pure vascular disease) had small sample sizes and limited our ability to derive adjusted relative frequency estimates.

It might be argued that some of the selection bias detected here may be attributable to survival bias. For example, in our sample, those who are still living are more likely to be female. It is conceivable that there may be unmeasured variables that influence both survival and np diagnosis for which we could not adjust. However, as of October 2003, only

71 (11%) of subjects are still alive; it is therefore unlikely that any survival bias would have a substantial effect on the autopsy estimates presented here.

To our knowledge, this is the first study both to use an incident-based sample and to quantify the effects of autopsy selection bias on np dementia relative frequency estimates. We found that relative frequency estimates of np diagnoses obtained from autopsied subjects were very similar before and after adjusting for selection bias. Therefore, for the np diagnoses considered in this study, the impact of selection bias is modest. This suggests that np diagnoses in the ADPR subjects provide reasonable dementia relative frequency estimates among the ADPR patients who were clinically demented. Additional incident-based autopsy series, including samples with a larger number of non-Caucasian subjects, are necessary to ascertain whether the effect of selection bias remains minimal in a population with a greater relative frequency of non-AD dementia.

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