Brain Changes in the Elderly and Mortality Risk

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Summary

In this prospective cohort study, 735 elderly, relatively healthy adults were followed after receiving magnetic resonance imaging (MRI) scans. We aim to determine whether brain changes as detected by MRI are associated with increased mortality risk over time. We consider MRI changes in the context of several other variables on a subject's demographic attributes, behavior, and disease status. Using Cox regression methods, we found that changes in the levels of atrophy and brain lesion volume were associated with earlier mortality, even after adjusting for several other known predictors of mortality risk including age, sex, history of coronary heart disease, creatinine levels, diabetes status, and systolic blood pressure ($p=0.0077$ and <0.0001, respectively). Each unit increase for atrophy (on a 0-100 point scale) and lesion volume (cm^3) was associated with a 1.9% (95% CI: 0.51%, 3.4%) and 1.1% (95% CI: 0.65%, 1.6%) increase in mortality risk on average, respectively. Measures of white matter changes were found not to be associated with early mortality after the same adjustments (5.4% higher hazard [95% CI: 6.4% lower, 18.8% higher]; $p=0.387$). We discuss the role of these brain changes in relation to commonly-used predictors of mortality risk and the potential role of MRI as a clinical diagnostic tool.

Background

In recent years, magnetic resonance imaging (MRI) have been utilized to great effect as a diagnostic tool for brain abnormalities. However, the clinical significance of many brain changes observed in the elderly remain uncertain. Further, it is uncertain whether these brain changes are a natural part of the aging process, a sign of other known disease processes, or a risk factor or measure of some other unknown disease processes. Of particular interest is the clinical significance of the phenomenon of brains shrinking (atrophying) with age, the phenomenon that white matter in the brain tends to show up brighter on MRI scans for elderly adults, and areas of the brain that look like dead tissue (infarct-like lesions) in elderly adults. For this analysis, we focus on these brain changes in elderly adults and how they relate to other disease processes and risk factors.

Questions of Interest

1. What associations exist between the prevalence of global brain atrophy, white matter changes, and infarct-like lesions detected on MRI and the available data on participant demographics (age, sex, weight, height), behavior (smoking, alcohol consumption, physical activity), disease status (self-perceived health status and pre-existing cardiovascular, cerebrovascular, or metabolic disease), and various clinical and laboratory measures of organ system functioning (e.g, blood pressure, liver function, kidney function, lung function, mental functioning)?

2. What associations exist between the prevalence of MRI changes and mortality?

3. Are any of the MRI changes predictive of mortality beyond the predictive capabilities of the available non- MRI variables?

4. Do the changes on MRI reflect underlying risk factors for death separate from other known disease processes (such as cardiovascular disease, kidney disease, diabetes, high blood pressure), or are the MRI changes merely signs of those disease processes?

Note that while question 3 asks about predictive capabilities of variables in the dataset, our analyses are solely concerned with explanatory modelling. While the models we fit in the analysis can technically be used for predictive purposes, the models were chosen and assessed based on current data only, and no evaluation of predictive ability was made. Hence, the following analyses will assess any evidence in favor of MRI changes having better explanatory ability for mortality beyond that of other non-MRI variables.

For question 4, while we are interested in whether or not the association of MRI changes with mortality are causally independent of other known disease processes. Our statistical analysis can provide evidence for or against MRI changes being associated with mortality and being associated with other disease processes, but to determine whether MRI changes are causally related to those disease processes we can only rely on prior beliefs.

Data source and description

Data source and study design

The MRI and Cerebral Atrophy dataset contains data collected from a prospective cohort study of adults aged 65 and older, where the subjects were generally healthy adults randomly selected from Medicare rolls. According to the data description, agreement to participation was high; hence it is likely that the sample reasonably accurately characterizes healthy elderly adult Americans. Incidence of cardiovascular disease and cerebrovascular disease as well as all serious medical events were observed over an 11 year period. Data regarding behavioral, functional and clinical measures were recorded at the time of enrollment as well as annually over the length of the study. Approximately three years into the follow-up for this study, magnetic resonance imaging (MRI) scans were performed on the brains of the participants.

Data description and completeness

Data are available for 735 participants on MRI, behavioral, functional, and clinical measures in the period of time prior to or at MRI, as well as incidences of death, cardiovascular disease, and cerebrovascular disease in the 6 years after the MRI scans were performed (conditional on follow-up time and death) and demographical data. Participants were followed for a minimum of 5 years. Time to death from date of MRI scan was recorded for participants who were observed to die during follow-up, and time to death from date of MRI scan was considered to be *censored* for participants who were still alive at the end of the study period or were lost to follow-up; that is, we know that the time to death is greater than the time of observation, but no more than that. The data available to us can be grouped into demographic data, behavioral data, disease status, MRI data, and functional and clinical measures data.

Under demographic characteristics, we have data on the participants' gender and race (black, white, Asian, or other), as well as age (in years), weight (in pounds), and height (in centimeters) at time of MRI. All of this data is complete.

Under behavioral data, we have data on the participants' smoking history (in pack years, where one pack year is equivalent to smoking one pack of cigarettes per day per year), years quit (number of years since quitting smoking, with 0 recorded for current smokers and never smokers), average alcohol intake in the two weeks prior to MRI (drinks per week, where 1 drink = 1 oz. whiskey, 4 oz. wine or 12 oz. beer), physical activity for the week prior to MRI (measured in 1000 kcal). 1 participant had missing data for smoking history.

Under disease status, we have data on diagnoses of congestive heart failure (chf), coronary heart disease(chd), stroke, and diabetes prior to MRI, and death of the participant (if observed during follow-up after the MRI), as well as the participants' views of their own health (1 = excellent, 2 = very good, 3 = good, 4 = fair, 5 = poor). This data was complete.

Under functional and clinical measures data, we have data on the participants' low density lipoprotein (LDL) (in mg/dl), albumin (in g/L), creatinine (in mg/dl), platelet count (in 1000s per cm^3), systolic blood pressure (SBP) (in mmHg), ratio of systolic blood pressure measured in the participant's ankle at the time of MRI to the systolic blood pressure measured in the participant's arm (AAI), forced expiratory volume (FEV) (in L/s), and score on the Digit Symbol Substitution Test (scored from 0-100) at time of MRI. Albumin is a marker for normal liver function, creatinine is a marker for normal kidney function, platelet counts are a marker for chronic disease or infections, LDL and SBP are risk factors for cardiovascular disease and heart disease, AAI is a marker for extent of arterial disease, and FEV is a marker for normal lung function, and DSST score is a measure of cognitive function. There were small amounts of missing data for these variables; see Table 1 for a complete count of missing data for each variable.

Under MRI measures data, we have data on a measure of global brain atrophy detected on MRI (measurements of the degree of ventricular enlargement relative to predicted ventricular size, rescaled to be from 0-100), with zero indicating no enlargement and 100 indicating the most severe degree of atrophy, a measure of white matter changes (a grade assigned by radiologists between 0-9, where zero is no changes and 9 is marked changes), number of distinct regions identified on MRI scan which were suggestive of infarcts, and a measure of the total volume of the infarct-like lesions (in cm^3). One participant was missing data for volume of infarct-like lesions, and one participant was missing data for the measure of white matter changes.

To help summarize the data, univariate descriptive statistics have been included in Table 1 for all variables except for number of years since quitting smoking. For many diseases, pack years is sufficiently informative, so for simplicity, pack years was used as a measure of smoking for participants.

Statistical Methods

In this analysis, if variables involved had missing data, those observations were dropped. This is called a *complete case analysis*; it assumes that the data is missing at random given the included variables. It is impossible to verify whether this assumption is valid or not. However, the number of missing observations is generally small relative to the sample size, and hence we can hope that it does not bias the analysis in a significant way.

Due to the presence of censored variables within the dataset, we used proportional hazard (Cox) regression to make inferences and Kaplan-Meier curves to visualize the relationship between predictor variables and mortality. These methods assume *non-informative censoring*; censored subjects are assumed to have the same mortality hazard rate as uncensored individuals. It is not only difficult to verify this assumption, but it is also potentially unrealistic; for example, participants who are sicker may be more likely to withdraw from the study due to the inconvenience and strain of study participation. It is impossible to detect informative censoring in the data set; however, we rely on the strength of the study design to minimize any potential bias that may result from subject loss to follow-up.

To examine the association between MRI changes and mortality, we conducted Cox regressions. In addition to tracking whether subjects had died by the end of the study, Cox regressions take advantage of information about how long subjects survived, and assumes that the ratio of instantaneous mortality rates is constant in time between groups defined by the predictors. We assess differences between groups in terms of the hazard rate, that is, how likely a subject is to die at any given point in the study. For research question 2, we conducted Cox regressions looking at the crude association between all-cause mortality and MRI changes (brain atrophy, white matter changes and infarct-like lesions). For question 3, we looked at the same associations, but adjusting for commonly used predictors of mortality, like age and sex. This allows us to

assess whether MRI changes may be used as a diagnostic tool to assess a patient's life expectancy, above and beyond what is commonly used in clinical practice. For question 4, we additionally adjusted for the presence of several diseases, including coronary heart disease, creatinine (an indicator of kidney disease), diabetes and systolic blood pressure (sbp). This reduces the possibility that an apparent association between MRI changes and mortality is truly just a reflection of being afflicted with a disease. For example, if having diabetes increases a subject's probability of death and also induces MRI changes, it would create a false association.

Statistical significance of associations are assessed with p-values from testing hypotheses that true regression parameters are zero using Wald tests. The regression parameters generally indicate amount of change in the response variable relative to amount of change in the predictors with all other included predictor variables equal. P-values can be interpreted as the probability of seeing results from the data equal to or more extreme than what we actually observed, given that the null hypothesis is true; if it is lower than a pre-specified significance level, then we say that we have evidence against the null hypothesis. In this report, the pre-specified significance level will be 0.05.

Results

Descriptive Statistics and Crude Associations (question 1)

Descriptive statistics are included in Table 1 for all non-MRI related variables, stratified by groups defined by global brain atrophy, white matter changes, and volume of infarct-like lesions detected on MRI. Groups defined by global brain atrophy and white matter changes were defined by tertiles. As the majority of the participants did not have infarct-like lesions, groups defined on infarct-like lesions were defined as > 0 volume of infarct-like lesions and zero volume infarct-like lesions. This is equivalent to grouping by whether the participant had infarct-like lesions or not. Hence, stratification on groups defined by number of infarct-like lesions were not included in Table 1. Note that while means and standard deviations are reported for patient behavior variables, as they are heavily skewed variables, in a table we would include in a manuscript, we would be more likely to report median and interquartile range; as such, those descriptive statistics are included in Table 1.3. Based on a linear regression analysis with all patient-related variables included as predictors and global brain atrophy as the response, we find that there is evidence that age, sex, and the score on the DSST are associated with global brain atrophy (p-values < 0.0001). In particular, the mean global brain atrophy for participants is 0.8160 higher than participants one year younger of the same sex and with the same score on DSS, the mean global brain atrophy for male participants is 6.168 higher than female participants of the same age scoring the same score on DSST, and the mean global brain atrophy for participants is 0.1578 higher than participants of the same age and sex scoring one value lower on the DSST.

The association between both age and sex and global brain atrophy are supported by stratified descriptive statistics in Table 1. Based on a linear regression analysis with all patient-related variables included as predictors and volume of infarcts as the response, we find evidence that age, height and DSST are associated with white matter changes (p-values = < 0.0001, 0.0120, 0.0046). In particular, the mean extent of white matter changes for participants is 0.05575 higher than participants one year younger of the same height who scored the same on the DSST. The mean extent of white matter changes for participants is 0.01090 lower than participants 1 cm shorter of the same age who scored the same on the DSST, and the mean extent of white matter changes for participants is 0.01578 lower than participants of the same age and height who scored one unit lower on the DSST.

Based on a linear regression analysis with log transformed response with all patient-related variables included as predictors and volume of infarcts as the response, we find evidence that a history of stroke is associated with infarct-like lesions (p-value < 0.0001). In particular, the geometric mean volume of infarct-like lesions for

participants with a history of stroke is 398.1% higher than participants without a history of smoke, adjusted for all other patient-related variables. Confidence intervals, estimates, and p-values were reported in Table 2.

Survival analyses, crude and adjusted (questions 2, 3 and 4)

For the Cox regressions examining the crude associations between mortality and MRI changes (question 2), all of the MRI changes were strongly associated with increased mortality risk (Table 3-1). A one-unit increase in atrophy was associated with a 3% higher (1.8% to 4.4% higher) hazard rate. A one-unit increase in white matter changes was associated with a 14% higher (2.7% to 27.4% higher) hazard rate. A one-unit increase in lesion volume was associated with a 1.4% higher (1.0% to 1.8% higher) hazard rate.

There were mixed results in the age- and sex-adjusted Cox regressions examining the association between MRI changes and mortality (question 3). Table 3-2 shows that atrophy and lesion volume remained strongly associated with mortality risk, but the association with white matter was no longer statistically significant. Adjusting for age and sex, a one-unit increase in atrophy was associated with a 1.8% higher (0.04% to 3.2% higher) hazard rate. There was no evidence of association with white matter changes ($p = 0.258$). A one-unit increase in lesion volume was associated with a 1.4% higher (0.9% to 1.8% higher) hazard rate.

For the regressions that adjusted for age, sex, coronary heart disease, creatinine, diabetes and systolic blood pressure (question 4), we found that the association with mortality risk remained statistically significant for atrophy and lesion volume, but there was no evidence of white matter changes ($p = 0.387$). A one-unit increase in atrophy level was associated with a 1.9% higher (0.5% to 3.4% higher) hazard rate. A one-unit increase in lesion volume was associated with a 1.1% higher (0.6% to 1.6% higher) hazard rate.

Kaplan-Meier survival curves were created to aid in visualizing the relationship between death and atrophy, white-matter, and lesion volume with 95% confidence intervals, as shown in Figure 1. Within group differences between the variables dichotomized by their median values suggest that there are differences in time to death when the MRI variables are examined as high versus low atrophy value, white matter count, and lesion volume.

Discussion

Although clinicians have identified changes in patients' brains between MRI visits, the relationship between data gleaned from MRIs and one's mortality risk has yet to be identified. The observational study examined whether brain changes observed from MRI imaging techniques (atrophy, white matter, lesions) can be used to predict mortality, and whether those predictions are beyond the current capabilities of the non-MRI variables. From these data, measures of atrophy, white matter changes, and brain lesion volume derived from MRIs were all found to be strongly associated with mortality unadjusted for other variables (atrophy: 3.1% hazard, $p<0.0001$, 95% CI (1.8%, 4.4%); white matter: 14.4% hazard, $p=0.0142$, 95% CI (2.7%, 2.74%); lesion volume: 1.4% hazard, $p<0.0001$, 95% CI (1.0%, 1.8%)) however the data was further scrutinized to see whether these predictions hold when controlling for demographic, behavioral, disease, and clinical measures. When controlling for demographic data, atrophy and lesion volume were still strong predictors of mortality (atrophy: 1.9% hazard, $p=0.0077$, 95% CI (0.51%, 3.4%); brain lesion: 1.1% hazard, $p<0.0001$, 95% CI (0.65%, 1.6%)), however, white matter changes were no longer a reliable predictor of an individual's mortality (5.4% hazard, $p=0.387$, 95% confidence interval (-6.4%, 18.8%)). These conclusions are supported by the high degree in statistical evidence (low p-values for atrophy and lesions), and the magnitude of the estimates.

Based upon these results, the measures of atrophy and lesion volume derived from MRIs appear to be of strong clinical importance in determining an estimate of an individual's mortality, with lower atrophy and lesion

volume levels being associated with a significant decrease in overall mortality. Of note, however, is how changes in white matter were not generally associated with mortality. As the association disappeared when adjusting for age and sex, we suspect that white matter increases may just be signs of one's sex or age, and not an indication of one's mortality risk. Of all the variables derived from an MRI, white matter was the only variable in which the values were subjective. We suspect that the subjectivity regarding the white matter score may be a factor in its lack of significance, and it would be of interest in future studies to look at inter-rater reliability between white matter scores to determine if it is truly associated with mortality. Note that a predictive analysis was not conducted for predictive ability of MRI measures for mortality risk; future analyses could include a predictive analysis as well.

Tables and Figures

Table 1: Univariate and stratified descriptive statistics for patient MRI measures, demographics, behavior, disease status, and measures of organ system functioning

Table 1.1

MRI Measures (N = 735)	Missing	Mean	S.D.	Interquartile Range	Min-Max
Atrophy (0-100)	0	35.98	12.92	27.00-44.00	5.00-84.00
White Matter Changes (0-9)	1	2.007	1.41	1.000-3.000	0.000-9.000
Volume of Infarct-like Lesions (cm3)	1	3.223	17.36	0.000 - 0.09420	0.000-197.0
Number of Infarct-like Lesions	0	0.6109	0.9895	0.000-1.000	0.000-5.000

Table 1.2

		Patients Stratified by MRI Measures (n = 735, NA = 2 ****)								
		Atrophy (0-100)			White Matter Changes (0-9)			Volume of Infarct-like Lesions (cm^3)		All Patients
		Low (0-29.56) (n = 242)	Moderate (29.89-41) (n = 260)	High (41-100) (n = 231)	Low (0-1) (n = 327)	Moderate (2) (n = 189)	High (3-9) (n = 217)	Zero volume (n= 466)	> Zero Volume (n= 267)	
Patient demographics	Age (yrs)	72.9 (4.49; 65.0 - 89.0) *	74.4 (5.29; 65.0 - 90.0)	76.5 (5.96; 67.0 - 99.0)	73.2 (4.52; 65.0 - 90.0)	74.8 (5.60; 65.0 - 99.0)	76.3 (6.07; 67.0 - 95.0)	74.0 (5.14; 65.0 - 95.0)	75.5 (5.84; 66.0 - 99.0)	74.6 (5.46; 65.0 - 99.0)
	Male	37.19% **	49%	64%	48%	49%	53%	48%	52%	50%
	Weight (lbs)	158.1 (31.48; 88.00 - 264.0)	159.3 (31.86; 74.00 - 253.0)	162.6 (28.66; 97.00 - 258.0)	161.4 (31.46; 88.00 264.0)	161.1 (29.48; 74.00 - 258.0)	156.8 (30.74; 86.00 - 244.0)	160.4 (31.47; 74.00 - 258.0)	159.1 (29.57; 86.00 264.0)	159.9 (30.77; 74.00 - 264.0)
	Height (cm)	164.5 (9.995; 139.0 - 189.5)	165.8 (9.545; 142.0 - 190.5)	167.0 (9.503; 140.5 - 188.3)	166.5 (9.985; 142.0 190.5)	165.2 (9.262; 140.5 - 185.0)	165.2 (9.691; 139.0 - 188.3)	166.0 (9.933; 139.0 - 189.5)	165.5 (9.353; 141.0 190.5)	165.8 (9.722; 139.0 - 190.5)
Patient behaviour	Smoking history (pack yrs) (NA = 1)	17.34 (24.29; 0.0 - 180.0)	20.96 (28.89; 0.0 - 240.0)	20.60 (27.85; 0.0 - 140.0)	19.03 (27.18; 0.0 - 240.0)	20.24 (27.99; 0.0 - 180.0)	20.08 (26.38; 0.0 - 111.0)	17.76 (23.63; 0.0 111.0)	22.97 (32.14; 0.0 - 240.0)	19.65 (27.13; 0.0 - 240.0)
	Alcohol consumption (drinks/wk)	1.497 (3.802; 0.0 - 21.50)	2.325 (5.297; 0.0 - 35.00)	2.517 (5.267; 0.0 - 28.50)	2.186 (4.733; 0.0 - 28.50)	1.341 (3.742; 0.0 - 23.00)	2.672 (5.756; 0.0 - 35.00)	2.384 (5.270; 0.0 35.00)	1.638 (4.004; 0.0 - 21.50)	2.112 (4.858; 0.0 - 35.00)
	Physical activity (1000 kcal)	2.118 (2.074; 0.0 - 13.04)	1.919 (2.192; 0.0 - 13.81)	1.709 (1.847; 0.0 - 13.25)	1.934 (1.970; 0.0 - 13.81)	1.822 (2.060; 0.0 - 12.25)	1.980 (2.173; 0.0 - 13.25)	1.905 (2.091; 0.0 13.81)	1.943 (1.989; 0.0 - 12.25)	1.919 (2.053; 0.0 - 13.81)
Disease status	CHF	3%	8%	5%	4%	6%	6%	4%	8%	5%
	CHD	27%	33%	41%	25%	41%	39%	26%	47%	33%
	Stroke	14%	23%	35%	14%	36%	27%	12%	43%	23%
	Diabetes	8%	13%	10%	10%	11%	12%	9%	15%	11%
	General health (1-5) *****	2 (3-3)***	2 (3-3)	2 (3-3)	2 (3-3)	2 (3-3)	2 (3-3)	2 (3-3)	2 (3-3)	2 (3-3)
Measures of organ system functioning	LDL (mg/dl) (NA = 10)	124.5 (32.59; 11.00 - 247.0)	128.8 (33.67; 57.00 - 218.0)	124.2 (34.39; 37.00 - 227.0)	126.7 (31.98; 11.00 225.0)	126.4 (33.30; 46.00 - 247.0)	124.3 (36.15; 37.00 - 227.0)	125.7 (32.27; 37.00 - 225.0)	126.3 (35.77; 11.00 247.0)	125.9 (33.57; 11.00 - 247.0)
	Albumin (g/L) (NA = 2)	3.969 (0.2538; 3.300 - 4.800)	4.006 (0.2739; 3.200 - 4.900)	4.010 (0.2785; 3.200 - 5.000)	3.991 (0.2614; 3.200 - 4.800)	4.030 (0.2845; 3.300 - 5.000)	3.971 (0.2650; 3.200 - 4.700)	4.001 (0.2620; 3.200 - 5.000)	3.984 (0.2815; 3.300 - 4.900)	3.995 (0.2692; 3.200 5.000)
	Creatinine (mg/dl) (NA = 2)	1.005 (0.2674; 0.5000 - 3.200)	1.066 (0.3380; 0.5000 - 4.000)	1.122 (0.2859; 0.5000 - 2.600)	1.012 (0.2313; 0.5000 - 1.800)	1.127 (0.3383; 0.6000 - 3.200)	1.087 (0.3506; 0.5000 - 4.000)	1.034 (0.2871; 0.5000 - 4.000)	1.116 (0.3232; 0.6000 - 3.200)	1.064 (0.3031; 0.5000 - 4.000)
	Platelet count (1000's per mm^3) (NA = 7)	248.3 (66.28; 103.0 - 539.0)	249.4 (67.58; 92.0 463.0)	240.1 (63.24; 100.0 - 462.0)	243.9 (66.39; 100.0 539.0)	246.0 (65.81; 92.0 463.0)	249.5 (65.22; 128.0 - 490.0)	246.8 (64.70; 100.0 - 464.0)	244.9 (67.93; 92.0 - 539.0)	246.1 (65.84; 92.0 - 539.0)
	SBP (mm Hg)	117.0 (129.0 - 139.0)	118.0 (130.0 - 144.0)	118.0 (129.0 - 145.0)	116.0 (128.0 - 137.5)	118.0 (131.0 - 144.0)	120.0 (133.0 - 147.0)	117.2 (129.0 - 139.0)	119.0 (133.0 - 146.0)	118.0 (130.0 - 142.0)
	AAI (NA = 9)	1.130 (0.1577; 0.5486 - 1.711)	1.087 (0.1869; 0.4211 - 1.652)	1.091 (0.1979; 0.3171 - 1.728)	1.134 (0.1693; 0.4605 - 1.728)	1.087 (0.1962; 0.3171 - 1.652)	1.069 (0.1816; 0.4540 - 1.632)	1.119 (0.1645; 0.4605 - 1.728)	1.074 (0.2071; 0.3171 - 1.711)	1.102 (0.1823; 0.3171 - 1.728)
	FEV (L/s) (NA = 10)	2.221 (0.6796; 0.5975 - 4.010)	2.184 (0.6938; 0.5695 - 4.471)	2.224 (0.6871; 0.4083 - 4.270)	2.300 (0.6961; 0.5975 - 4.270)	2.127 (0.6906; 0.4083 - 4.471)	2.142 (0.6536; 0.5695 - 4.095)	2.247 (0.7024; 0.4083 - 4.471)	2.143 (0.6537; 0.5695 - 4.270)	2.209 (0.6864; 0.4083 - 4.471)
	DSST (0-100) (NA = 12)	40.70 (11.64; 0.000 - 81.00)	40.88 (12.54; 0.000 - 73.00)	41.75 (13.94; 8.000 - 82.00)	44.02 (12.22; 0.00 - 81.00)	40.16 (13.16; 10.00 - 82.00)	37.37 (11.94; 0.00 68.00)	42.72 (12.82; 0.0 82.00)	38.21 (11.98; 0.0 - 69.00)	41.09 (12.70; 0.000 - 82.00)

* Mean (S.D.; Min - Max) *** Median (interquartile range) ***** Self-reported (high to low)

** Proportion **** Missing cases were not included in summary statistics.

Table 1.3

		Patients Stratified by MRI Measures (n = 735, NA = 2 ****)								
		Atrophy (0-100)			White Matter Changes (0-9)			Volume of Infarct-like Lesions (cm^3)		All Patients
		Low (0-29.56) (n = 242)	Moderate (29.89-41) (n = 260)	High (41-100) (n = 231)	Low (0-1) (n = 327)	Moderate (2) (n = 189)	High (3-9) (n = 217)	Zero volume (n= 466)	> Zero Volume (n= 267)	
Patient behaviour	Smoking history (pack yrs) (NA = 1)	5.500 (0.0-29.35)	8.700 (0.0, 34.31)	6.250 (0-36.88)	5.500 (0.0, 34.50)	7.750 (0.0, 35.50)	6.750 (0.0, 32.63)	5.600 (0.0, 32.00)	9.404 (0.00, 39.00)	6.750 (0.0, 33.76)
	Alcohol consumption (drinks/wk)	0.000 (0.0, 0.692)	0.01920 (0.0-1.250)	0.05700 (0.0-2.000)	0.01920 (0.0, 1.269)	0.00 (0.00-0.750)	0.01920 (0.0, 1.750)	0.01920 (0.00, 1.264)	0.000 (0.000-1.000)	0.01920 (0.0, 1.038)
	Physical activity (1000 kcal)	1.478 (0.6347, 3.007)	1.260 (0.5400, 2.2502)	0.5325 (1.140, 2.291)	1.369 (0.5850, 2.509)	1.185 (0.5400, 2.332)	1.369 (0.5850, 2.509)	1.266 (0.5738, 2.430)	1.365 (0.4750, 2.756)	1.305 (0.5520, 2.510)

* Median (Interquartile range)

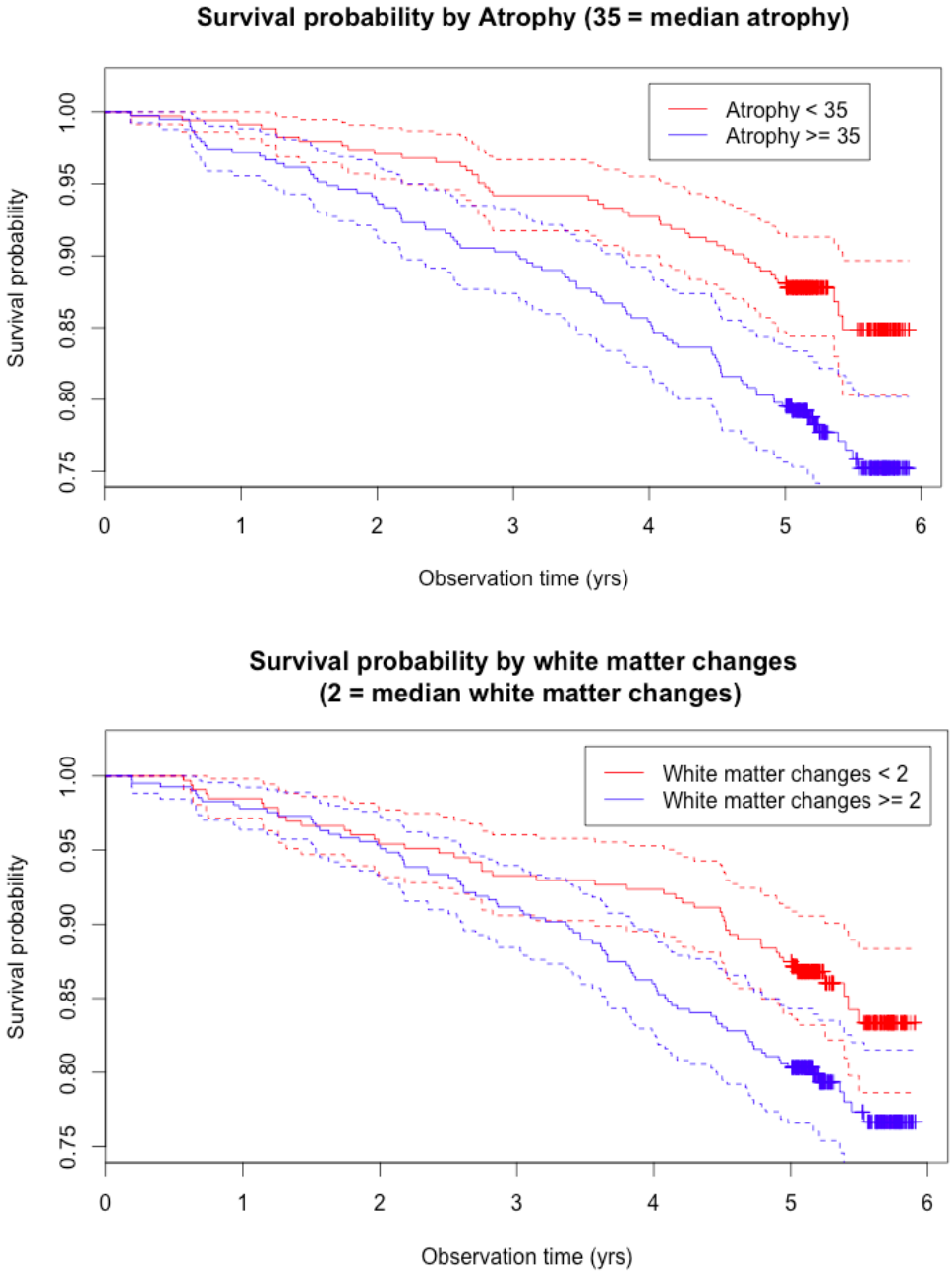
Table 2: Inferential Statistics for Question 1

Atrophy model	Estimates	95% Robust S.E. Confidence Interval	P-Value
Age	0.8160	(0.6340, 0.9980)	<0.0001
Male	6.168	(4.449, 7.887)	<0.0001
DSST	0.1578	(0.08398, 0.2317)	<0.0001

White matter model	Estimates	95% Robust S.E. Confidence Interval	P-Value
Age	0.8160	(0.6340, 0.9980)	<0.0001
Height	-0.01090	(-0.02059, -1.202e-03)	0.0277
DSST	-0.01578	(-0.02375, -7.81e-03)	0.0001

Volume of Infarct-like lesions model	Exponentiated Estimates	95% Robust S.E. Confidence Interval	P-Value
Stroke	4.981	(3.362, 7.379)	<0.0001

Figure 1: Survival curves, stratified by groups defined by MRI measures as well as potential confounders and precision variables



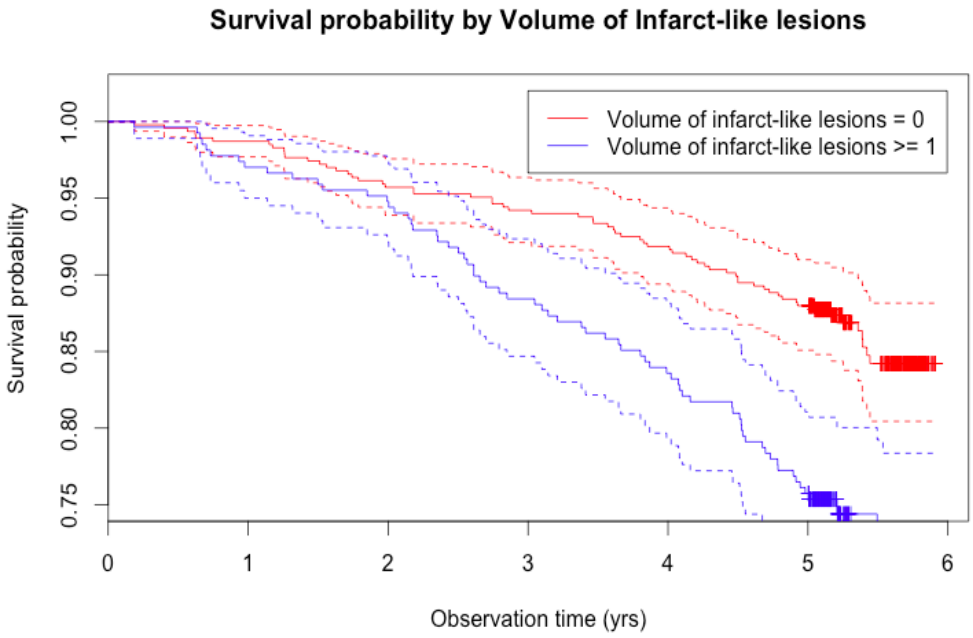


Table 3: Inferential statistics for Questions 2-4

3-2. Cox Regression

Unadjusted MRI	Hazard	95% Confidence Interval	P-Value
Atrophy	1.030879	1.018, 1.044	<0.0001
White matter changes	1.14412	1.027, 1.274	0.0142
Lesion volume	1.014064	1.01, 1.018	<0.0001

3-3. Cox Regression Adjusting for Age and Sex

Adjusted MRI (age, sex)	Hazard	95% Confidence Interval	P-Value
Atrophy	1.018	1.004, 1.032	0.01001
White matter changes	1.068	0.9529, 1.197	0.258
Lesion volume	1.013619	1.009, 1.018	<0.0001

3-4. Cox Regression Adjusting for Age, Sex, CHD, CRT, Diabetes, and SBP

Adjusted MRI (age, sex, chd, crt, diabetes, sbp)	Hazard	95% Confidence Interval	P-Value
Atrophy	1.019	1.0051, 1.034	0.007699
White matter changes	1.054	0.9356, 1.188	0.386540
Lesion Volume	1.011	1.0065, 1.016	<0.0001