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# Association Between Cerebrovascular Pathology and Anti-Hypertensive Treatment in Diabetics

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Association Between Cerebrovascular Pathology and  
Anti-Hypertensive Treatment in Diabetics

Master of Public Health Capstone

Gary Owen

March 23, 2017

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## **ABSTRACT**

### *Background*

Dementia is a growing public health concern as the population ages. Vascular dementia is the second most common type of dementia behind Alzheimer's, and is caused by cerebrovascular damage, such as infarcts and hemorrhages. As in systemic cardiovascular disease, diabetes and hypertension are leading risk factors for cerebrovascular pathology. Anti-hypertensive treatment (AHT), therefore, may have a role in preventing cerebrovascular damage.

### *Methods*

A case-control study design was utilized to evaluate any association between AHT during life and cerebrovascular pathology in autopsy in diabetic participants from the National Alzheimer's Coordinating Centers (NACC). Pathology outcomes included infarcts of various sizes and arteriolosclerosis. Exposure was classified as any reported use, use at last visit, and percentage of visits with reported use. Adjusted logistic regression was used to compare cases and controls.

### *Results*

Among 484 study participants, 74-90% reported exposure to AHT. Among exposed participants, CVD (54% vs 23%) and hypercholesterolemia (76% vs 61%) were more common. In unadjusted logistic analyses, any infarct and large infarct cases were associated with 1.64 and 2.22 times greater odds of exposure reported at last visit than controls. In multiple adjusted analyses, only cases with large infarct pathology were associated with greater odds of exposure reported at last visit [OR, 95% CI = 2.59 (1.02-

6.59)]. Large infarcts were also associated with increasing percentage of visits with reported AHT.

*Conclusions*

Large infarct pathology was associated with exposure to AHT at last visit and with increased percentage visits with reported AHT. Though not significant for all pathology or exposure definitions, consistent direction and magnitude of effects were seen, suggesting that cerebrovascular pathology may be associated with AHT exposure. Most notably, the odds of exposure to AHT for participants with large infarcts were consistently more than double the odds for controls, regardless of exposure definition or adjustment.

Based on pathophysiology of cardiovascular and cerebrovascular disease, an association between pathology and AHT is surprising and questionable. Despite adjustment for confounders, residual confounding is likely present. This result highlights the complicated time course cerebrovascular pathology and the importance of accurate measurement of risk factors and exposure during life.

## LITERATURE REVIEW

As the population ages, dementia is quickly becoming a major public health concern. Estimates of the prevalence of worldwide dementia range from 27 to 36 million,<sup>1</sup> and annual worldwide costs are estimated to be greater than 600 billion dollars as of 2010.<sup>2</sup> The proportion of the world's population that is over 65 years of age is projected to more than double by 2030.<sup>3</sup> Dementia is primarily a syndrome of the elderly, and all forms of dementia are presently incurable. The risks for Alzheimer's Disease (AD) and vascular dementia (VaD), which are the most common forms of dementia, increase with age, doubling every 4.5 and 5.3 years, respectively.<sup>4</sup> Therefore, the burden of dementia is expected to greatly increase, demanding focused public health intervention.

Vascular dementia is primarily due to small vessel disease in the brain and is estimated to account for approximately 15% of clinically diagnosed AD cases, and 15-20% of all dementia cases, making it the second leading cause of dementia behind Alzheimer's.<sup>3,4</sup> VaD appears to be caused by arteriosclerosis and atherosclerosis of blood vessels in the brain. Brain arteriosclerosis has been associated with decreased cognitive scores and hypertension.<sup>5</sup> In addition to arteriosclerosis and atherosclerosis, specific brain pathology findings of VaD include both large and small infarcts, which can confirm diagnosis at autopsy.

While the exact association between VaD and AD is still unclear, they are not mutually exclusive as several risk factors and pathologic changes in the brain overlap both disorders.<sup>3,6</sup> Mixed dementias (e.g., dementia in the presence of multiple pathologies, such as AD and cerebrovascular disease) become more common with age,

further complicating diagnosis, classification, and treatment.<sup>4</sup> In fact, VaD is often diagnosed as AD and treated with the same medications as AD (acetylcholinesterase inhibitors and NMDA antagonists), despite lack of evidence of benefit.<sup>4</sup>

### ***Diabetes and Dementia***

Diabetes is an enormous public health concern. Between 1980 and 2014, the number of new diabetes diagnoses tripled,<sup>9</sup> and the annual total cost in 2012 was estimated to be \$245 billion.<sup>10</sup> Diabetes is a well-established risk factor for cardiovascular disease and often accompanied by comorbid hypertension. This would suggest that diabetes might also be contributory to VaD and other dementias. However, with studies finding mixed results, the association between diabetes and dementia remains complex and controversial.

Historically, diabetes has been considered a risk factor for dementia, and a recent meta-analysis found diabetes to be associated with greater mortality in dementia.<sup>11</sup> Diabetes has consistently been associated with cognitive decline, and several studies have shown diabetes to be associated with higher risk for AD and VaD, infarcts, brain atrophy, and cellular death in the brain, inflammation, and increased amyloid plaques.<sup>12, 13</sup> There has long been discussion of AD as a potential “type 3 diabetes” due to similarities in insulin resistance and oxidative damage mechanisms.<sup>14</sup> In mouse models, AD pathology has been associated with and induced by diabetes, but human studies with autopsy verified measures have not found an association between diabetes and Alzheimer’s pathology.<sup>12</sup>

For example, an investigation by Sonnen et al. found dementia in diabetics to be associated with vascular pathology more than AD pathology, while dementia in non-

diabetics was associated with more AD pathology. Diabetes was also associated with greater severity of cerebral atherosclerosis.<sup>15</sup> The prospective Vantaa 85+ study found similar results among the “oldest old” (i.e. >85 years). Incidence of dementia for diabetics was twice that of nondiabetics, mortality was 30% higher, and diabetics were more likely to have cerebrovascular pathology and less likely to have Alzheimer’s pathology.<sup>16</sup> In a large neuropathologic study of >2300 participants, diabetics were estimated to have 54-57% greater odds of having any infarct compared to participants without diabetes. No association was found between AD and diabetes for multiple measures of AD pathology.<sup>17</sup> These results were recently confirmed by Pruzin et al. and support the association between diabetes, cerebrovascular disease, and dementia.<sup>18</sup>

### ***Hypertension and Dementia***

In the United States, nearly one-third of adults over 18 years of age have been diagnosed with hypertension, and the prevalence of hypertension increases to nearly two-thirds for adults age 60 and older. Over 80% of adult cases over the age of 60 are treated with medications, while about one-half are controlled (blood pressure less than 140/90).<sup>7</sup> Mid-life hypertension is an established risk factor for dementia and cognitive decline, but the relationship is complex and difficult to fully elucidate given the progressive and long-term nature of hypertension, cardiovascular disease, and dementia.<sup>6</sup>

Hypertension is contributory to both cerebrovascular and cardiovascular diseases, which have been associated with both cerebrovascular and AD pathology.<sup>4</sup> Specifically, hypertension has been associated with pathologic changes in small blood vessels in the brain, including atrophy, microbleeds, and lacunar infarcts. To complicate matters further, AD has also been associated with cerebrovascular disease, and the apolipoprotein

E (*APOE*)  $\epsilon$ 4 allele, an established risk factor for AD, has been associated with cardiovascular disease as well.<sup>6</sup>

Given the interconnectedness of dementia and cardiovascular disease, increasing interest is being focused on early prevention and the role for antihypertensive therapy (AHT). Recent findings from the Framingham Heart Study suggest that observed decreases in incidence of dementia in study participants over the past three decades may be associated with improved cardiovascular health and large increases in the use of AHT.<sup>8</sup>

### ***Antihypertensive Treatment***

Based on the known and suspected pathophysiology of dementia, many studies have investigated the role for AHT in preventing or decreasing progression of dementia. AHTs, including angiotensin converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs),  $\beta$ -blockers, and angiotensin receptor blockers (ARBs), have been shown to decrease or slow cognitive decline in some observational studies, while AHT has shown mixed results in randomized trials.<sup>6,19,20</sup> In addition, some meta-analyses have shown decreased risk of VaD but not AD with AHT.<sup>19</sup> Significant differences in study samples and methods likely contribute to variation in study results.

Most studies have focused on outcomes of cognitive decline or incident dementia and are limited by relatively short follow up times and lack of neuropathology. The long time course of the development of dementia makes for difficult, lengthy, and expensive follow up. Mid-life blood pressure measurements and full knowledge of lifetime exposure to AHT would be ideal but nearly impossible for most studies.

Hajjar et al. investigated the association between ARBs and AD neuropathology at autopsy<sup>21</sup> in participants from the National Alzheimer's Coordinating Center (NACC) database.<sup>22</sup> Their cross-sectional analysis found that ARB treatment was associated with fewer amyloid plaques when compared to other AHT medications and compared to no treatment.<sup>21</sup> ARB treatment was also associated with large artery infarcts and hemorrhage. However, confounding by indication likely explains this, as patients treated with ARBs were more likely to report a history of stroke.

In a longitudinal study of NACC participants without dementia at baseline, Qiu et al. found ACEIs to be inversely associated with diagnosis of dementia (OR: 0.32-68, depending on model) in participants without the *APOE*  $\epsilon$ 4 allele but no association in participants with the allele, suggesting that *APOE*  $\epsilon$ 4 positive clinical AD is less associated with vascular risks than *APOE*  $\epsilon$ 4 negative AD.<sup>23</sup> A limitation of the study is the lack of autopsy to confirm clinical diagnosis, since clinical and neuropathological diagnoses are often discordant.<sup>24</sup>

AHT has also been associated with slowing progression from mild cognitive impairment (MCI) to AD. Wharton et al. showed an association between the use of renin-angiotensin system modifying drugs (ACEIs and ARBs) and lower conversion rates from MCI to AD.<sup>25</sup> The study did not report results for treatment with other medications, and vascular pathology was not investigated. Finally, another study found that AHT with CCB was associated with delayed progression in cognitive impairment regardless of *APOE*  $\epsilon$ 4 allele status.<sup>4</sup>

### ***Hypothesis***

Diabetes and hypertension are well-established risk factors for cardiovascular and cerebrovascular disease, which would suggest a logical association with cerebrovascular pathology typical of vascular cognitive impairment and dementia. Furthermore, observational studies support such an association. The current body of literature shows mixed results regarding the impact of AHT in preventing and slowing development of dementia, but few studies have specifically considered vascular dementia or had the benefit of autopsy confirmation of diagnosis. The novelty of this study is that it investigates the association of AHT with cerebrovascular pathology in a high-risk population of participants with comorbid diabetes. The study hypothesis is that AHT will be associated with less cerebrovascular pathology in our sample of diabetics.

### **METHODS**

#### ***Sample***

The source of data was the National Alzheimer's Coordinating Center (NACC) combined Uniform Data Set (UDS) and Neuropathology Data Set (NP), which compile standardized, longitudinal data on enrolled participants from 34 past and present Alzheimer's Disease Centers (ADCs) across the United States. NACC data have been described previously and are freely available to researchers at [https://www.alz.washington.edu/WEB/researcher\\_home.html](https://www.alz.washington.edu/WEB/researcher_home.html). Because the NACC data are de-identified, no Institutional Review Board (IRB) approval was required for the

current study. However, all ADC studies were covered by IRBs at their home institutions, and all participants provided written informed consent.

Participants were included in the study if diabetes was indicated during follow-up and an autopsy was performed upon death. Diabetes was defined as self-reported history of diabetes or use of any diabetes medication, including insulins, sulfonylureas, biguanides, oligosaccharides, thiazolidinediones, meglitinides, dipeptidyl-peptidase-IV (DPP-IV) inhibitors, amylin analogues, and incretin mimetics. Participants were excluded if information regarding exposure to anti-hypertensive medication was unavailable.

### ***Study Design***

Association between exposure to anti-hypertensive therapy and cerebrovascular pathology was investigated using multiple case-control analyses. Cases were defined by presence of cerebrovascular pathology, including large infarcts (at least 1cm in largest diameter), lacunes (small arterial infarcts or hemorrhages less than 1cm in diameter), microinfarcts (detected microscopically), and amount of arteriolosclerosis (none, mild, moderate, severe). Exposure was considered separately as any reported use of AHT, AHT reported at last visit, and percentage of total visits with reported use of AHT.

### ***Variables***

Continuous variables of interest included age at death, years of education, body mass index (BMI), year of death, and years of smoking. Categorical variables of interest included sex, race (white, black, other), Hispanic ethnicity (yes/no), living situation (alone or with others), residence (private residence; retirement community or independent group living; assisted living, adult family home, or boarding home; skilled nursing facility, nursing home, hospital, or hospice); ADC; history of alcohol abuse (yes/no);

established diagnosis of dementia (yes/no); and current diabetes medication (yes/no). Past medical history of the following comorbidities was considered positive if self-reported as either present/active or remote/inactive: hypertension, stroke (combined transient ischemic attack or stroke), atrial fibrillation, heart attack, congestive heart failure, and hypercholesterolemia. Any history of stroke, atrial fibrillation, heart attack, or congestive heart failure was considered positive for a history of “cardiovascular disease.” Presence of significant Alzheimer’s pathology was also considered and defined as Braak stage V/VI plus moderate to severe CERAD plaque rating.<sup>26</sup>

### ***Statistical Methods***

All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc.; Cary, NC, USA). Descriptive statistics are reported for all variables and outcomes, including frequencies and percentages for categorical variables and mean and standard deviation for continuous variables. Between group comparisons based on any AHT exposure were made using t-tests for continuous variables and chi-square or Fisher’s exact tests for categorical variables.

Unadjusted logistic regression was performed to evaluate any association between exposure to AHT (any AHT, AHT at last visit, and percentage of visits with reported AHT) and cerebrovascular pathology (any infarct, large infarct, lacunar infarct, microinfarct, arteriolosclerosis) with absence of that pathology being the reference category.

Variables were considered as potential confounders based on literature review and known pathophysiology.<sup>5, 13, 27</sup> DAGitty software<sup>28</sup> was utilized to create a directed acyclic diagram (DAG) of the hypothetical relationships of variables (Figure 1) and to

determine the following minimum sufficient adjustment sets to evaluate the association between exposure to AHT and cerebrovascular disease pathology: (1) history of hypertension, history of cardiovascular diseases; (2) history of hypertension, history of cardiovascular diseases, age at death, history of hypercholesterolemia, genetics/family history. Considering CVD as composite variable versus individual cardiovascular disease components (i.e. stroke, myocardial infarction, atrial fibrillation, congestive heart disease) did not significantly change results. Therefore, the composite CVD variable was used for final models. Model 1 adjusted for past medical history of hypertension and past medical history of cardiovascular diseases, while Model 2 also included age at death and hypercholesterolemia. Genetics/family history was excluded from model 2 due to lack of available data.

Using a case-control design, adjusted odds ratios with 95% confidence ratios were calculated for the relationship between each cerebrovascular pathology of interest and exposure to AHT, including any exposure, exposure at last visit, and percentage of visits with reported exposure.

## **RESULTS**

### ***Descriptive Statistics***

From the entire NACC UDS of 32,938 participants, 3,920 (59% of deaths) completed autopsy and 501 autopsied participants were considered diabetics. Of those, 17 participants were excluded for missing data regarding exposure to AHT bringing the total sample size to 484. This sample size varied among analyses based on missing pathology data for each outcome. Figure 2 shows participant inclusion and exclusion.

Study participants were mostly well educated, elderly, white, male, non-smokers living with others. Any exposure to AHT was reported in 81.4% (394/484) of participants, while AHT during last visit was present in 74% (352/475) of participants. On average, exposed participants reported AHT use during 89.7% of visits. The most frequent anti-hypertensive medication classes reported at last visit were:  $\beta$ -blockers (34.9%), ACE inhibitors (28.1%), diuretics (27.9%), calcium channel blockers (19.6%), anti-adrenergics (15.9%), angiotensin II blockers (13.2%), and vasodilators (5.4%).

Comparing exposure groups, those with any exposure to AHT were slightly older (80.1 vs 75.5 years,  $p=0.0005$ ), died about one calendar year later on average (2011.2 vs 2010.4,  $p=0.0061$ ), and had about one more visit on average than unexposed participants (3.5 vs 2.3,  $p<0.0001$ ). Composite cardiovascular disease (54.1 vs 23.1,  $p<0.0001$ ) and individual disease components were more common in those exposed to AHT. Hypercholesterolemia (76.2% vs 60.7%,  $p=0.0028$ ) and length of smoking (13.1 vs 9.2 years,  $p=0.0349$ ) were also greater in the exposed group. Diagnosis of dementia and Alzheimer's pathology were both less common among those with AHT exposure (37.3 vs 51.1%,  $p=0.05$ ). Full descriptive and bivariate statistics can be found in Tables 1 and 2.

Non-significant differences in cerebrovascular pathology were observed between exposure groups. Presence of any infarct and large infarcts were more common in exposed participants, while presence of lacunes, microinfarcts, and arteriolosclerosis were similar. Table 3 shows full results for distribution of cerebrovascular pathology.

### ***Unadjusted Logistic Regression***

Unadjusted logistic regression showed consistent direction and magnitude of association between AHT exposure and cerebrovascular pathology (Table 4). The

presence of any size infarct was associated with 1.64 to 1.72 times greater odds of AHT exposure for different measures of exposure, though the increase was not significant for “any AHT.” The odds of AHT exposure were 2.18 to 2.56 times greater when large infarcts were present compared to lack of large infarcts, though the increase was again nonsignificant for “any AHT.” Likewise, a nonsignificant increase in odds of AHT exposure was seen when lacunes and microinfarcts were present (OR: 1.39-1.51 and 1.05-1.13, respectively). Mild and moderate arteriolosclerosis were also associated with nonsignificantly increased odds of AHT exposure ranging from 18% to 44% for mild and 49% to 59% for moderate. Severe arteriolosclerosis was not associated with any consistent or significant change in odds of AHT exposure.

### ***Adjusted Logistic Regression***

#### **Any AHT**

Neither Model 1 nor Model 2 found any statistically significant association between any cerebrovascular pathology and any known exposure to AHT, though odds of exposure were greater when any size infarcts, large infarcts, mild arteriosclerosis, and moderate arteriolosclerosis were present versus absent. Odds of exposure were 5-35% greater when an infarct of any size was present compared to absence of any infarct. That increase was driven by large infarcts with 2-2.6 times the odds of exposure compared to when large infarcts were absent.

Odds of exposure were 18-24% greater when mild arteriolosclerosis was present versus absent, and odds of exposure were 32-43% greater when moderate arteriolosclerosis was present versus absent. For severe arteriolosclerosis, odds of exposure were lower (OR: 0.61-0.66).

AHT at Last Visit

Similar results were observed when considering exposure as reported AHT at last visit. Odds of exposure were 19-37% greater when infarcts of any size were present versus absent and 18-37% greater when lacunes were present versus absent, though no statistically significant associations were found. The presence of large infarcts, however, was associated with significantly greater odds of exposure in model 1 (OR, 95% CI: 2.59, 1.02-6.58). Model 2 found a much lower and non-significant increase in odds of exposure when large infarcts were present (OR, 95% CI: 2.11, 0.83-5.39).

Odds of exposure were 43-46% and 31-34% greater when mild and moderate arteriolosclerosis was present versus absent, respectively. For severe arteriolosclerosis, odds of exposure were again lower (OR: 0.83-0.85).

Percentage of Visits with AHT

Similar results were again observed when considering exposure as a percentage of total visits with reported AHT. For each unit increase in percentage of visits with reported AHT, odds of pathology increased 18-39% for infarcts of any size and 2-19% for microinfarcts, though no statistically significant associations were found. However, model 1 found that odds of large infarct pathology increased over 300% for each unit increase in percentage of visits with reported AHT (OR, 95% CI: 3.15, 1.13-8.78). Model 2 found a lower increase in odds of large infarct pathology (OR, 95% CI: 2.72, 0.95-7.76).

Odds of arteriosclerosis increased by 10-13% for mild and 26-33% for moderate pathology for a unit increase in percentage of visits with reported AHT, while odds of severe arteriolosclerosis decreased (OR: 0.64-0.68).

## DISCUSSION

In this study sample of elderly diabetic patients, presence of large cerebrovascular infarcts in autopsy was associated with exposure to AHT reported at last visit in one of two models. In addition, odds of large infarct pathology increased with increasing percentage of total visits reporting AHT.

Across multiple definitions of exposure to AHT, consistent direction and magnitude of effects were seen, suggesting that cerebrovascular pathology may be associated with AHT exposure. Most notably, the odds of exposure to AHT for participants with large infarcts were consistently more than double the odds for controls, regardless of exposure definition or adjustment. This larger effect on large infarcts is consistent with past studies of cerebrovascular pathology that have shown more variability in visible infarcts (i.e. large infarcts and lacunes) compared to microinfarcts.<sup>17,18,21</sup>

Given the protective effect of blood pressure control in cardiovascular and cerebrovascular disease, these results should be questioned. Participants exposed to AHT tended to have more comorbidities for which AHT would be indicated, including stroke, hypertension, heart attack, congestive heart failure, and atrial fibrillation. In addition, hypercholesterolemia was more frequent among exposed participants. Cardiovascular diseases and hypercholesterolemia are known risk factors for vascular pathology in the brain and systemically, including vessel stenosis, atherosclerosis, and infarcts. These covariates were included in adjusted models, but residual confounding cannot be ruled out.

The pathophysiological time course must also be taken into consideration. Midlife blood pressure values and lifelong AHT exposure were not known for the study sample. Even participants with multiple visits would have had information limited to the last few years of life, which may not accurately reflect long term cerebrovascular damage or AHT exposure. It is likely that participants exposed to AHT accumulated cerebrovascular damage due to the comorbidities requiring AHT. In that case, significant damage may have already been done regardless of late life AHT.

The same concern exists for diabetes control. In the study sample of diabetics, only 65.9% reported pharmacologic treatment for diabetes at last visit. Likewise, treatment with an ACE inhibitor or ARB is standard of care for diabetic patients with renal or cardiovascular disease (including HTN)<sup>29</sup>, but only 28.1% and 13.2% of participants, respectively, reported use of those medications at last visit. While deviations from standards of care may be warranted in some cases, especially during end-of-life care, early and sustained intervention is vital to prevention of cardio- and cerebrovascular diseases.

It is unlikely that AHT, known to decrease risk of cardiovascular disease, is truly associated with increased cerebrovascular pathology. Given the likely confounding by indication described above, it is possible that the AHT was even somewhat protective against cerebrovascular pathology. Consider the following: those exposed to AHT should be at higher risk of cerebrovascular damage due to underlying disease. If long term damage and/or residual confounding existed, one would expect exposed participants to have more resulting damage. While a consistent trend in that direction was found, perhaps a stronger or more widespread association might have been seen if those

participants had not been exposed to AHT and experienced the full course of their underlying diseases. Thus, the results of this study would fall between the hypothetical results of: (1) a fully controlled comparison of exposed participants (who are adequately treated for underlying disease) and unexposed (i.e. untreated) participants, and (2) the results of a comparison between people with untreated cardiovascular disease and disease-free controls. In the first scenario, AHT should be protective, and in the second, cerebrovascular pathology should be much more common in the group with CVD. Without adequate control for CVD and HTN in the present study, the results should fall in the middle of the hypothetical studies.

To my knowledge, this is the first study of its kind. Other studies have considered AD pathology and AHT as well as diabetes and cerebrovascular pathology but not an association of AHT with cerebrovascular pathology (AD or vascular) specifically in diabetics. Diabetes has consistently been shown to be associated with cerebrovascular pathology, which contributes significantly to dementia especially in older patients. One would expect that effective hypertension and diabetes management throughout life should decrease risk of damage, but the exact association and magnitude of potential protection is unknown without large, lengthy longitudinal studies.

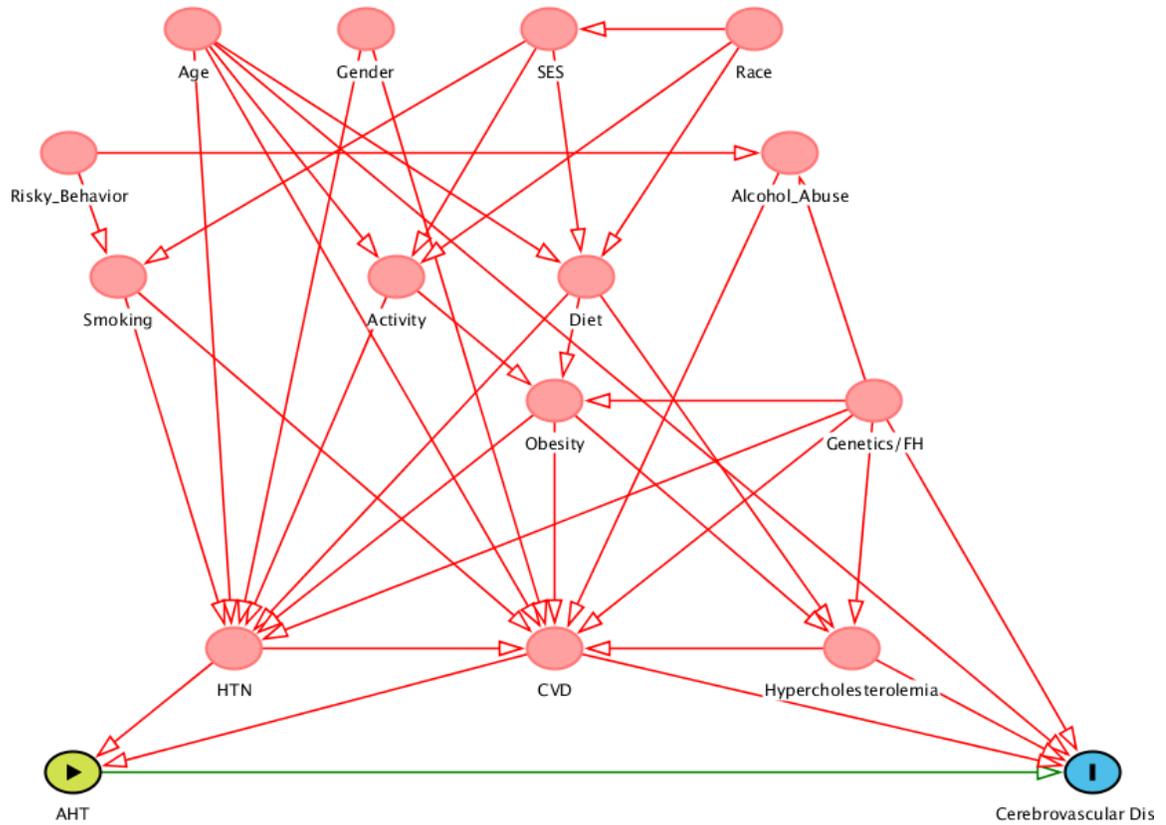
Strengths of this study include multiple measures of AHT exposure, consideration of many AHT medications, consideration of multiple pathological outcomes, and consideration of causal pathways and adjustment for confounders using a DAG model. As mentioned earlier, this study is limited by the quality of exposure measurements, as fully measuring lifetime exposure and degree of cardiovascular disease was not possible.

The study is also limited by selection bias common to a longitudinal study of this nature, as evidenced in the homogeneity of the study sample.

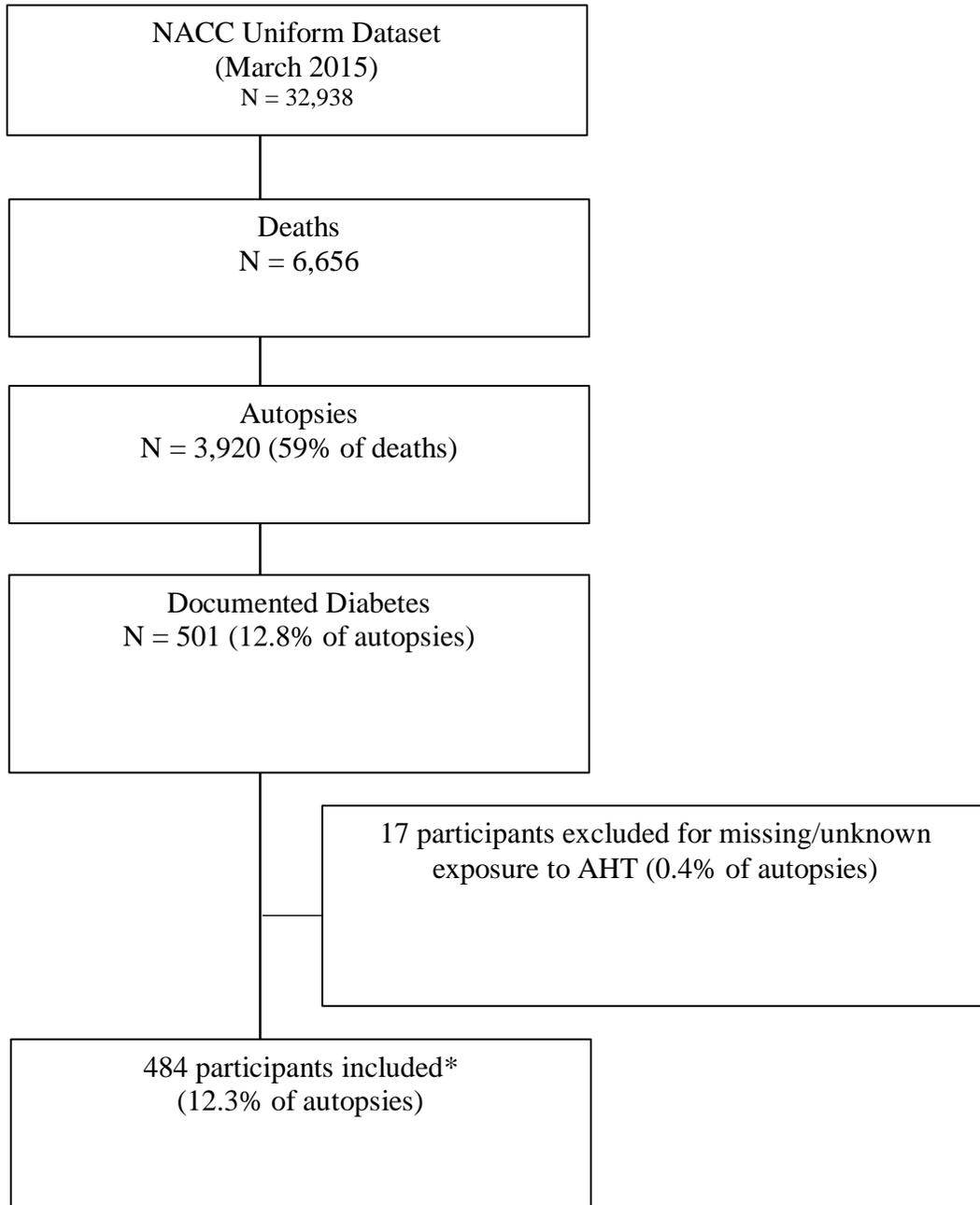
More work is needed to more fully investigate the potential for AHT to protect against cerebrovascular pathology. Ideally, lifelong follow up gathering information regarding morbidities, blood pressure, medications, etc. would be combined with autopsy data to provide a more comprehensive assessment of how blood pressure control affects brain pathology and cognitive impairment. The SPRINT Trial, which tested whether a lower-than-currently-recommended systemic blood pressure goal would be beneficial, included secondary cognitive endpoints, including incidence of dementia and brain volume.<sup>30</sup> However, the study was still limited in follow up and was ultimately discontinued early. As decades-long randomized controlled trials would be unfeasible, more thorough observational studies are the best avenue for future research.

**TABLES AND FIGURES**

**Figure 1: Directed Acyclic Diagram (DAG).** Relationships of covariates and the outcome are shown. Developed using [www.dagitty.net](http://www.dagitty.net). AHT = anti-hypertensive treatment; HTN = hypertension; CVD = cardiovascular disease including atrial fibrillation, congestive heart failure, stroke, and heart attack; SES = socioeconomic status; FH = family history



**Figure 2: Study inclusion and exclusion.**



\*Sample size varied by outcome analyses

**Table 1: Distribution and bivariate analysis of demographic variables.**

<b>Variable</b>	<b>All n = 484</b>	<b>No AHT n = 90</b>	<b>Any AHT n = 394</b>	<b>P-value</b>
Age at Death	79.2 ± 9.7	75.5 ± 11.3	80.1 ± 9.2	0.0005*
Year of Death	2011 ± 2.4	2010.4 ± 2.6	2011.2 ± 2.4	0.0061*
Male	303 (62.6%)	57 (63.3%)	246 (62.4%)	0.8740
Caucasian Race	426 (90.1%)	81 (91.0%)	345 (89.8%)	0.8554
Hispanic Ethnicity	41 (8.5%)	11 (12.2%)	30 (7.7%)	0.1611
Body Mass Index	27.6 ± 5.9	26.3 ± 5.6	27.8 ± 6.0	0.0836
Years of Education	14.5 ± 3.7	14.2 ± 3.9	14.6 ± 3.6	0.3525
Living Alone	57 (11.8%)	6 (6.7%)	51 (12.9%)	0.1014
Residence Type				0.1506
<i>Private Residence</i>	313 (66.2%)	54 (60.7%)	259 (67.5%)	
<i>Retirement Community     or Independent Group     Living</i>	32 (6.8%)	5 (5.6%)	27 (7.0%)	
<i>Assisted living, adult     family home, or     boarding home</i>	54 (11.4%)	9 (10.1%)	45 (11.7%)	
<i>Skilled nursing facility,     nursing home, hospital,     or hospice</i>	74 (15.6%)	21 (23.6%)	53 (13.8%)	
Total Visits	3.3 ± 2.0	2.3 ± 1.9	3.5 ± 2.0	<0.0001*

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as number and percentage.

\* Statistically significant (p<0.05)

**Table 2: Distribution and bivariate analysis of past medical history.**

<b>Variable</b>	<b>All n = 484</b>	<b>No AHT n = 90</b>	<b>Any AHT n = 394</b>	<b>P-value</b>
Hypertension	390 (80.6)	34 (38.6)	356 (90.4)	<0.0001*
Stroke	119 (24.6)	15 (16.7)	104 (26.5)	0.0517
Atrial Fibrillation	96 (19.8)	4 (4.4)	92 (23.5)	<0.0001*
Myocardial Infarction	84 (17.4)	5 (5.6)	79 (20.1)	0.0010*
Congestive Heart Failure	65 (13.4)	1 (1.1)	64 (16.4)	0.0001*
Cardiovascular Disease	234 (48.4)	21 (23.3)	213 (54.1)	<0.0001*
Hypercholesterolemia	352 (72.37)	54 (60.7)	298 (76.2)	0.0028*
Alcohol Abuse	61 (12.6)	6 (6.7)	55 (14.0)	0.0590
Years of Smoking	12.3 ± 16.6	9.2 ± 14.6	13.1 ± 17.0	0.0349*
Diabetes Treatment	319 (65.9)	54 (60.7)	265 (68.7)	0.1485
Dementia	372 (76.9)	82 (91.1)	290 (73.6)	0.0004*
Alzheimer's Pathology	193 (40.7)	46 (52.3)	147 (38.1)	0.0145*

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as number and percentage.

\* Statistically significant (p<0.05)

**Table 3: Distribution and bivariate analysis of cerebrovascular outcomes.**

<b>Neuropathology</b>	<b>All</b>	<b>No AHT</b>	<b>Any AHT</b>	<b>P-value</b>
Any Infarcts (n=373)	147 (39.4%)	23 (29.9%)	124 (41.9%)	0.0545
Large Infarcts (n=373)	52 (13.9%)	6 (7.8%)	46 (15.5%)	0.0804
Lacunae (n=372)	95 (25.5%)	16 (20.8%)	79 (26.8%)	0.2823
Microinfarcts (n=372)	70 (18.8%)	14 (18.2%)	56 (19.0%)	0.8727
Arteriolosclerosis (n=428)				0.4304
None	72 (16.8%)	16 (19.8%)	56 (16.1%)	
Mild	158 (36.9%)	29 (35.8%)	129 (37.2%)	
Moderate	131 (30.6%)	20 (24.7%)	111 (32.0%)	
Severe	67 (15.7%)	16 (19.8%)	51 (14.7%)	

Results expressed as number and percentage.

**Table 4: Unadjusted logistic regression.**

<b>Neuropathology</b>	<b>Any AHT</b>	<b>Last Visit</b>	<b>% of Visits on AHT</b>
Any Infarct	1.69 (0.99-2.90)	1.64 (1.01-2.67)*	1.72 (1.01-2.94)*
Large Infarct	2.18 (0.89-5.31)	2.22 (1.01-4.91)*	2.56 (1.07-6.11)*
Small Infarct	1.39 (0.76-2.56)	1.51 (0.86-2.63)	1.41 (0.77-2.57)
Microinfarct	1.05 (0.55-2.02)	1.08 (0.6-1.96)	1.13 (0.58-2.17)
Arteriolosclerosis			
Mild	1.27 (0.64-2.52)	1.44 (0.78-2.66)	1.18 (0.59-2.37)
Moderate	1.59 (0.76-3.30)	1.52 (0.8-2.87)	1.49 (0.72-3.09)
Severe	0.91 (0.41-2.01)	1.03 (0.50-2.11)	0.91 (0.4-2.04)

Odds ratios and 95% confidence intervals shown.

\* Statistically significant (p<0.05)

**Table 5: Adjusted logistic regression.**

<b>Neuropathology</b>	<b>Any AHT Exposure</b>		<b>Last Visit AHT</b>		<b>% of Visits on AHT</b>	
	<i>Model 1</i>	<i>Model 2</i>	<i>Model 1</i>	<i>Model 2</i>	<i>Model 1</i>	<i>Model 2</i>
Any Infarct	1.35 (0.71-2.56)	1.05 (0.54-2.05)	1.37 (0.78-2.40)	1.19 (0.67-2.12)	1.39 (0.75-2.61)	1.18 (0.62-2.25)
Large Infarct	2.60 (0.88-7.67)	2.02 (0.68-6.05)	2.59 (1.02-6.58)*	2.11 (0.83-5.39)	3.15 (1.13-8.78)*	2.72 (0.95-7.76)
Lacune	1.19 (0.57-2.45)	0.88 (0.42-1.86)	1.37 (0.72-2.60)	1.18 (0.61-2.27)	1.20 (0.59-2.44)	0.97 (0.47-2.02)
Microinfarct	1.09 (0.50-2.39)	0.89 (0.40-1.97)	1.12 (0.56-2.24)	0.97 (0.48-1.95)	1.19 (0.54-2.59)	1.02 (0.46-2.26)
Arteriolosclerosis						
Mild	1.24 (0.56-2.76)	1.18 (0.53-2.66)	1.46 (0.74-2.90)	1.43 (0.71-2.86)	1.13 (0.51-2.49)	1.10 (0.50-2.43)
Moderate	1.43 (0.60-3.43)	1.32 (0.55-3.19)	1.34 (0.65-2.77)	1.31 (0.63-2.72)	1.33 (0.57-3.11)	1.26 (0.54-2.97)
Severe	0.66 (0.26-1.68)	0.61 (0.24-1.57)	0.85 (0.38-1.90)	0.83 (0.37-1.87)	0.68 (0.27-1.75)	0.64 (0.25-1.65)

Model 1 adjusted for HTN and CVD. Model 2 adjusted for HTN, CVD, age at death, and history of hypercholesterolemia. Odds ratios and 95% confidence intervals shown.

\* Statistically significant (p<0.05)

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## **BIOGRAPHICAL SKETCH**

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