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Diabetes, Hemoglobin A1C, and Regional Alzheimer's Disease and Infarct Pathology

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Abstract

We examined the relationship of diabetes and hemoglobin A1C (A1C) to two common causes of dementia. The study included 1,228 subjects who underwent annual clinical evaluations and a brain autopsy at death, as part of a Rush longitudinal cohort study of aging. 433 subjects had A1C data available. Neuropathological evaluations documented the size and location of infarcts. Modified silver stain-based Alzheimer's disease (AD) measures included global and regional scores. We used regression analyses to examine associations of diabetes and A1C with overall and regional neuropathology. Diabetes (OR=0.94, 95%CI:0.73-1.20) and A1C (OR=0.83, 95%CI: 0.62-1.10) were not associated with global AD pathology across the brain, nor with overall or individual measures of neuropathology in mesial temporal or neocortical regions separately (all p>0.05). Diabetes was associated with a higher odds of any infarct (OR=1.43, 95%CI:1.07-1.90), and particularly with gross (OR=1.53, 95%CI:1.14-2.06) but not microinfarcts (p=0.06), and subcortical (OR=1.79, 95%CI:1.34, 2.39) but not cortical infarcts (p=0.83). In summary, we found no relationship of diabetes or A1C with global or regional AD pathology, including in the mesial temporal lobe. Diabetes is associated with gross subcortical infarcts. Our results suggest that the

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Contributions

JJP and ZA conducted the literature search, drafted the first version of the manuscript, and revised the manuscript. ZA conceptualized the study, collected data, designed the study, analyzed and interpreted data, and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. JAS conceptualized the study, collected data, and revised the manuscript. AWC analyzed and interpreted data, and revised the manuscript. SEL, LLB, RSA, SAE, and DAB collected data and made critical revisions to the manuscript. DAB, LLB, JAS, and ZA obtained study funding.

Conflict of interest

None of the authors have a conflict of interest related to this work to declare.

diabetes-dementia link is based on subcortical vascular pathology and not on regional AD pathology.

Keywords

Alzheimer's disease; Neuritic plaques; Tangles; Cerebrovascular disease; Infarction; Pathology; Diabetes; Hemoglobin A_{1c}; Epidemiology

Introduction

From 1990-2013, the worldwide number of persons with diabetes has increased 133% to 410 million, the largest increase for any medical condition.[1] While complications are well-recognized, less is known about diabetes effects on the brain. Yet, prospective studies have consistently shown that diabetes, as well as its' most clinically used biomarker hemoglobin A1C (A1C), increase dementia risk, and even clinically diagnosed Alzheimer's disease (AD).[2-7] Indeed, a meta-analysis found that the pooled adjusted risk ratio for AD risk was 1.57, with a population-attributable risk of ~8%, corresponding to 432,000 persons out of 5.4 million Americans with AD.[8]

In a recent white paper from a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) workshop, an interdisciplinary panel of experts identified the urgent need to elucidate mechanisms underlying the diabetes-dementia association.[9] One mechanism needing further elucidation concerns cerebrovascular disease, given that diabetes and A1C are established risk factors for stroke,[10] and cerebrovascular disease is a common cause of dementia.[11] Yet another mechanism to examine may involve the most common single cause of dementia, AD pathology.[12] However, both neuroimaging and clinical-pathologic studies have produced mixed results to date, with some studies showing increased AD pathology,[3,13] others no association,[14-16] and even some showing decreased AD pathology.[5,17] One possible explanation for the mixed results may be that diabetes affects neuropathology preferentially in select brain regions, and considering only total estimates of pathology overlooks regional associations. Indeed, tangle pathology is known to preferentially affect the mesial temporal lobe in early AD, and imaging studies suggest that diabetes and blood biomarkers are associated with smaller mesial temporal lobe volume, even when taking vascular processes into account,[18,19] and others suggest subcortical vascular changes preferentially occur in diabetes.[20] Of the clinical-pathologic studies considering regional AD pathology, most have focused on the mesial temporal lobe with mixed findings.[2,21-23] An autopsy study with larger numbers of persons with and without diabetes using measures of several brain regions, as well as individual regional measures of AD pathology (e.g., plaques and tangles), may be better poised to address this issue. Further, examination of A1C may provide additional insight, given the limited data on A1C and dementia neuropathology.

This study expands on our previous work on diabetes and neuropathology[24,25] by examining associations of diabetes and A1C with regional AD and brain infarct pathologies. We used data from >1,200 autopsied persons who participated in a community-based study of aging, to test whether diabetes, and A1C in a subset, increased the odds of having more AD pathology, using measures of overall pathology and regional pathology in the mesial

temporal cortex and neocortex, as well as regional individual pathologies of plaques and tangles. In addition, we examined associations of diabetes with regional infarcts.

Subjects and Methods

Subjects

Subjects were deceased older men and women who participated in one of three epidemiologic studies of aging, the Religious Orders Study (ROS), the Rush Memory and Aging Project (MAP), or the Minority Aging Research Study (MARS), all conducted through the Rush Alzheimer's Disease Center, and approved by the Institutional Review Board of the Rush University Medical Center. These studies are ongoing, prospective longitudinal cohort studies, enrolling community-dwelling older individuals without known dementia.[26-28] Subjects signed a consent form agreeing to annual clinical evaluations and an Anatomical Gift act agreeing to brain donation at time of death, with brain donation being optional for MARS participants. The large overlap in study design across the three studies, including participant recruitment and biospecimen and data collection, facilitates analysis across studies.

ROS enrolls older Catholic clergy from >40 groups across the US starting in 1994.[26] Of 1,301 persons enrolled, 696 died and 639 came to autopsy, of whom 628 had complete data at the time of the current study and were included in analyses. MAP participants have been recruited from the Chicagoland area since 1997, and include 1,798 persons of whom 761 died, 615 came to autopsy, and 590 had complete data to be included in current analyses.[27] MARS participants are black and also from the Chicagoland area. Since 2004, there have been 694 enrolled, and 113 of these died.[28] In 2011, MARS began recruiting for autopsy and of the 23 deaths since autopsy recruitment started, 18 came to autopsy, of which 10 had neuropathological data available for inclusion in analyses. Across the three cohorts, 1,228 subjects were included in the current study.

Clinical Evaluations

Baseline and annual clinical evaluations were conducted as described elsewhere.[26-28] Briefly, structured evaluations include a medical history with direct visual inspection of all medications, blood sample collection, neuropsychological testing, and physical exam. The medical history included four questions to identify the presence of diabetes, as reported previously in the three cohorts,[29-31] and also documented hypertension and other factors. Names and dosage of over-the-counter and prescription medications were recorded and coded.[32] Consistent with the chronic nature of diabetes, a subject was considered diabetic if taking an antihyperglycemic medication or reported a history of diabetes at any time point in the study.[29-31]

Blood collection and processing followed a protocol which included, starting in 2007, a revision to allow for quantification of A1C, which was conducted by a commercial laboratory (Quest Diagnostics, Inc, Wood Dale, IL), using an immunoturbidimetric assay (Cobas Integra, Roche Diagnostics), with certification by the National Glycohemoglobin Standardization Program (NGSP). We used the first available A1C values obtained from

each subject, as a continuous measure for primary analyses. In secondary analyses, values were categorized following the American Diabetes Association recommendations (<5.7% for normal; 5.7% – 6.4% for borderline; ≥6.5% for elevated).[33] Apolipoprotein E (*APOE*) genotype data were also available.

Neuropathological measures

Brain autopsies (mean postmortem interval =8.8 [SD=8.0] hours) and uniform neuropathologic evaluations were conducted, as previously described.[34] Briefly, brains were weighed, and tissue was either frozen or fixed in paraformaldehyde. All data were reviewed by a board-certified neuropathologist, blinded to clinical data. Each brain was examined for AD pathology. Sections (6μm thick) were cut from fixed, paraffin embedded tissue from the midfrontal cortex, superior or middle temporal cortex, inferior parietal cortex, entorhinal cortex, and hippocampus and mounted on glass slides. Markers of AD were visualized via a modified Bielschowsky silver stain and quantified following a previously described protocol.[34] Summary scores of each of neuritic plaques, diffuse plaques, and neurofibrillary tangles in each subject from all brain regions were used to create a composite measure of global AD pathology.[34] In order to examine the relationship of diabetes to regional pathology, we used a similar approach for the separate brain regions. Data on neuritic plaques, diffuse plaques, and neurofibrillary tangles in each of the hippocampus and entorhinal cortex were combined to create a mesial temporal score, while data in midfrontal cortex, superior or middle temporal cortex, and inferior parietal cortex were combined to create a neocortical score.

The presence and location of gross infarcts were determined by visual inspection of the entire brain before processing, as well as of coronal slabs of one hemisphere, as described before.[34] All suspected gross infarcts were confirmed histologically using H&E, and assessed for age (acute, subacute, or chronic). Microscopic infarcts were defined as infarcts not visible to the naked eye and identified on H&E stained sections of predetermined brain regions: entorhinal cortex, CA1/subiculum, dorsolateral prefrontal cortex, inferior temporal cortex, angular gyrus/supramarginal (inferior parietal) cortex, and calcarine cortex.[35] For all analyses, only chronic infarcts were included and data were dichotomized by presence of any infarct (1 or more, of any size and in any location) versus not present. Additional dichotomous measures considered gross and micro-infarcts separately, as well as cortical and subcortical infarcts separately.

Statistical Analysis

We first looked for group differences among those with and without diabetes, using t-tests and chi-square tests. All subsequent analyses controlled for age-at-death (centered at 88 years) and sex. Because sensitivity analyses allowing for cohort effects did not change findings, we present analyses combining data from all three cohorts. In the first set of analyses, we examined the relation of diabetes, and separately A1C, to AD pathology outcomes. Because the measures of AD were highly skewed, measures were analyzed as quartiles using ordinal logistic regression analyses that assumed proportional odds. First, we examined the relationship of diabetes and A1C to the global AD score. Next, we considered two brain regions, using first the overall mesial temporal and neocortical measures, then the

mesial temporal and neocortical measures for each of three individual markers of AD, specifically neuritic plaques, diffuse plaques, and neurofibrillary tangles. Finally, we conducted secondary analyses controlling for *APOE* and hypertension, and checked for any interactions between diabetes (and separately A1C) with *APOE*ε4.

In the next set of analyses, we examined the association of diabetes and A1C with brain infarcts. In logistic regression analyses controlling for age-at-death and sex, we examined the odds of any chronic infarct in those with diabetes compared to those without. In separate models, we examined the odds of gross and micro-infarcts, and of cortical and subcortical infarcts.

Analyses were programmed in SAS version 9.3 (SAS Institute Inc., Cary, NC) and models were evaluated for violations of core model assumptions.

Results

Demographic, clinical, and neuropathologic characteristics

Of the 1,228 subjects (mean age-at-death = 88.8 years; 65% female), 250 (20%) had diabetes (Table 1). A subset of 433 (35%; mean age-at-death = 87 (SD=6.3) years; 73% female) had A1C data available for analyses. The first available measure was collected an average of 35.2 months (SD=22.2) before death. As expected, A1C was higher among the 96/433 (22%) subjects who had diabetes compared to those without, with values being elevated in half of the subjects with diabetes (45/96; 47%), borderline in a third (32/96; 33%), and normal in the remaining (19/96; 18%). *APOE* data were available in 1,168 (95%) subjects. Overall, subjects with diabetes were younger (p=0.0001), more likely to be male (p<0.001), have higher A1C values (p<0.001), less likely to be *APOE*ε4 carriers (p=0.04), but not more likely to have hypertension (p=0.16). AD pathology was present to some degree in most subjects, and there was mostly no difference among those with and without diabetes (all p>0.08), except for fewer tangles in the mesial temporal (p=0.03) and neocortical regions (p=0.05) among those with diabetes. Half of subjects had at least one infarct (597/1228; 49%), and there was no difference in the rates of infarcts between those with and without diabetes. A total of 186 (15%) subjects had both gross and microinfarcts, and 174 (14%) had both cortical and subcortical infarcts. Subjects with diabetes were more likely to have gross infarcts (p=0.02) but not microinfarcts (p=0.12), and more subcortical (p=0.001) but not cortical infarcts (p=0.95).

Relation of Diabetes and A1C to AD Pathology

Overall, in models adjusted for age-at-death and sex, diabetes did not increase the odds of having more AD pathology (Table 2). Results were essentially unchanged when controlling for *APOE*ε4 (OR=1.07, 95%CI: 0.82, 1.39) and in a separate analysis, there was no evidence for an interaction of diabetes with *APOE*ε4 (p= 0.90), suggesting that results were similar among those with and without *APOE*ε4. Using a similar set of analyses with A1C replacing diabetes as the predictor, we found no association between A1C and the global AD score (Table 2). This result was unchanged when controlling for *APOE*ε4 (OR=1.01, 95%CI: 0.74, 1.36) and there was also no interaction of A1C with *APOE*ε4 (p=0.67). In

secondary analyses using the A1C as an ordinal variable, results were similar suggesting that borderline and elevated A1C are not associated with the global AD score, compared to normal A1C (both p>0.3).

Because diabetes may affect some brain regions more than others,[36] we examined the relation of diabetes and A1C to regional AD pathology. First, we used outcome measures of overall mesial temporal and neocortical pathology, and then used individual measures of regional neuritic plaques, diffuse plaques, and neurofibrillary tangles within the two regions. There was no association between diabetes and any of the regional overall or regional individual AD pathology measures (Table 2). Results were similar when controlling for *APOE*ε4 (all p>0.18) and there was no interaction of diabetes with *APOE*ε4 (all p>0.09). We then considered the predictor of A1C using the same approach as with diabetes, to test for associations with overall and individual measures of regional pathology. No associations were found, though a borderline association (p=0.052) was noted with diffuse plaques in the neocortical region (Table 2). Results were unchanged when controlling for *APOE*ε4 (all p>0.19) and there were no interactions of A1C with *APOE*ε4 (all p>0.19).

Relation of Diabetes and A1C to Infarcts

Diabetes increased the odds of infarcts of any size and location by 43%. In particular, diabetes increased the odds of gross infarcts, the association with microinfarcts was not significant (p= 0.064; Table 3). In separate analyses controlling for hypertension, results were similar for associations of diabetes with any infarct (OR=1.42, 95%CI: 1.06, 1.89), gross infarcts (OR=1.53, 95%CI:1.13, 2.05), and microinfarcts (OR=1.31, 95%CI: 0.97,1.78), suggesting the effect of diabetes on infarcts is independent of hypertension. We next examined the interactions between diabetes and *APOE*ε4 on outcomes of any infarcts, of gross and of microinfarct, and found no interactions, suggesting no effect modification of the relationship of diabetes with infarcts by *APOE*ε4 (all p>0.16). We conducted a set of similar analyses using A1C as the predictor, and results were similar to those for diabetes (Table 3). Again, we found no interaction between A1C and *APOE*ε4 with any of the three infarct outcomes (all p>0.28).

We next considered infarct pathology by brain region, using separate outcomes for cortical and subcortical regions. Diabetes was associated with a nearly 80% increase in the odds of subcortical infarcts but not with cortical infarcts (Table 3). In similar analyses controlling for hypertension, results were essentially unchanged (OR=1.77, 95%CI: 1.32, 2.37 for subcortical infarcts, and OR=1.04, 95%CI: 0.75, 1.43 for cortical), suggesting independence of the effect of diabetes on infarcts from hypertension. In secondary analyses by both infarct region and size, diabetes was associated with both gross subcortical (OR=1.79, 95%CI: 1.32, 2.42) and micro- subcortical infarcts (OR=1.65, 95%CI: 1.15, 2.37), but neither gross cortical nor micro- cortical infarcts (both p>0.86). Separate analyses did not show associations of A1C with either subcortical or cortical infarcts (Table 3). In additional analyses of both infarct region and size, A1C was associated with gross subcortical infarcts (OR=1.41 95%CI: 1.01, 1.98) but not micro- subcortical infarcts (OR=1.26 95%CI: 0.84, 1.89), or gross cortical and micro- cortical infarcts (both p>0.32).

Discussion

In this clinical-pathologic study of >1,200 community-dwelling persons with and without diabetes, diabetes did not increase the odds of overall or regional AD pathology in the mesial temporal or neocortical cortices, nor individual markers of plaques or tangles in these regions. And, as expected, diabetes was associated with about a 50% increase in the odds of having infarcts, an association that was particularly strong for subcortical infarcts, both gross and microscopic. Findings were similar in analyses using A1C as the predictor. None of the main results were modified by the presence of *APOE*ε4.

Given the large and increasing public health burden of both diabetes and dementia, and that these conditions are recognized as being associated, researchers are aiming to elucidate the underlying mechanisms responsible for this link.[9] Such knowledge would facilitate the identification of potential therapeutic targets and eventual prevention of at least some forms of dementia.[37,38] Because AD, usually in combination with other pathology, is among the most common cause of dementia, and because AD affects selective brain regions, especially in the earlier stage, the examination of regional AD pathology as a possible mechanism linking diabetes to dementia is a logical step. While methods to measure in vivo AD biomarkers are developing, including most recently with amyloid and tau PET imaging, clinical-pathologic studies continue to be the gold-standard for the identification of pathological markers of AD.[39,40] Further, in contrast to using cerebrospinal fluid or other biofluids, using brain specimens allows for definition of regional pathology, a factor which may be important in linking diabetes to dementia, given selective vulnerability of the brain to specific pathologies, including to AD. While many clinical-pathologic studies, including from our group, have examined the relation of diabetes to AD pathology, and found mixed results,[5,13-15,17,24,25,40,41] we are aware of only four studies relating diabetes to AD pathology that directly considered specific brain regions.[3,21-23] The first study, comparing autopsies from about 50 persons with and 50 persons without diabetes, found no relation of diabetes with overall senile plaque or neurofibrillary tangle (Braak stage) scores, but of relevance here, also no relation with either hippocampal or entorhinal neurofibrillary tangles.[21] In the second study of 216 autopsies from the Honolulu-Asia Aging Study, persons with diabetes and *APOE*ε4 (but not diabetes alone) had a three-fold increase in the number of neuritic plaques and a two-and-a-half fold increase in tangles in the hippocampus, as well as an increase in cortical tangles.[3] A third study of nearly 400 autopsies from nursing home residents (16% with diabetes), showed fewer neuritic plaques in the hippocampus, and fewer plaques and tangles in the cerebral cortex, of persons with diabetes compared to those without, in analyses controlling for *APOE*ε4.[22] The fourth study, of 50 persons with diabetes and 89 without from an AD center, showed that persons with diabetes had fewer tangles in the subiculum (p=0.004) and fewer plaques in the temporal lobe (p=0.04), compared to those without diabetes; and there were no associations noted in the other 8 region-specific pathologies.[23]

A clinical-pathologic study with more cases with and without diabetes, and with cases that are derived from community-dwelling persons, may help shed light unto the relation of diabetes with AD. In our study of 250 persons with diabetes and nearly a thousand without, we found that diabetes was not associated with overall or regional measures of AD in the

mesial temporal lobe or neocortex. Also, because some studies have suggested differential relations of diabetes to neuritic plaques and neurofibrillary tangles,[13] we examined individual markers of AD pathology by brain region as well, but found no association of diabetes with neuritic plaques, diffuse plaques, or neurofibrillary tangles in either the mesial temporal lobe or neocortex. To investigate the question further, we considered A1C. To our knowledge, there is no previous pathologic study of A1C and AD pathology, and while A1C is closely related to diabetes, it may better characterize specific groups of persons at risk for complications. Yet our findings were essentially similar in analyses of the subgroup of >400 persons with A1C data (of whom nearly 100 had diabetes), supporting the validity of the findings with diabetes itself. Finally, because the literature suggests that *APOE*ε4 may affect the relationship of diabetes with dementia, including AD dementia, as well as to AD pathology itself,[3,13,41] we conducted additional analyses to explore this possibility. We did not find evidence for effect modification by *APOE*ε4 on either overall or regional measures of AD pathology. Taken as a whole, our study does not support some previously published data that diabetes is associated with AD pathology. Other markers of AD and neurodegeneration such as specific forms of amyloid or tau, synaptic loss, AD pathology in more specific brain regions (e.g., CA1 of the hippocampus), brain insulin resistance, and other factors remain to be explored.[42-46] Likewise, diabetes-related factors not taken into account here could affect results (e.g., age at onset of diabetes, duration of exposure to insulin resistance),[14] and associations may be present in a subgroup of subjects (e.g., defined by medication use;[22] or by biomarkers[13]). Other factors such as genetics (e.g., gene for insulin degrading enzyme), advanced glycation end products, hormones, and their receptors (e.g., insulin, adipokines), inflammatory and immune factors, oxidative stress, and other factors may be involved.[47-50]

Cerebrovascular disease is a likely mechanism linking diabetes to dementia. Indeed, diabetes and elevated A1C increase stroke risk by two-fold,[10,51,52] and clinically and pathologically-defined cerebrovascular disease is amongst the most common causes of dementia.[53-55] Our study confirms that the odds of infarcts is higher in diabetes, in keeping with previously published smaller neuropathologic studies by us and others.[3,5,23,24] Though diabetes has been found to be associated with microinfarcts,[23] in a recent and very large study of >2,300 older persons across several cohorts including ours, diabetes was associated with a higher odds of infarct, and of lacunes in particular, but not microinfarcts, though only cortical infarcts were included.[25] While we did not specifically consider lacunes in the current study, our results are also in keeping with infarcts of a larger size (visible to the naked eye) rather than microscopic infarcts being associated with diabetes. Our understanding of the effect of diabetes on the brain may be enhanced by better defining the location of associated pathology. In this regard, neuroimaging studies have shown that subcortical abnormalities are common.[20] Yet, with current technology, most neuroimaging cannot definitely detect microinfarcts, which remain most accurately identified on neuropathologic evaluation. Our study expands knowledge by considering both size (including very small) and location of infarcts. We found that diabetes is associated with about 80% higher odds of subcortical infarcts, even after controlling for hypertension, and that diabetes is associated with higher odds of both subcortical gross and micro-infarcts. However diabetes was not associated with cortical infarcts, either as a whole or separately for cortical gross or cortical microinfarcts. In

the subgroup with blood biomarker data, A1C was associated with subcortical gross infarcts, but not subcortical microinfarcts or cortical infarcts, whether large or small. Mechanisms linking diabetes to subcortical infarcts, both large and small, may involve systemic and cerebral vessel disease such as atherosclerosis and arteriolosclerosis, inflammation, breakdown of the blood brain barrier, abnormalities in the glymphatic system, and others.[56-58] Finally, diabetes may increase the risk of all-cause dementia, including dementia clinically attributed to AD, by lowering the threshold for the clinical expression of the syndrome of dementia, through the additive effects of cerebrovascular disease and other factors.[55]

Weaknesses and strengths of the study are worth noting. On the one hand, an important limitation is that neuropathology studies cannot determine the direction of associations, specifically whether diabetes occurred before or after the brain pathology. Also, the measure of diabetes was dichotomous and we did not capture potentially important features such as the severity, duration, and complications of disease, nor the management of diabetes. Furthermore, A1C was only measured in about a third of subjects, and was considered at a single time point, not capturing fluctuations in glycemic control over time. On the other hand, several strengths of the study warrant highlighting. Subjects included 250 persons with diabetes and nearly a thousand without, participating in one of three community-dwelling cohort studies with similar design and methodology, and who came to autopsy. Subjects underwent a systematic neuropathologic evaluation, blinded to clinical data. And, neuropathologic data documented the two most common causes of dementia, AD and infarcts, with analyses taking regional pathology into account. Finally, analyses considered whether associations of diabetes with pathology were modified by *APOE*.

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Table 1

Demographic, clinical, and neuropathologic characteristics of subjects*

	Without diabetes	With diabetes	Total
Number of subjects	*978*	*250*	*1,228*
DEMOGRAPHIC			
Age-at-death, years (SD)	88.8 (6.7)	86.9 (6.6)	88.4 (6.7)
Female, n (%)	659 (67%)	135 (54%)	794 (65%)
CLINICAL			
A1C, mean % value (SD)**	5.83 (0.43)	6.52 (0.79)	5.98 (0.60)
Apolipoprotein ε4, n (%)	259 (28%)	50 (21%)	309 (26%)
Hypertension, n (%)	682 (70%)	187 (75%)	869 (71%)
NEUROPATHOLOGIC			
AD pathology***			
Global AD score	0.65 (0.19, 1.13)	0.55 (0.14, 1.05)	0.62 (0.18, 1.11)
Mesial Temporal AD pathology			
Overall Measure	0.65 (0.25, 1.21)	0.54 (0.19, 1.17)	0.64 (0.24, 1.21)
Neuritic Plaques	0.51 (0.00, 1.29)	0.32 (0.00, 1.37)	0.46 (0.00, 1.30)
Diffuse Plaques	0.29 (0.11, 0.89)	0.23 (0.00, 0.77)	0.29 (0.00, 0.86)
Neurofibrillary Tangles	0.76 (0.30, 1.45)	0.55 (0.22, 1.41)	0.73 (0.28, 1.45)
Neocortical AD pathology			
Overall Measure	0.58 (0.09, 1.07)	0.53 (0.06, 0.94)	0.57 (0.08,1.05)
Neuritic Plaques	0.73 (0.05, 1.37)	0.72 (0.03, 1.35)	0.73 (0.05, 1.36)
Diffuse Plaques	0.57 (0.09, 1.25)	0.46 (0.09, 1.01)	0.54 (0.09, 1.21)
Neurofibrillary Tangles	0.05 (0.00, 1.26)	0.03 (0.00, 0.21)	0.03 (0.00, 0.25)
Brain infarcts			
Any infarct(s) present, n (%)	462 (47%)	135 (54%)	597 (49%)
Gross infarcts, n (%)	326 (33%)	103 (41%)	429 (35%)
Microinfarcts, n (%)	272 (28%)	82 (33%)	354 (29%)
Cortical infarcts, n (%)	252 (26%)	65 (26%)	317 (26%)
Subcortical infarcts, n (%)	325 (33%)	112 (45%)	438 (36%)

*Mean (SD), unless otherwise specified

**A1C data available in a subset of 433 subjects

***All AD pathology scores are showing the median (25^{th} percentile, 75^{th} percentile)

Table 2

Relation of diabetes and A1C to AD pathology*

AD pathology measure (outcome)	Odds ratio (95% confidence interval)	
	Diabetes	**A1C**
Global AD score	0.94 (0.73, 1.20)	0.83 (0.62, 1.10)
Mesial Temporal AD pathology		
Overall Measure	0.95 (0.74, 1.22)	0.93 (0.70, 1.23)
Neuritic Plaques	1.05 (0.82, 1.35)	0.94 (0.71, 1.25)
Diffuse Plaques	0.90 (0.69, 1.16)	1.02 (0.77, 1.35)
Neurofibrillary Tangles	0.95 (0.74, 1.22)	0.96 (0.72, 1.27)
Neocortical AD pathology		
Overall Measure	0.97 (0.75, 1.24)	0.79 (0.59, 1.05)
Neuritic Plaques	1.08 (0.84, 1.38)	0.90 (0.68, 1.19)
Diffuse Plaques	0.92 (0.72, 1.19)	0.75 (0.56, 1.00)
Neurofibrillary Tangles	0.85 (0.66, 1.11)	0.79 (0.59, 1.06)

*Separate ordinal logistic models adjusted for age-at-death, centered at 88 years, and sex

Table 3

Relation of diabetes and A1C to infarcts*

Infarct measure (outcome)	Odds ratio (95% confidence interval)	
	Diabetes	**A1C**
Any infarct	1.43 (1.07, 1.90)	1.51 (1.08, 2.12)
Gross infarcts	1.53 (1.14, 2.06)	1.45 (1.04, 2.02)
Microinfarcts	1.33 (0.98, 1.81)	1.21 (0.86, 1.69)
Cortical infarcts	1.03 (0.75, 1.43)	1.18 (0.84, 1.65)
Subcortical infarcts	1.79 (1.34, 2.39)	1.31(0.94, 1.82)

* Separate logistic regressions adjusted for age-at-death, centered at 88 years, and sex