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Cerebral white matter hyperintensity in African Americans and European Americans with type 2 diabetes

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Abstract

Prior studies involving inner city populations detected higher cerebral white matter hyperintensity (WMH) scores in African Americans (AAs), relative to European Americans (EAs). This finding may be attributable to excess cardiovascular disease (CVD) risk factors in AAs and poorer access to healthcare. Despite racial differences in CVD risk factor profiles, AAs have paradoxically lower levels of subclinical CVD. We hypothesized that AAs with diabetes and access to healthcare would have comparable or lower levels of WMH as EAs.

Racial differences in the distribution of WMH were analyzed in 46 AAs and 156 EAs with type 2 diabetes (T2D) enrolled in the Diabetes Heart Study (DHS)-MIND, and replicated in a sample of 113 AAs and 61 EAs patients who had clinically-indicated cerebral MRIs. Wilcoxon two-sample tests and linear models were used to compare the distribution of WMH in AAs and EAs and test for association between WMH and race.

The unadjusted mean WMH score in AAs from DHS-MIND was 1.9, compared to 2.3 in EAs (p=0.3244). Among those with clinically-indicated MRIs, WMH scores were 2.9 in AAs and 3.9

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Contribution statement

B.I.F, J.D, J.A.M and K.M.S. are responsible for the conception and design of the study. J.D conducted the statistical analyses with input from C.H., B.I.F, J.A.M, and K.M.S. Y.G. wrote the application that search through the hospital database and identified the sample of patients with clinically-indicated MRIs. C.T.W. and E. L. worked with J.A.M to score the WMH. J.D, B.I.F, C.H, J.A.M and K.M.S. interpreted the results of the analyses and drafted the manuscript. J. D. W. and D. W. B. critically revised the manuscript and provided valuable input. All authors have read and approved the final version of this manuscript.

Duality of interest

The authors have no conflicts of interest to disclose.

in EAs ($p=0.0503$). Adjustment for age and gender showed no statistically significant differences in WMH score between AAs and EAs.

These independent datasets reveal comparable WMH scores between AAs and EAs. This result suggests that disparities in access to healthcare and environmental exposures likely underlie the previously reported excess burden of WMH in AAs.

Keywords

African American; cognitive performance; diabetes mellitus; MRI; race; white matter hyperintensity

Introduction

Leukoaraiosis, a common white matter pathologic lesion in older adults, is associated with demyelination, loss of oligodendrocytes, and vacuolization (1). These findings appear as regions of increased signal intensity on T2-weighted magnetic resonance images (MRIs) and are commonly termed white matter hyperintensities (WMH). WMH are thought to reflect chronic microvascular ischemic disease and often develop in those with type 2 diabetes (T2D) (2;3). Higher white matter disease burden is associated with cardiovascular disease (CVD) risk factors, including diabetes, hypertension and tobacco use (4). The overall burden of white matter (WM) disease in the brain is a predictor of stroke, dementia, and cognitive decline (5–8).

Epidemiologic studies report equal or greater rates of WMH in African Americans (AAs) compared to European Americans (EAs), a finding consistent with the greater amount and severity of conventional cerebrovascular disease (CVD) and CVD risk factors (diabetes mellitus and hypertension), as well as the primary outcomes of stroke and vascular dementia (9;10). However, more recent data from the Framingham Heart Study challenged this paradigm, demonstrating somewhat lower WMH disease burden in AAs relative to EAs (11). A potential explanation for these conflicting data is that the greater burden of WMH among AAs in the older literature may reflect healthcare disparities including inequality in access to and quality of healthcare (12–14). Such disparities have been described in AA populations and low-income families, as well as in those with T2D. For example, AAs and patients of lower socio-economic status (SES) with T2D are less likely to receive diabetes care services and continuity care from consistent healthcare providers relative to EAs and those with higher SES (15). AAs and lower SES patients with T2D are also hospitalized more frequently for diabetes-related complications relative to EAs and higher SES patients (15).

We compared the distribution of WMH in AAs and EAs from studies of T2D-associated complications, the Diabetes Heart Study (DHS)-MIND which is currently recruiting EAs, and the African-American Diabetes Heart Study MIND (AA-DHS-MIND) enrolling AAs. An independent sample of AA and EA patients with T2D who had clinically indicated cerebral MRIs performed at Wake Forest Baptist Medical Center (WFBMC) served as a replication sample. Marked healthcare disparities between AAs and EAs appear unlikely in participants enrolled in the Wake Forest Diabetes Heart Studies. AAs in these studies generally had similar frequencies of receiving angiotensin converting enzyme (ACE) inhibitors and statins, and achieved levels of blood pressure that are comparable to EAs. These factors have the potential to minimize the effects of racial differences in SES and allow for detection of biologic factors involved in susceptibility to WMH based upon ancestry.

Methods

Study Populations

For analyses in DHS-MIND (including AA-DHS MIND participants), a subsample was chosen consisting of all 46 unrelated AA participants recruited to date and 156 age- and sex-matched unrelated EAs selected to match the demographic and clinical characteristics of AA participants. Recruitment and ascertainment of DHS participants has been described. Briefly, the DHS recruited siblings concordant for T2D without evidence of advanced renal insufficiency through internal medicine clinics and community advertising (16). EA participants were considered to have T2D if diagnosed after the age of 34 years (AA participants after the age of 30 years) in the absence of historical evidence of ketoacidosis. The DHS studies are currently re-recruiting EAs and AAs, adding cerebral MRI and cognitive testing to existing subclinical CVD and renal phenotypes. Examinations are conducted in the Wake Forest School of Medicine (WFSM) Clinical Research Unit, including completion of medical questionnaires, measurement of vital signs and clinical chemistries. History of prior CVD is provided by self-report and chart review. Additional details regarding the study design and the data collected in the DHS, DHSMIND, AA-DHS, and AA-DHS MIND have been reported (17). DHS-MIND and AA-DHS MIND are enrolling some subjects who were not part of the original studies; however, the present analyses include only prior participants. Participants provided written informed consent and the study was approved by the WFSM institutional review board (IRB) in accordance with the Declaration of Helsinki.

The replication dataset was collected from 174 individuals with T2D (113 AA, 61 EA) who underwent a clinically indicated cerebral MRI during the prior 3 years at Wake Forest Baptist Medical Center. Individuals were included if they were at least 34 years old and actively receiving diabetes-related medications. De-identified data from these patients was obtained from the WFBMC Clinical Research Data Warehouse based on the Informatics for Integrating Bench and Bedside (www.i2b2.org) platform. Study procedures were approved by the WFSM IRB and in accordance with the Declaration of Helsinki.

MR Imaging Methods

EA and AA participants from the DHS-MIND were scanned on a 1.5T General Electric scanner with twin speed gradients using a neurovascular head coil (GE Healthcare, Milwaukee, WI). Fluid Attenuated Inversion Recovery (FLAIR) images were acquired in the axial plane for the purpose of evaluating WMH (TR=8002, TE=108.5, TI=2000, flip angle=90, 24 cm FOV, matrix size=256x256, 3 mm slice thickness). For the independent clinical cohort, the imaging protocol included a similar FLAIR sequence at 5 mm slice thickness in the coronal plane, as well as an axial fast-spin-echo T2 acquisition (TR = 5200, TE= 108, 24 cm FOV, matrix size = 256x256, 5 mm thickness), standardized across several clinical MRI scanners including GE 1.5T, GE 3T, and Siemens 1.5T Avanto scanners.

Semi-quantitative white matter rating scale

The WMH signal changes of each individual were assessed independently by two board certified radiologists using a semi-quantitative 10-point (0 to 9) scale with predefined methodology (18;19). WMH were estimated as the total extent of periventricular and subcortical white matter signal abnormality on FLAIR images that successively increase from no or barely detectable changes (grades 0 and 1, respectively) to almost all white matter involved (grade 9). This scale has an inter-reader reliability agreement within 1 grade of 85.7%, with relaxed kappa of 0.81; intra-reader reliability for agreement within 1 grade is 96.9%, with relaxed kappa of 0.96 (19). Internal data revealed 100% inter-reader agreement within one grade for two readers.

Statistical Analyses

The Wilcoxon two-sample test was employed as the primary statistical tool to test for evaluating racial differences in the distribution of the continuous variables presented in Table 1 for DHS-MIND. Association between race and the binary variables in this Table was evaluated using Fisher's exact test. The non-parametric and the exact test are known to be more robust against departure from normality in small samples, although they can be less powerful when the normality assumption holds. We also ran robust regression to obtain diabetes duration- and sex-adjusted distributions of WMH. The Box-Cox method was applied to identify the appropriate transformation that would best approximate the distributional assumptions of conditional normality and homogeneity of variance of the residuals (20). This method suggested taking the natural log of (WMH + 1) to minimize the influence of extremely large covariate values on parameter estimates in the models. The same analytical plan was used in the replication dataset.

Results

The distribution of WMH was compared in the 46 AAs and 156 matched EAs in the DHS-MIND. As in the full AA-DHS sample (21), AAs had similar mean T2D durations despite being on average 6 years younger than EAs (Table 1). Baseline data revealed that AAs in the DHS had higher diastolic blood pressure (73.0 vs. 68.6 mm Hg) and slightly lower BMI (33.7 vs. 36.0 kg/m²). There were no statistically significant differences in smoking history current/former smokers (13.0%/37.0%) than EAs (8.3%/45.5%), and in the baseline proportion of AAs and EAs who received ACE inhibitors (56.5% vs. 54.7%), oral diabetes medications (80.4% vs. 80.1%), insulin injections (37.9% vs. 38.4%), or had hypertension (93.5% versus 81.1%). These data demonstrate that AAs in the DHS generally comprise a well-treated population, potentially with better access to healthcare compared to previous reports (9;10). In the DHS, AAs and EAs had mean WMH scores of 1.9 and 2.3, respectively (p=0.3224). The racial difference in WMH distribution did not attain statistical significance; although, the equal variance two-sample T-test had a p-value=0.1793.

An independent dataset containing 174 individuals with T2D (113 AA, 61 EA) who had a clinically indicated cerebral MRI at WFBMC within the last 3 years was also evaluated. There was no overlap with participants in the DHS-MIND study. Distributions of WMH were compared between AA and EA patients; Table 2 contains the mean, median and standard deviation of demographic, clinical and WMH scores stratified by race and sex. The data in Table 2 also suggest that AAs were well matched to EAs in term of diabetes duration, sex distribution and glycemic control (HbA_{1c}). As in the DHS-MIND, AA patients from WFBMC were younger than EAs, but had similar diabetes duration. AA patients had higher blood pressures than EA patients. The mean WMH score in AA and EA patients was 2.9 and 3.9, respectively; Wilcoxon two-sample p-value was 0.0503, and two-sample T-test p-value was 0.02. This trend for a significant effect in this dataset goes one step further than what we observed in the DHS-MIND dataset, which only suggested that WMH scores observed between the 2 racial groups were not statistically different.

A linear model that included age, gender and diabetes duration showed that age was the strongest predictor of WMH. This was an expected result, as it has been previously reported (22). Age-and-sex adjusted analyses showed that WMH was not statistically different between races, although AAs had lower adjusted mean WMH than EAs. AAs tend to develop diabetes at a younger age relative to EAs, which implies that the ethnic difference in WMH may be confounded with the age difference. In this case, adjusting for age could reduce the power to detect the effect of race. Therefore, we repeated the same analyses adjusting for diabetes duration instead of age. In this analysis, the association between WMH and race trended toward significance in the DHS-MIND dataset, with a diabetes

duration- and sex-adjusted parameter estimate [standard error] for the association test with log (WMH+1) of (−0.1745 [0.1083]; p-value = 0.1090). In the replication WFBMC patients, the parameter estimate was similar (−0.1144 [0.1372], p-value = 0.4066). Both models consistently demonstrated that WMH was not positively associated with race.

Discussion

The current analyses in independent Wake Forest datasets containing patients with T2D residing in North Carolina revealed equal (or slightly lower) levels of WMH in AAs, relative to EAs. These findings stand in stark contrast to two prior reports. The Chicago Health and Aging Project (CHAP) and Washington Heights-Inwood Columbia Aging Project (WHICAP) previously reported that AAs had equal or greater WMH scores relative to EAs, along with far higher burdens of conventional CBVD risk factors. CHAP assessed relationships between WMH and cognitive function in 335 AAs and 240 EAs (9). Race did not modify associations between MRI structural measures and cognitive performance in these participants. In those without dementia, inverse associations were observed between cognitive performance and both WMH score and infarct number, while positive associations were seen between cognitive performance and total brain volume. WHICAP assessed racial differences in brain morphology in a sample from New York City, but did not report associations with cognitive measures (10). The 243 AA WHICAP participants had greater brain volumes and higher WMH, relative to the 203 EA participants. Racial differences were attributed to the "greater likelihood of vascular disease in AAs". Neither of these reports adjusted for co-existing conventional CBVD risk factors (*e.g.*, level of blood pressure, HbA1c, or LDL cholesterol), degree of European ancestry in minority participants or SES, limiting the conclusions that can be drawn.

CHAP and WHICAP results conflict with the Framingham Heart Study ethnic minority cohort findings, where 55% of the sample was AA. In the Framingham Heart Study ethnic minority cohort, AAs had significantly lower WMH than EAs in the Framingham offspring group (11). We are unaware of other studies that evaluated racial differences in WMH and cerebral structure in subjects with diabetes. In addition to controversy surrounding the impact of race on WMH, the longstanding belief that large vessel atherosclerosis (calcified atherosclerotic plaque) is more severe in AAs than EAs has proven to be incorrect. AAs are an admixed population, comprised of ~80% African and ~20% European-derived alleles (23). AAs with greater degrees of European ancestry have higher levels of coronary artery calcified atherosclerotic plaque (CAC) (24). In contrast to the observation that AAs in the general community have higher CVD rates than EAs, when AAs and EAs with T2DM receive equivalent healthcare (Veterans Administration, Kaiser-Permanente, and Medicare-insured dialysis studies), AAs have a highly significant 50% *lower* incidence rate of myocardial infarction (25–27). Published AA-DHS results and other reports document lower levels of CAC in AAs, relative to EAs (16;28;29). The presence and severity of CAC is predictive of CVD events in all race groups (30). Hence, the longstanding concept that AAs have higher CVD rates than EAs, as stated in the WHICAP report, likely reflect adverse environmental exposures, lack of healthcare access and lower SES in AAs from these older reports.

We conclude that WMH scores are generally similar in AAs with T2D, relative to EAs. This result supports the results from the Framingham Heart Study ethnic minority cohort and suggests that improved access to healthcare in DHS-MIND, relative to the CHAP and WHICAP studies, may contribute to the different conclusions between studies. Most importantly, these results suggest that analyzing AAs and EAs with similar access to healthcare is necessary to determine the effects of race and novel risk factors on WM disease

burden. Improving healthcare access in AAs and those with lower SES could protect from development of WMH and associated risk of stroke and cognitive decline.

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ABBREVIATION KEY

WMH	white matter hyperintensity
AAs	African Americans
EAs	European Americans
CVD	cardiovascular disease
DHS	Diabetes Heart Study
MRI	Magnetic Resonance Imaging
T2DM	type 2 diabetes mellitus
CBVD	cerebrovascular disease
SES	socio-economic status
ACE	angiotensin converting enzyme
WFBMC	Wake Forest Baptist Medical Center
WFSM	Wake Forest School of Medicine
IRB	institutional review board
WFU	Wake Forest University
FLAIR	Fluid Attenuated Inversion Recovery
T2	spin-spin or transverse relaxation time
TR	repetition time
TE	echo time
TI	inversion time
FOV	field of view
CAC	coronary artery calcified atherosclerotic plaque

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Table 1

Demographic and clinical characteristics of diabetes duration-matched DHS-MIND participants

Variable	African American									European American									P-value of the Wilcoxon two-sample test							
	Males (N=17)				Females (N=29)					All (N=46)				Males (N=86)				Females (N=70)					All (N=156)			
	Mean	Median	Std		Mean	Median	Std			Mean	Median	Std			Mean	Median	Std			Mean	Median	Std				
Continuous																										
Age (years)	61.1	58.1	11.1		61.1	60.8	7			61.1	60.6	8.6			69.4	69.3	8.2		67.6	66.4	10.2		68.4	67.5	9.4	<.0001
Diabetes duration (years)	9.8	8.1	5.1		9.4	7.6	7.2			8.4	6.5	6.4			8.4	6.5	6.5		11.2	8.5	8.7		10	7	7.9	0.6928
Systolic BP (mm Hg)	132	129	20.1		140	139	19.4			139	133	19.8			139	140	18.5		133	131	18.3		136	135	18.5	0.9167
Diastolic BP (mm Hg)	72.9	71	14.6		73	72	8.6			73	71.8	11			69.1	70	10.2		68.2	67.5	9		68.6	69	9.5	0.0175
BMI (kg/m ²)	32.6	32.7	6.1		34.4	34.2	7.3			33.7	33.6	6.9			34.2	29.7	24.9		37.4	31	36.2		36	30.1	31.6	0.0427
Glucose (mg/dl)	155	135	61.3		157	134	76.8			156	134	70.8			153	144	56.5		153	141	55.5		153	142	55.8	0.591
Hemoglobin A1c (%)	8.4	7.3	2.4		8.1	8.4	1.8			8.2	7.6	2			8.1	7.7	2		8.4	8.2	2		8.2	7.8	2	0.7964
Serum creatinine (mg/dl)	0.9	0.9	0.2		1	0.9	0.3			1	0.9	0.3			1	0.9	0.3		1	1.1	0.2		1	1	0.3	0.4101
High sensitivity CRP (mg/dl)	0.6	0.3	0.7		1.7	0.8	3.8			1.3	0.5	3			0.8	0.3	1.3		0.6	0.3	0.9		0.7	0.3	1.1	0.0339
HDL-cholesterol (mg/dl)	47.1	46	9.9		44.5	44	11			45.5	44.5	10.6			49.4	47	13.2		46.8	46	11.8		48	46	12.5	0.3092
LDL-cholesterol (mg/dl)	114	103	42		114	107	41.3			114	107	41.1			114	110	36.4		104	101	36.4		108	106	36.6	0.6105
Triglycerides (mg/dl)	109	109	36.5		165	120	193			144	111	156			110	93	60.9		120	105	61.8		116	99	61.4	0.216
Urine ACR (mg/g)	294	18.4	597		405	23.3	901			366	23.3	800			109	8.5	405		209	13.7	785		163	10.5	640	0.0888
GFR, ml/min/1.73m ²	101	95.8	34.9		89.9	87.2	29.9			94	90.4	31.9			94.6	92.1	25.5		90.4	86.4	29		92.3	89.1	27.5	0.9598
Aorta CP (mass score)	784	6	1728		1488	102	2494			1227	39.5	2247			1715	280	2746		1697	349	2949		1705	333	2849	0.1359
Carotid CP (mass score)	28.2	0	68.1		39.9	0	146			35.6	0	122			48.9	0	99.4		33.2	0	84.4		40.2	0	91.5	0.1187
Coronary CP (mass score)	206	2.5	430		361	27.5	891			303	15.8	752			201	6.3	422		436	40	850		330	21.3	700	0.5955
White matter hyperintensity	1.9	2	1		1.9	1.5	1.5			1.9	1.5	1.3			2.4	2	1.7		2.1	2	1.6		2.3	2	1.6	0.3224

Binary variables	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	Frequency	Percent	P-value
Oral diabetes med use (Yes)	13	76.5	24	82.8	37	80.4	56	80	69	80.2	125	80.1			0.9634
Insulin use (Yes)	7	41.2	11	37.9	18	39.1	23	32.9	36	41.9	59	37.8			0.8723
Presence of hypertension (Yes)	15	88.2	28	96.6	43	93.5	52	77.6	68	84	120	81.1			0.045
ACE/ARB use (Yes)	12	70.6	14	48.3	26	56.5	30	44.8	51	63	81	54.7			0.831
Statin use (Yes)	9	52.9	18	62.1	27	58.7	29	43.3	47	56	76	50.3			0.32

<i>Binary variables</i>	<i>Frequency</i>	<i>Percent</i>	<i>Frequency</i>	<i>Percent</i>	<i>Frequency</i>	<i>Percent</i>	<i>Frequency</i>	<i>Percent</i>	<i>Frequency</i>	<i>Percent</i>	<i>Frequency</i>	<i>Percent</i>	<i>P-value</i>
Smoking (past)	8	47.1	9	31	17	37	46	65.7	25	29.1	71	45.5	0.4615
Smoking (current)	1	5.9	5	17.2	6	13	6	8.6	7	8.1	13	8.3	

ACR – albumin:creatinine ratio; BMI – body mass index; BP – blood pressure; ACE – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; CP – calcified plaque; GFR – glomerular filtration rate; LDL – low density lipoprotein; HDL – high density lipoprotein; CRP – C-reactive protein; Std – standard deviation. The p-value compares the distribution of each variable between the 2 races using the Wilcoxon 2 sample test for continuous traits and Fisher's exact test to test for association between the binary traits and race.

Table 2

Demographic and clinical characteristics of patients with clinically indicated MRI scans at WFBMC

Variable	African American												European American						P-value of the Wilcoxon two-sample test
	Males (N=68)			Females (N=45)			All (N=113)			Males (N=33)			Females (N=28)			All (N=61)			
	Mean	Median	Std	Mean	Median	Std	Mean	Median	Std	Mean	Median	Std	Mean	Median	Std	Mean	Median	Std	
Continuous																			
Age (years)	58.4	58	9.6	59.1	58.5	11.3	58.8	58	10.6	65.5	63.5	11.6	65.6	64	12.8	65.6	64	12.2	
Diabetes duration (years)	2.4	1.4	2.2	3.7	3.8	2.3	3.2	3	2.3	3.1	2.1	3	2.9	1.6	3.5	3	1.8	3.2	
Systolic BP (mm Hg)	147.4	144.5	32.4	146.2	140	32.9	146.7	140	32.6	143.6	142	27	139.8	138.5	30.6	141.5	142	28.8	
Diastolic BP (mm Hg)	85.4	83	15.4	81.3	80	17.7	82.9	80	16.9	76.5	74	16.1	72	73	14.8	74	74	15.4	
BMI (kg/m ²)	29	27.6	6.5	32.7	32.3	8.9	31.2	30.7	8.2	28.2	28.8	5.9	27.1	26.3	7.8	27.6	27.7	7	
Serum glucose (mg/dl)	156.2	125	92.3	161.2	131.5	97	159.1	127	94.7	173.6	150	92.4	133.9	119.5	56	152.1	126	76.8	
Hemoglobin A1c (%)	7.7	6.9	2.3	8	7	2.5	7.9	7	2.4	7.8	6.9	2.2	7.2	6.6	1.6	7.5	6.8	2	
Serum creatinine (mg/dl)	1.2	1.1	0.3	0.9	0.9	0.3	1	1	0.3	1	1	0.3	0.8	0.8	0.3	0.9	0.9	0.3	
HDL-cholesterol (mg/dl)	39.1	33	15.3	44.8	42	14.4	42.6	40	14.9	29.9	31	10.4	41.1	34.5	13.7	35.9	33	13.4	
LDL-cholesterol (mg/dl)	113.9	113	41.9	122.5	105.5	42	119.1	107	41.9	87.1	63	47	107.4	96	57.2	98.7	84	53.3	
Triglycerides (mg/dl)	121.9	107	60.9	126.3	108.5	65.9	124.6	108	63.6	152.7	132.5	100.1	151.1	116	85.4	151.8	123	91.4	
White matter hyperintensity	3.3	3	2.2	2.7	3	2.1	2.9	3	2.1	4.2	3.5	2.9	3.6	3	2.6	3.9	3	2.7	

Std – standard deviation; BMI – body mass index; BP – blood pressure; LDL – low density lipoprotein; HDL – high density lipoprotein; WFBMC – Wake Forest Baptist Medical Center. The p-value compares the distribution of each variable between the 2 races using the Wilcoxon 2 sample test for continuous traits and Fisher’s exact test to test for association between the binary traits and race.

Table 3

Clinical indication for MRI by race / ethnicity

Clinical indication for MRI in the replication sample	Race / ethnicity		
	African-American	European-American	Total
Unknown / Other	29 (26.1%)	17 (27.0%)	46 (26.4%)
Falls / Trauma	2 (1.8%)	2 (3.2%)	4 (2.3%)
Cancer	11 (9.9%)	9 (14.3%)	20 (11.5%)
Stroke / TIA / Altered mental status / Seizure	62 (55.9%)	30 (47.6%)	92 (52.9%)
Inner ear / Dizziness	0 (0.0%)	3 (4.8%)	3 (1.7%)
Headache	7 (6.3%)	2 (3.2%)	9 (5.2%)
Total	111	63	174