MAP: ABP and CBF/CVR
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1 Project Overview

1.1 Background

- Alzheimer's disease (AD) impairs short-term memory and affects one's ability to manage through daily life.
- Disease progresses from normal cognition through a stage of mild cognitive impairment (MCI) and finally to AD.
- Since there are currently no treatments for AD, research focuses on prevention and early detection so that effective strategies may be implemented once treatments are available.
- Cardiovascular measures may be associated with and useful in identifying early symptoms of AD.
- Cerebral vascular reactivity (CVR), possibly useful in early identification of patients at risk for AD, is a measurement of the change in cerebral blood flow when the vascular system is challenged by presence of carbon dioxide.
- The current project goal is to determine if there is an association between cardiovascular measures (based on ambulatory monitoring of systolic blood pressure) and cerebral vascular reactivity.

1.2 Project Goals

Primary Aim

- Characterize the associations between ambulatory blood pressure (ABP) monitoring measurements and cerebral vascular reactivity.
- **Hypothesis:** Patients with abnormal variability or surge patterns will be associated with decreased CVR.

Secondary Aim

- Investigate which ABP predictor is most predictive of cognitive function, as measured by CVR.

1.3 Relevant Variables

Outcomes: CVR measures for different regions of interest within the brain, derived from MRI scans.

- `asl.reac.left.hemisphere.hct`
- `asl.reac.right.hemisphere.hct`
- `asl.reac.left.frontal.lobe.hct`
- `asl.reac.right.frontal.lobe.hct`
- `asl.reac.frontal.lobe.hct`
- `asl.reac.left.occipital.lobe.hct`
- `asl.reac.right.occipital.lobe.hct`
- `asl.reac.occipital.lobe.hct`
- `asl.reac.left.temporal.lobe.hct`
- `asl.reac.right.temporal.lobe.hct`
- `asl.reac.temporal.lobe.hct`
- `asl.reac.left.parietal.lobe.hct`
- `asl.reac.right.parietal.lobe.hct`
- `asl.reac.parietal.lobe.hct`

Predictors: ABP measurements

- `systolic.prewaking.surge`: Mean SBP in two hours after self-reported wake time minus mean SBP in two hours prior to self-reported wake time
- `systolic.rising.surge`: First SBP reading after self-reported wake time minus last SBP before self-reported wake time
- `nocturnal.systolic.diff.sleep.self.reported`: Mean SBP during self-reported wake time minus mean SBP from self-reported asleep time

Model Covariates
Variables corresponding to some comorbidities were not adjusted for in models due to low prevalence in the analyzed data (see section 3).

- `age`
- `education`
- `sex.factor`
- `enrolled.dx.factor`: diagnosis group (dementia excluded)
  - Normal
  - MCI
  - Ambiguous at risk
- `raceethnicity.factor`
- `apoe4pos.factor`
- `htnrx.factor`

Regional brain volume variables
Models for outcome in a given region are controlled for the corresponding variable for brain volume in that region

- `ma.left.hemisphere.vol`
- `ma.right.hemisphere.vol`
- `ma.left.frontal.lobe.vol`
- `ma.right.frontal.lobe.vol`
- `ma.frontal.lobe.vol`
- `ma.left.occipital.lobe.vol`
- `ma.right.occipital.lobe.vol`
- `ma.occipital.lobe.vol`
- `ma.left.temporal.lobe.vol`
- `ma.right.temporal.lobe.vol`
- `ma.temporal.lobe.vol`
- `ma.left.parietal.lobe.vol`
- `ma.right.parietal.lobe.vol`
- `ma.parietal.lobe.vol`

2 Statistical Analysis Plan

2.1 Primary Aim: CVR-ABP Association

- Cross-sectional analysis of patients from the Memory and Aging Project, conducted by the Vanderbilt Memory and Alzheimer's Center.
- Ordinary least squares regression models for each of the 14 CVR outcomes against each of the 3 ABP variables (42 models), controlling for covariates listed in section 1.3.
- To allow for a non-linear relationship between CVR outcomes and ABP predictors, we model ABP as a restricted cubic spline with 3 knots.
- Knots are placed at 0 and interquartile range values (25^{th} and 75^{th} percentiles) of the positive ABP values to capture abnormal values (e.g. negative ABP surge measurements) and patients at the low and high ends of positive ABP values.
- Wald tests for linearity of ABP measurements are performed.
- Since tests for linearity suggested a lack of evidence for associations being truly non-linear, we present results for models with a linear association between ABP measurements and CVR outcomes.
- Use multiple imputation to recover missing data in ABP predictors.

2.2 Secondary Aim: Predictive Power of ABP

- Compare R^2 between the models fit for the primary aim.
- Higher R^2 indicates that the model better explains variability/trends in CVR outcomes.
- Present correlation matrix between ABP predictors and CVR outcomes.

2.3 Supplemental Analyses

- Graphically compare of observed and imputed values for ABP measurements to ensure distributions are consistent.
- Fit a linear association between ABP and CVR outcomes.

3 Inclusion/Exclusion Criteria

- Exclude patients with dementia at baseline
  - `enrolled.dx.factor`, exclude = "Dementia", n = 1 (`map.id` = 112)
- Quality check
  - `asl.reac.usuable`, exclude = 0, n = 112
- At least 39 readings
  - `time.reading.indicator`, exclude = "No" or NA, n = 49

Excluded vs. Included Patients

- The following table displays all of the descriptive statistics for the excluded patients versus the patients in the analysis.
- Continuous variables have a mean (standard deviation), and discrete variables have a count (percentage).
- The p-value for the univariate comparison of the each variable between the excluded and included patients is presented. Kruskal-Wallis tests are used for continuous variables and Chi-square tests for categorical.
- A significant p-value (< 0.05) indicates that the excluded and included populations are significantly different for that variable.
- Some Chi-square approximations may be inaccurate due to low counts in certain groups.

Table 1: Comparison of Demographics for Excluded and Included Data

Variable	Excluded N=162	Analyzed Data N=174	P-Value
Nocturnal Systolic Difference	14.5 (10.5)	13.4 (9.4)	0.6075
Systolic Prewaking Surge	11.1 (12.3)	12.3 (12.2)	0.4331
Systolic Rising Surge	8.6 (14.2)	8.4 (13.6)	0.8162
ICV (calculated)	1403.7 (144.4)	1364.9 (138.4)	0.0247
Education (years)	16.3 (2.6)	15.5 (2.6)	0.0095
Age at medhx.date, recalculated	73.1 (7.5)	72.7 (7.1)	0.6214
Sex			0.0103
– Male	108 (67%)	91 (52%)	
– Female	54 (33%)	83 (48%)	
Two-level race/ethnicity			0.3688
– Non-Hispanic White	137 (85%)	154 (89%)	
– Other	25 (15%)	20 (11%)	
ApoE4+ (at least one E4 allele)			0.7182
– Yes	58 (36%)	58 (33%)	
– No	104 (64%)	116 (67%)	
Consensus Decision for Diagnosis			0.1202
– Normal	75 (46%)	101 (58%)	
– MCI	70 (43%)	62 (36%)	
– Dementia	1 (1%)	0 (0%)	
– Ambiguous At Risk	16 (10%)	11 (6%)	
Taking at least 1 anti-hypertensive med			0.622
– Yes	85 (52%)	97 (56%)	
– No	77 (48%)	77 (44%)	
Diabetic			0.1947
– Yes	35 (22%)	27 (16%)	
– No	127 (78%)	147 (84%)	
Current smoker (or quit in this or last calendar yr)			0.3898
– Yes	5 (3%)	2 (1%)	
– No	157 (97%)	172 (99%)	
CVD			0.622
– Yes	4 (2%)	7 (4%)	
– No	158 (98%)	167 (96%)	
A-fib			1
– Yes	9 (6%)	10 (6%)	
– No	151 (93%)	164 (94%)	
LV Hypertrophy			0.6958
– Yes	9 (6%)	7 (4%)	
– No	153 (94%)	166 (95%)	

- Method for exclusion may not be random. Patients with a larger intracranial volume were unable to fit into the equipment to gather the readings.
- It follows that more men were excluded since men tend to be larger in general.
- Included patients have a lower education level, though the difference is not large and may not be meaningful (mean difference: 0.74 years).

4 Descriptive Statistics

4.1 All Variables by Diagnosis

In the following table:

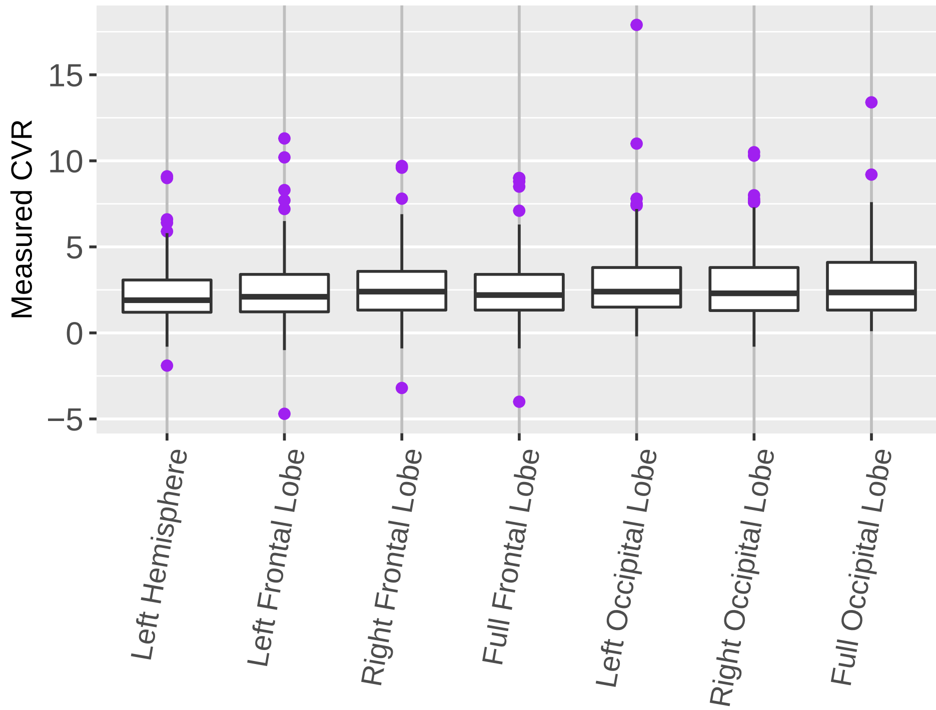
- Continuous variables have a mean (standard deviation), and discrete variables have a count (percentage).
- The p-value (significance < 0.05) for the univariate comparison of the each variable between the diagnosis groups is presented. Kruskal-Wallis tests are used for continuous variables and Chi-square tests for categorical.
- Some Chi-square approximations may be inaccurate due to low counts in certain groups.

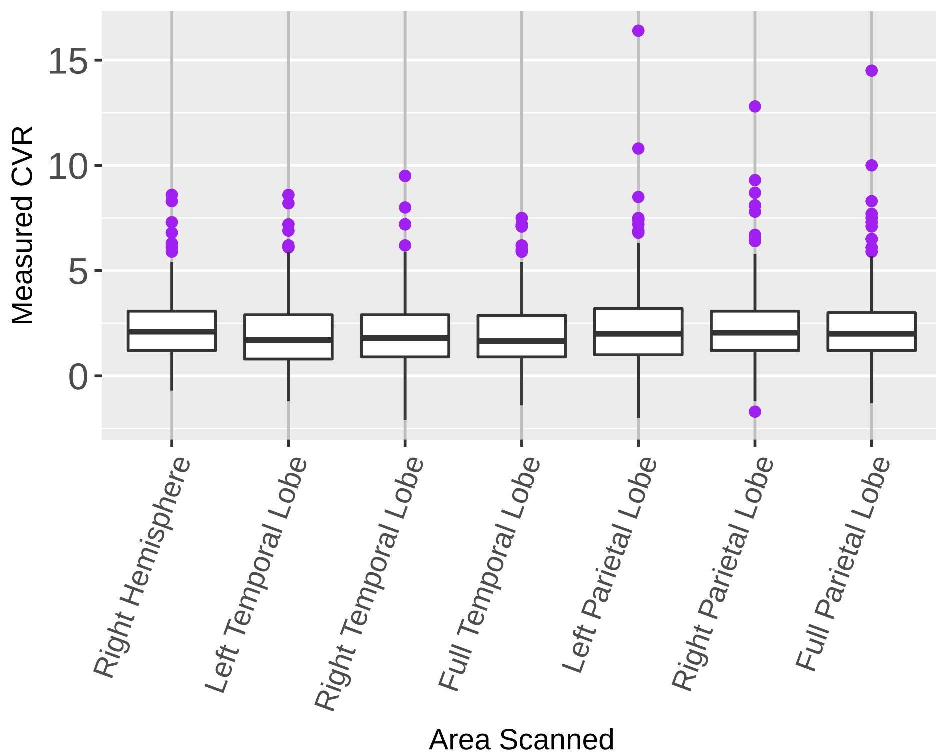
Table 2: Comparison of Demographics by Consensus Diagnosis (N = 174)

Variable	Normal N=101	MCI N=62	Ambiguous At-Risk N=11	P-value
Nocturnal Systolic Difference	15.3 (9.4)	9.5 (8.7)	17.7 (6.2)	3e-04
Systolic Prewaking Surge	14.1 (12.9)	8.9 (10.3)	12.4 (11.9)	0.0529
Systolic Rising Surge	11.4 (12.9)	3.7 (12.5)	4.9 (18.7)	0.0011
ICV (calculated)	1369.2 (140)	1345.9 (135.9)	1431.9 (122.9)	0.1649
Education (years)	16.1 (2.4)	14.6 (2.6)	15.5 (3.3)	0.0021
Age at medhx.date, recalculated	72.6 (7.3)	73.2 (7.2)	71.4 (4.8)	0.743
Sex				0.7049
– Male	53 (52%)	31 (50%)	7 (64%)	
– Female	48 (48%)	31 (50%)	4 (36%)	
Two-level race/ethnicity				0.896
– Non-Hispanic White	90 (89%)	54 (87%)	10 (91%)	
– Other	11 (11%)	8 (13%)	1 (9%)	
ApoE4+ (at least one E4 allele)				0.5298
– Yes	34 (34%)	22 (35%)	2 (18%)	
– No	67 (66%)	40 (65%)	9 (82%)	
Taking at least 1 anti-hypertensive med				0.9005
– Yes	55 (54%)	36 (58%)	6 (55%)	
– No	46 (46%)	26 (42%)	5 (45%)	
Diabetic				0.0863
– Yes	12 (12%)	11 (18%)	4 (36%)	
– No	89 (88%)	51 (82%)	7 (64%)	
Current smoker (or quit in this or last calendar yr)				0.1608
– Yes	0 (0%)	2 (3%)	0 (0%)	
– No	101 (100%)	60 (97%)	11 (100%)	
CVD				0.6743
– Yes	5 (5%)	2 (3%)	0 (0%)	
– No	96 (95%)	60 (97%)	11 (100%)	
A-fib				0.1502
– Yes	4 (4%)	4 (6%)	2 (18%)	
– No	97 (96%)	58 (94%)	9 (82%)	
LV Hypertrophy				0.576
– Yes	3 (3%)	3 (5%)	1 (9%)	
– No	97 (96%)	59 (95%)	10 (91%)	

- Patients diagnosed with MCI appear to have some lower ABP measurements. However, these are all univariate relationships; these trends may not hold in the adjusted analyses.
- We also see a difference in education level, with the apparent ordering of highest average years of education to lowest being Normal, Ambiguous At-Risk, then MCI.

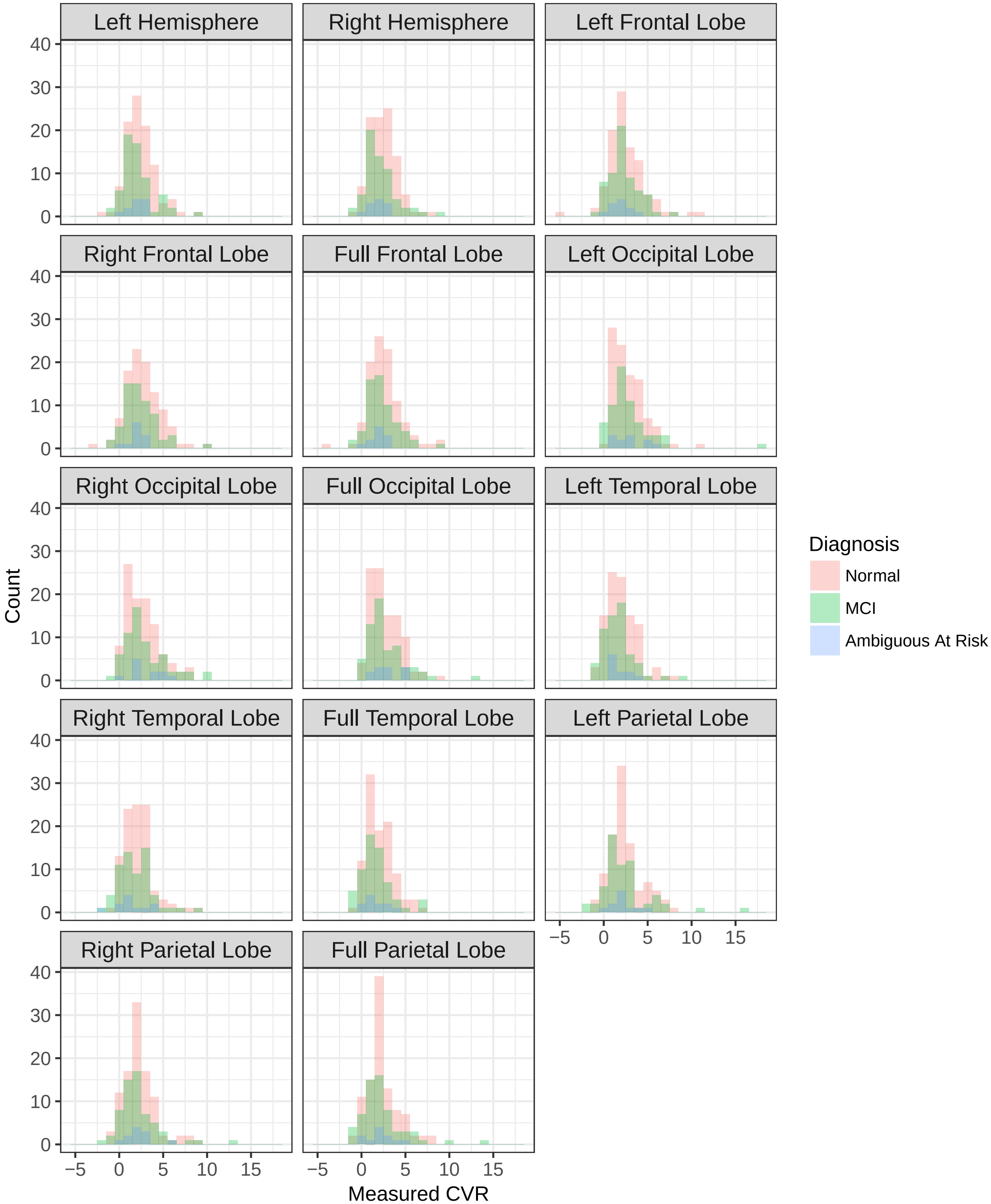
4.2 CVR Outcome Distribution





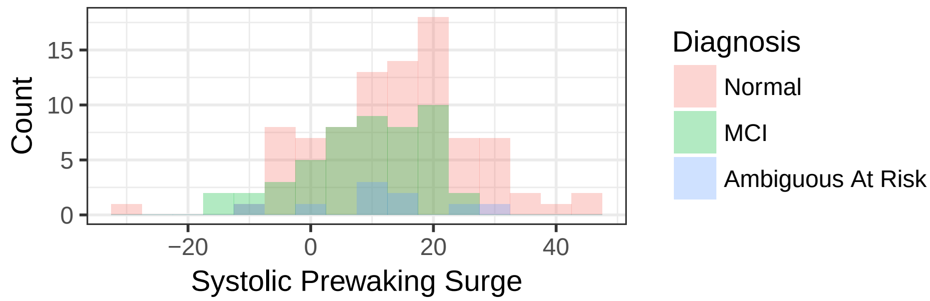
- Most of the outliers are for larger values of CVR.
- Outliers within each part of the brain are likely highly correlated. If a patient is an outlier for left frontal lobe, then she may be an outlier for the right side as well.
  - E.g. The low outliers of the frontal lobe regions: which are all from the patient with `map.id` = 034.

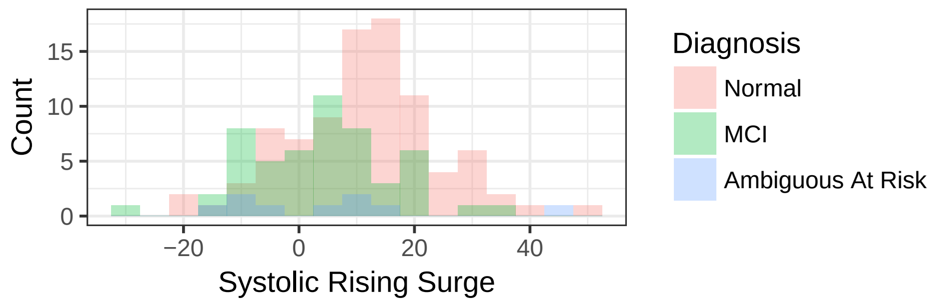
4.3 Distribution of CVR Outcomes by Diagnosis

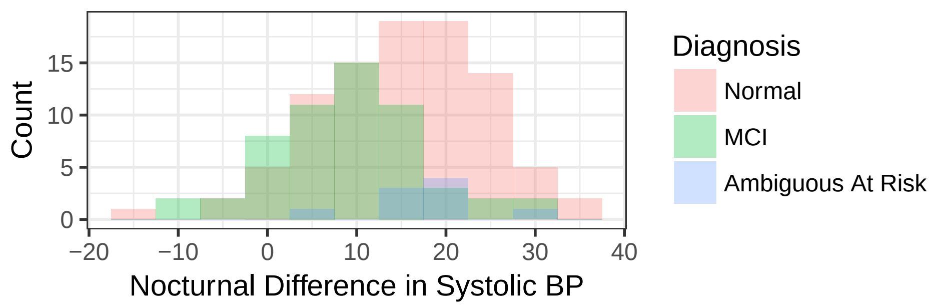


- Positive outliers in MCI group for some CVR outcomes.

4.4 ABP Measure Distribution by Diagnosis

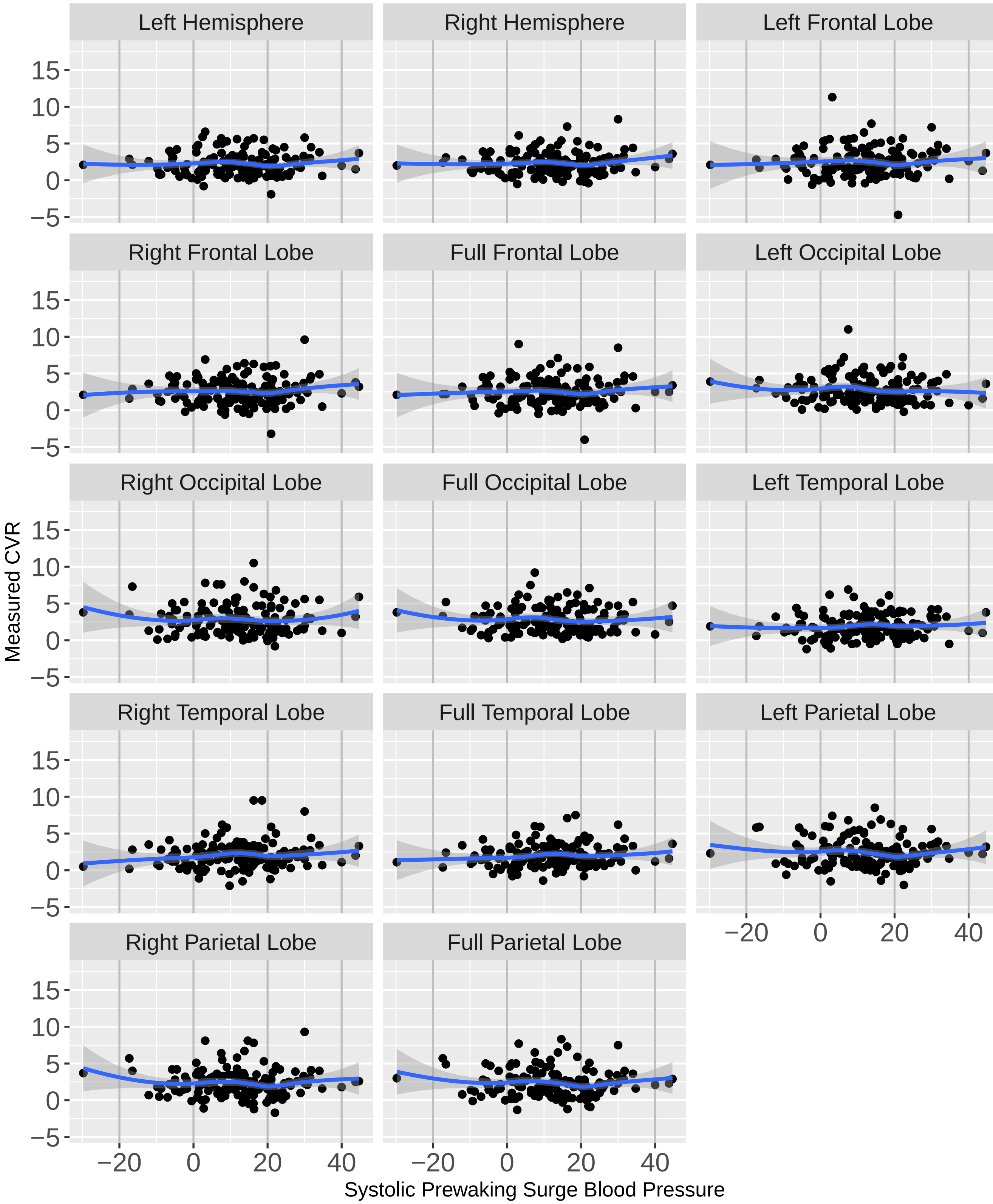




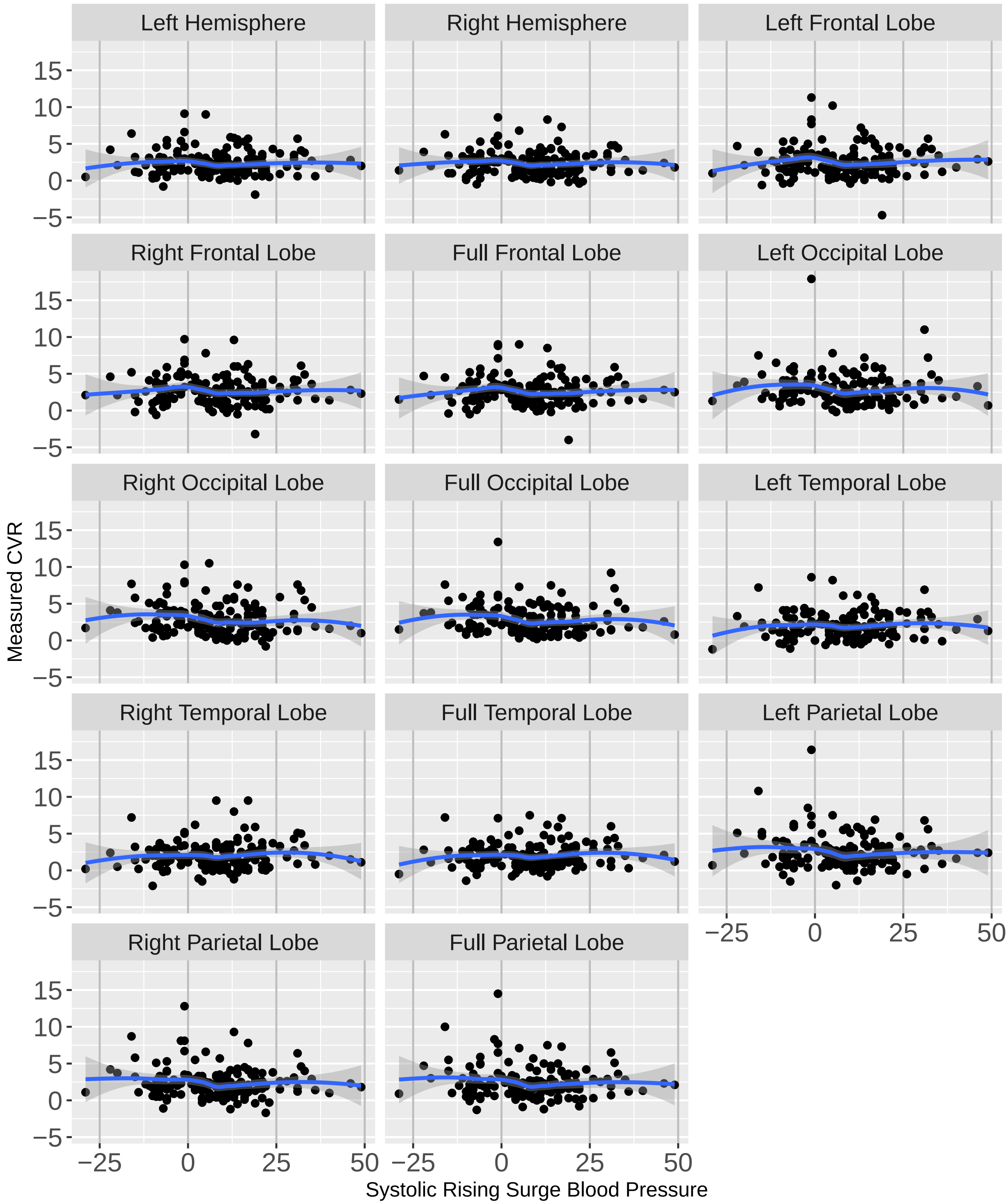


4.5 Unadjusted ABP-CVR Associations

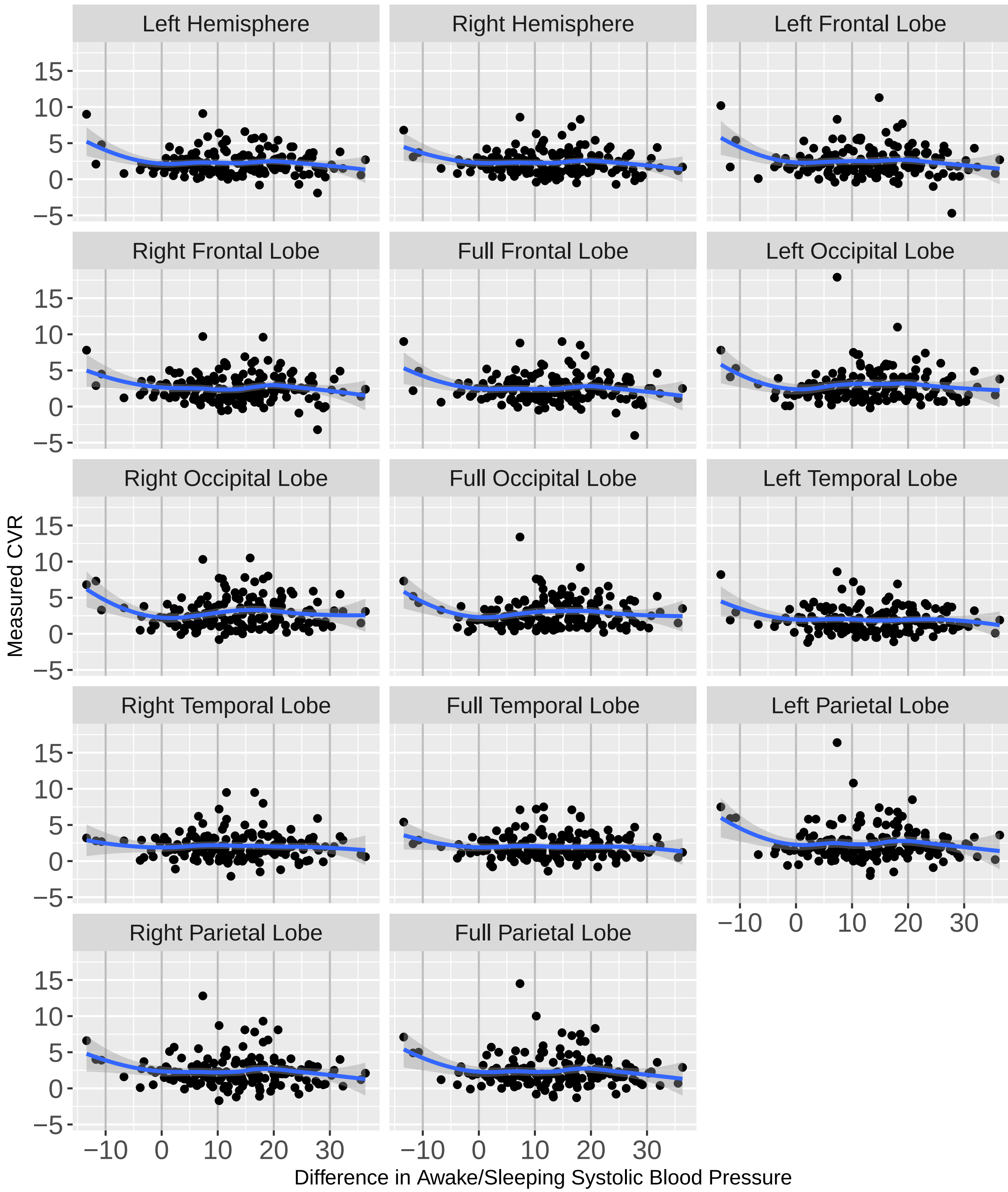
4.5.1 SBP Prewaking Surge



4.5.2 SBP Rising Surge



4.5.3 Nocturnal Decline in SBP

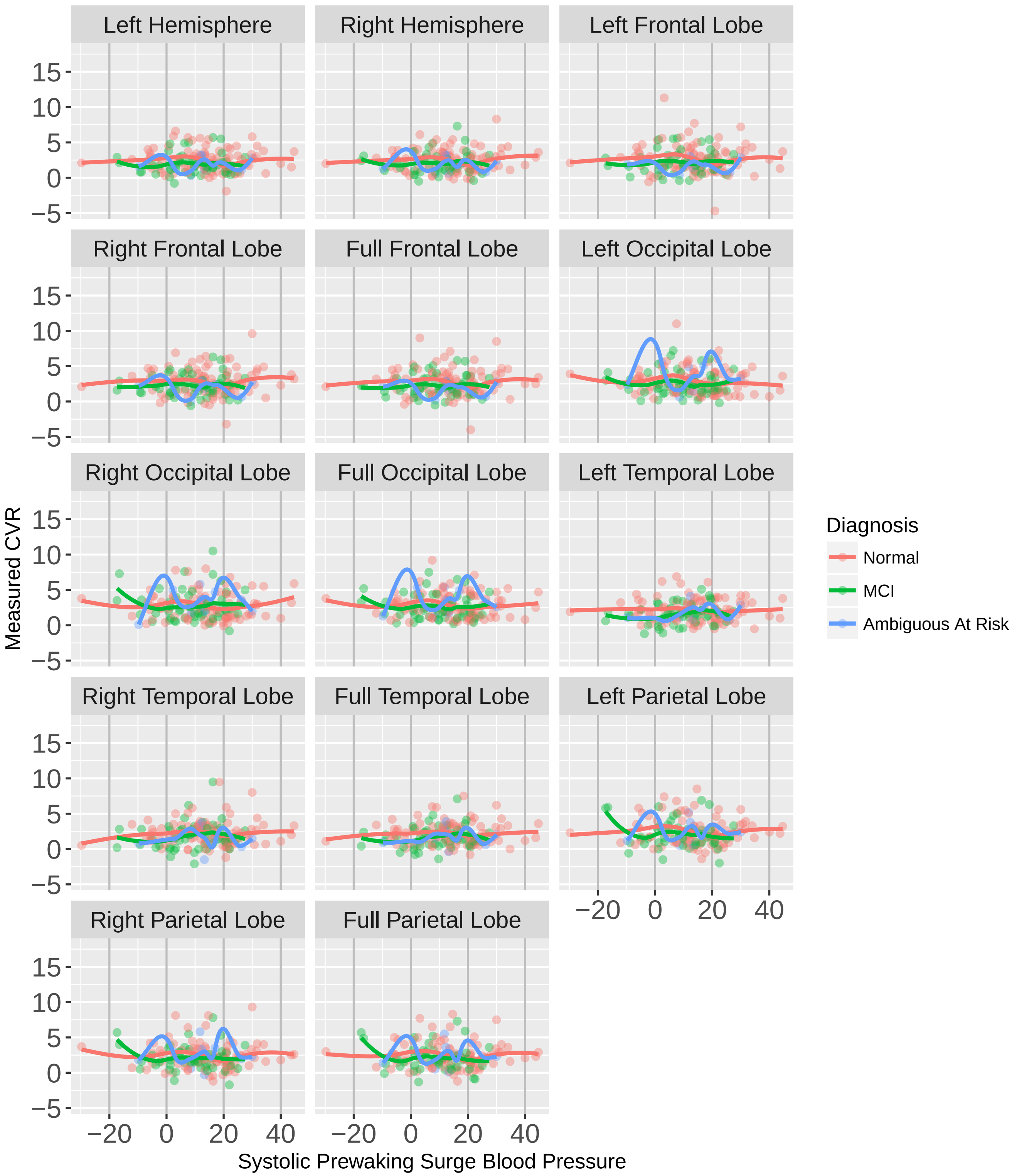


- Most of the outcomes have no trend over the predictors, with a slope around 0.
- The plots for nocturnal difference in systolic blood pressure has a slight downward slope on the left hand side (where data are very sparse).
- Univariate trends may not hold in the adjusted analyses.

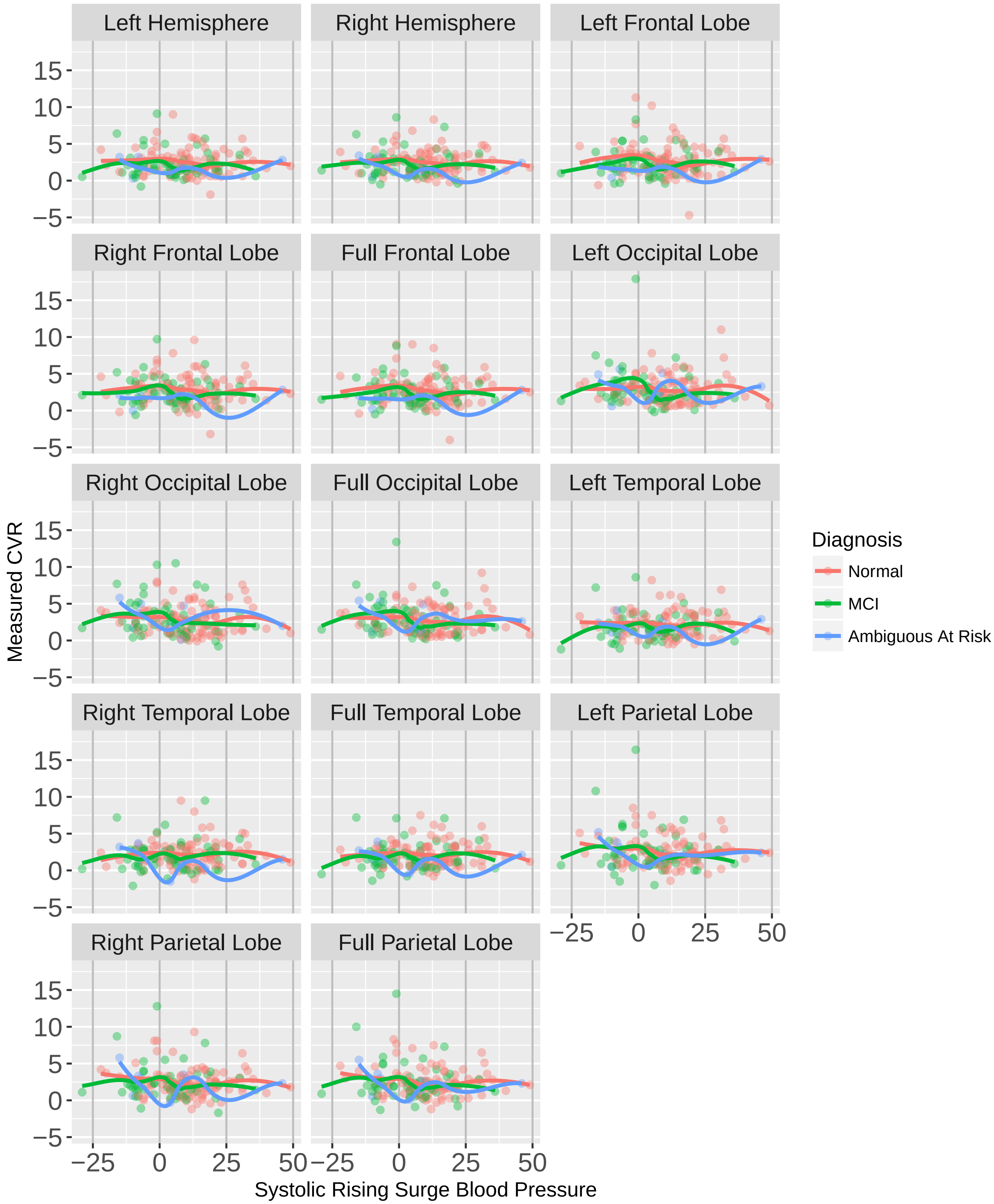
4.6 Unadjusted ABP-CVR Associations by Diagnosis

To examine whether or not an interaction between the ABP predictors of interest and diagnosis group seems to be present. Since our interaction analysis will not include the "Ambiguous At Risk" group, the plots are restricted to data for the MCI and Normal cognition groups.

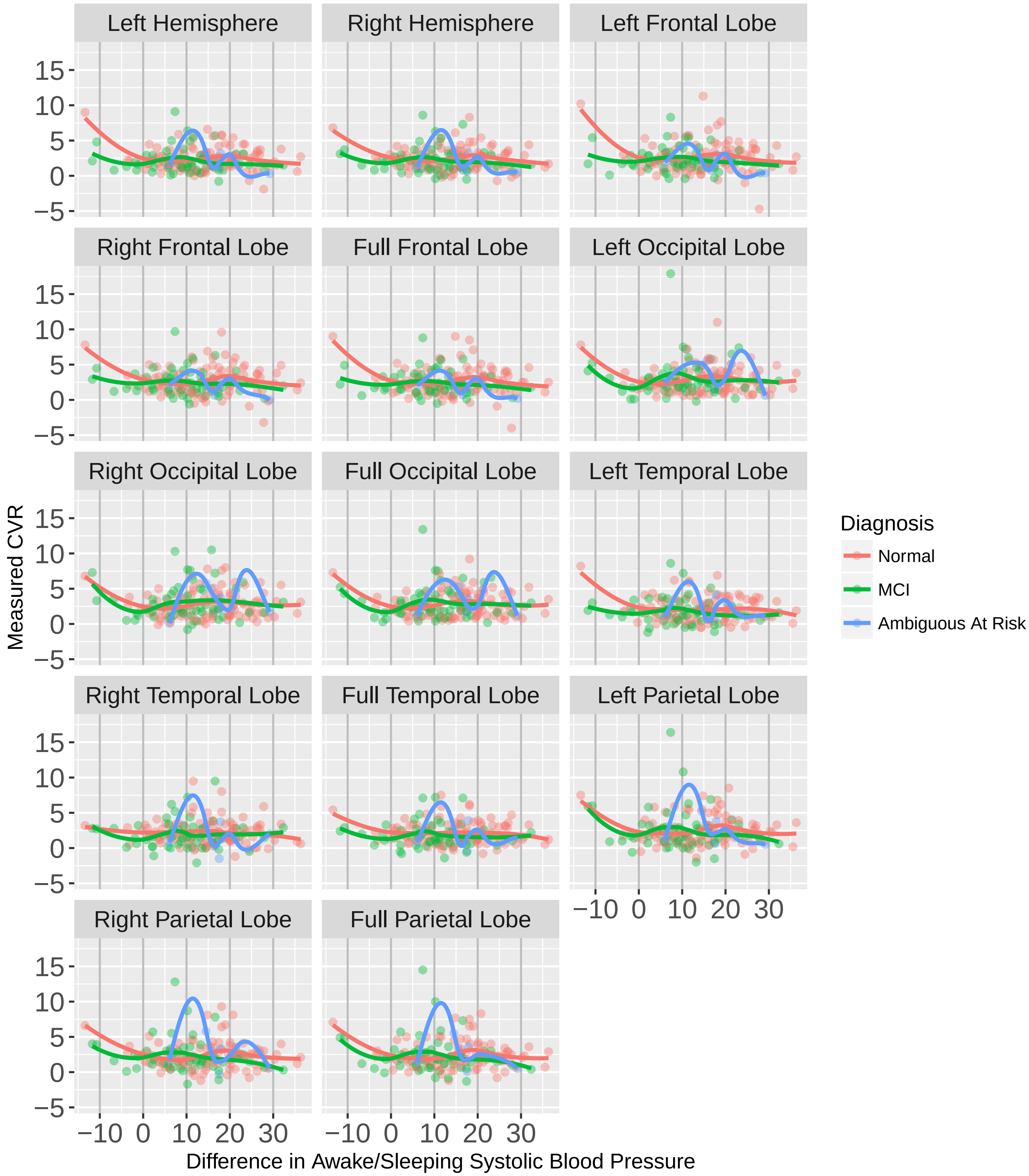
4.6.1 SBP Prewaking Surge



4.6.2 SBP Rising Surge



4.6.3 Nocturnal Difference in SBP



- It does not appear an interaction is present. All lines generally follow the same flat trend.
- For some brain regions, the MCI and Normal trends differ slightly in the tails of the ABP distribution, though this is driven by few data points.
- Lines for the Ambiguous At Risk group have more variability. However, there are only 11 patients in this group, and this diagnosis category will ultimately be excluded in the interaction analysis.

5 Analysis Results

5.1 Missing Data

Table 3: Variables with Missing Observations

Variable	Missingness
LV Hypertrophy	1 (0.57%)
Systolic Rising Surge	23 (13.22%)
Systolic Prewaking Surge	27 (15.52%)
nocturnal.systolic.diff.sleep.self.reported	15 (8.62%)

- LV hypertrophy not included as a covariate
- For this analysis: only missing data on the ABP measurements
- Implement multiple imputation using predictive mean matching

5.2 CVR Outcome Models

5.2.1 Model with Linear Effect of ABP Predictors

Original models were fit with restricted cubic splines. However, tests of linearity indicated a lack of evidence that effects were truly non-linear. Thus, primary results are presented for a linear association between ABP predictors and CVR outcomes.

Visual representations (partial effect plots) of ABP-CVR associations both overall and stratified by diagnosis can be found in section 6.3.

- Results for the coefficients associated with predictors of interest (ABP measurements) are presented on the next page. Full regression outputs of all 42 models are provided as supplementary results (see section 6.1).
- No significant p-values at the 0.05 level: Insufficient evidence that any of the ABP measurements have an effect on CVR in any brain region.
- Generally, we would recommend a multiple comparisons adjustment for fitting the 42 models (e.g. using a Bonferroni-corrected significance level of $\frac{.05}{42} = .0012$).
- Coefficients are interpreted as the effect on CVR outcome for a one-mmHg increase in ABP measurement.
- Multiply coefficients by 10 to interpret the effect on CVR for a 10-mmHg increase in ABP measurement.
  - E.g. For a 10-mmHg increase in the systolic blood pressure prewaking surge, CVR in the left hemisphere is expected to decrease by .083, holding other model variables constant.

Table 4: Coefficients for Linear ABP with CVR

	SBP Prewaking Surge			SBP Rising Surge			Nocturnal Decline in SBP		
	Coefficient	Standard Error	P-value	Coefficient	Standard Error	P-value	Coefficient	Standard Error	P-value
Left Hemisphere	-0.0083	0.0120	0.4930	-0.0058	0.0105	0.5819	-0.0262	0.0155	0.0931
Right Hemisphere	-0.0028	0.0115	0.8054	-0.0071	0.0104	0.4932	-0.0240	0.0151	0.1133
Left Frontal Lobe	-0.0041	0.0141	0.7705	-0.0038	0.0120	0.7510	-0.0289	0.0178	0.1050
Right Frontal Lobe	0.0002	0.0130	0.9870	-0.0078	0.0115	0.4972	-0.0262	0.0170	0.1238
Full Frontal Lobe	-0.0016	0.0131	0.9024	-0.0056	0.0113	0.6237	-0.0268	0.0167	0.1114
Left Occipital Lobe	-0.0202	0.0149	0.1772	-0.0130	0.0127	0.3069	-0.0144	0.0187	0.4435
Right Occipital Lobe	-0.0079	0.0141	0.5756	-0.0201	0.0125	0.1100	-0.0044	0.0181	0.8095
Full Occipital Lobe	-0.0136	0.0134	0.3125	-0.0159	0.0117	0.1767	-0.0088	0.0171	0.6072
Left Temporal Lobe	-0.0015	0.0119	0.8993	0.0019	0.0103	0.8523	-0.0207	0.0151	0.1708
Right Temporal Lobe	0.0066	0.0127	0.6055	0.0054	0.0111	0.6246	-0.0140	0.0171	0.4150
Full Temporal Lobe	0.0024	0.0112	0.8298	0.0036	0.0098	0.7186	-0.0165	0.0147	0.2650
Left Parietal Lobe	-0.0189	0.0159	0.2373	-0.0185	0.0143	0.1983	-0.0254	0.0211	0.2303
Right Parietal Lobe	-0.0125	0.0140	0.3736	-0.0140	0.0126	0.2683	-0.0254	0.0183	0.1670
Full Parietal Lobe	-0.0157	0.0146	0.2828	-0.0169	0.0132	0.2005	-0.0251	0.0192	0.1936

5.2.2 Linear CVR Outcome Models with Interaction

- For the interaction results, patients who were diagnosed as "Ambiguous At Risk" were excluded from analysis (n = 11).
- Results suggest no evidence for the presence of an interaction between any of the SBP predictors and CVR outcomes at the 0.05 level.

Table 5: Coefficients for ABP:CVR Interaction

	SBP Prewaking Surge			SBP Rising Surge			Nocturnal Decline in SBP		
	Coefficient	Standard Error	P-value	Coefficient	Standard Error	P-value	Coefficient	Standard Error	P-value
Left Hemisphere	-0.0003	0.0294	0.9919	0.0137	0.0232	0.5571	-0.0074	0.0333	0.8233
Right Hemisphere	-0.0093	0.0287	0.7468	0.0085	0.0231	0.7135	-0.0116	0.0333	0.7285
Left Frontal Lobe	0.0138	0.0338	0.6834	0.0231	0.0266	0.3865	-0.0025	0.0377	0.9473
Right Frontal Lobe	-0.0026	0.0321	0.9362	0.0068	0.0257	0.7922	-0.0077	0.0360	0.8307
Full Frontal Lobe	0.0074	0.0319	0.8163	0.0166	0.0252	0.5115	-0.0048	0.0354	0.8929
Left Occipital Lobe	-0.0009	0.0445	0.9830	-0.0160	0.0304	0.5984	0.0019	0.0389	0.9607
Right Occipital Lobe	-0.0169	0.0368	0.6464	-0.0118	0.0283	0.6761	-0.0095	0.0384	0.8057
Full Occipital Lobe	-0.0106	0.0379	0.7802	-0.0140	0.0273	0.6077	-0.0041	0.0358	0.9093
Left Temporal Lobe	0.0182	0.0281	0.5172	0.0169	0.0228	0.4593	-0.0053	0.0318	0.8676
Right Temporal Lobe	0.0056	0.0293	0.8473	0.0106	0.0276	0.7006	0.0151	0.0370	0.6832
Full Temporal Lobe	0.0101	0.0259	0.6963	0.0128	0.0222	0.5653	0.0012	0.0315	0.9707
Left Parietal Lobe	-0.0346	0.0398	0.3871	-0.0050	0.0324	0.8787	-0.0351	0.0452	0.4384
Right Parietal Lobe	-0.0286	0.0338	0.3983	0.0075	0.0277	0.7869	-0.0373	0.0387	0.3372
Full Parietal Lobe	-0.0316	0.0359	0.3801	0.0007	0.0293	0.9813	-0.0349	0.0410	0.3956

5.3 Secondary Aim

Table 6: R-squared for ABP predictor models

	SBP Prewaking Surge	SBP Rising Surge	Nocturnal SBP Difference
Left Hemisphere	0.056	0.055	0.072
Right Hemisphere	0.040	0.043	0.056
Left Frontal Lobe	0.068	0.068	0.084
Right Frontal Lobe	0.056	0.059	0.071
Full Frontal Lobe	0.065	0.066	0.081
Left Occipital Lobe	0.093	0.087	0.084
Right Occipital Lobe	0.056	0.069	0.054
Full Occipital Lobe	0.065	0.069	0.060
Left Temporal Lobe	0.053	0.053	0.064
Right Temporal Lobe	0.023	0.023	0.026
Full Temporal Lobe	0.034	0.035	0.042
Left Parietal Lobe	0.037	0.039	0.037
Right Parietal Lobe	0.049	0.052	0.055
Full Parietal Lobe	0.043	0.046	0.046

Table 7: Correlation Matrix for ABP Predictors and CVR Outcomes

	SBP Prewaking Surge	SBP Rising Surge	Nocturnal Decline in SBP
Left Hemisphere	-0.044	0.094	0.030
Right Hemisphere	-0.014	0.088	0.026
Left Frontal Lobe	-0.013	0.096	0.029
Right Frontal Lobe	0.018	0.117	0.039
Full Frontal Lobe	0.003	0.109	0.036
Left Occipital Lobe	-0.064	0.109	0.114
Right Occipital Lobe	-0.007	0.078	0.091
Full Occipital Lobe	-0.035	0.098	0.108
Left Temporal Lobe	0.003	0.177	0.095
Right Temporal Lobe	-0.026	0.044	-0.004
Full Temporal Lobe	0.000	0.131	0.059
Left Parietal Lobe	-0.087	0.046	0.030
Right Parietal Lobe	-0.040	0.080	0.044
Full Parietal Lobe	-0.068	0.063	0.039

- Nocturnal decline in SBP has slightly higher R^2 in overall hemispheres, frontal, and temporal lobes. SBP rising surge is highest in the occipital and parietal lobes.
- All R^2 values are very low, indicating these models generally do not have extensive predictive ability. In other words, less than 1% of the variability in CVR outcomes is explained by any of the models fitted in this analysis.
- SBP rising surge has all positive correlations, though numbers are small.
- No correlations were statistically significant at the 0.05 level.

6 Supplemental Analyses

6.1 Full Regression Output for Linear Models

The following tables provide full regression outputs for our primary results: ordinary least squares models on the data with multiply imputed ABP predictors to account for missing data. Since all the data are utilized (i.e. Ambiguous At Risk is not excluded), these models do not contain the predictor-diagnosis interaction.

Table 8: Regression for ABP with CVR: SBP Prewaking Surge and Left Hemisphere

	Coefficient	StdError	95% Conf. Int.
Intercept	4.390	2.420	(-0.353, 9.13)
systolic.prewaking.surge	-0.008	0.015	(-0.0386, 0.0221)
ma.left.hemisphere	-0.000	0.000	(-8.84e-06, 1.27e-06)
age	-0.002	0.019	(-0.0403, 0.0358)
sex.factor=Female	-0.365	0.321	(-0.993, 0.264)
raceethnicity.factor=Other	-0.119	0.409	(-0.921, 0.682)
education	0.041	0.054	(-0.0659, 0.147)
enrolled.dx.factor=MCI	-0.272	0.295	(-0.85, 0.307)
enrolled.dx.factor=Ambiguous At Risk	-0.333	0.537	(-1.39, 0.72)
apoe4pos.factor=No	-0.112	0.282	(-0.665, 0.441)
htnrx.factor=No	0.571	0.265	(0.0508, 1.09)*

Table 9: Regression for ABP with CVR: SBP Prewaking Surge and Right Hemisphere

	Coefficient	StdError	95% Conf. Int.
Intercept	3.220	2.430	(-1.54, 7.97)
systolic.prewaking.surge	-0.003	0.015	(-0.0324, 0.0267)
ma.right.hemisphere	-0.000	0.000	(-7.12e-06, 3.18e-06)
age	-0.007	0.019	(-0.0444, 0.03)
sex.factor=Female	-0.203	0.322	(-0.833, 0.428)
raceethnicity.factor=Other	-0.137	0.397	(-0.914, 0.64)
education	0.064	0.053	(-0.0398, 0.167)
enrolled.dx.factor=MCI	-0.157	0.287	(-0.72, 0.406)
enrolled.dx.factor=Ambiguous At Risk	-0.425	0.524	(-1.45, 0.601)
apoe4pos.factor=No	-0.110	0.275	(-0.649, 0.43)
htnrx.factor=No	0.378	0.259	(-0.129, 0.886)

Table 10: Regression for ABP with CVR: SBP Prewaking Surge and Left Frontal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	2.720	2.200	(-1.59, 7.02)
systolic.prewaking.surge	-0.004	0.018	(-0.0389, 0.0307)
ma.left.frontal.lobe.vol	-0.000	0.000	(-3.15e-05, 9.84e-06)
age	-0.004	0.022	(-0.0473, 0.0392)
sex.factor=Female	-0.003	0.334	(-0.658, 0.652)
raceethnicity.factor=Other	-0.003	0.469	(-0.923, 0.917)
education	0.070	0.062	(-0.0527, 0.192)
enrolled.dx.factor=MCI	-0.182	0.342	(-0.852, 0.488)
enrolled.dx.factor=Ambiguous At Risk	-0.489	0.630	(-1.72, 0.747)
apoe4pos.factor=No	-0.053	0.327	(-0.695, 0.588)
htnrx.factor=No	0.819	0.309	(0.214, 1.42)*

Table 11: Regression for ABP with CVR: SBP Prewaking Surge and Right Frontal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.850	2.190	(-2.43, 6.14)
systolic.prewaking.surge	0.000	0.017	(-0.033, 0.0334)
ma.right.frontal.lobe.vol	-0.000	0.000	(-2.64e-05, 1.76e-05)
age	-0.004	0.021	(-0.045, 0.0375)
sex.factor=Female	-0.032	0.323	(-0.664, 0.601)
raceethnicity.factor=Other	0.121	0.445	(-0.751, 0.994)
education	0.088	0.059	(-0.0284, 0.204)
enrolled.dx.factor=MCI	-0.140	0.325	(-0.778, 0.497)
enrolled.dx.factor=Ambiguous At Risk	-0.604	0.601	(-1.78, 0.573)
apoe4pos.factor=No	-0.098	0.311	(-0.709, 0.512)
htnrx.factor=No	0.615	0.293	(0.04, 1.19)*

Table 12: Regression for ABP with CVR: SBP Prewaking Surge and Full Frontal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	2.460	2.110	(-1.68, 6.6)
systolic.prewaking.surge	-0.002	0.017	(-0.0344, 0.0312)
ma.frontal.lobe.vol	-0.000	0.000	(-1.46e-05, 6.11e-06)
age	-0.005	0.021	(-0.0456, 0.0357)
sex.factor=Female	-0.028	0.316	(-0.647, 0.592)
raceethnicity.factor=Other	0.037	0.440	(-0.825, 0.899)
education	0.078	0.059	(-0.0367, 0.193)
enrolled.dx.factor=MCI	-0.162	0.321	(-0.791, 0.468)
enrolled.dx.factor=Ambiguous At Risk	-0.558	0.592	(-1.72, 0.603)
apoe4pos.factor=No	-0.081	0.307	(-0.683, 0.521)
htnrx.factor=No	0.709	0.290	(0.141, 1.28)*

Table 13: Regression for ABP with CVR: SBP Prewaking Surge and Left Occipital Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	4.650	2.760	(-0.756, 10.1)
systolic.prewaking.surge	-0.020	0.019	(-0.0568, 0.0165)
ma.left.occipital.lobe.vol	-0.000	0.000	(-0.000145, 4.46e-06)
age	0.025	0.025	(-0.0228, 0.0731)
sex.factor=Female	-1.080	0.383	(-1.83, -0.33)*
raceethnicity.factor=Other	-0.507	0.523	(-1.53, 0.518)
education	0.003	0.068	(-0.131, 0.137)
enrolled.dx.factor=MCI	-0.065	0.371	(-0.792, 0.662)
enrolled.dx.factor=Ambiguous At Risk	0.192	0.674	(-1.13, 1.51)
apoe4pos.factor=No	-0.212	0.356	(-0.91, 0.486)
htnrx.factor=No	0.745	0.335	(0.0883, 1.4)*

Table 14: Regression for ABP with CVR: SBP Prewaking Surge and Right Occipital Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.600	2.470	(-3.24, 6.44)
systolic.prewaking.surge	-0.008	0.018	(-0.0435, 0.0277)
ma.right.occipital.lobe.vol	-0.000	0.000	(-8.01e-05, 4.42e-05)
age	0.011	0.024	(-0.0357, 0.0572)
sex.factor=Female	-0.452	0.365	(-1.17, 0.264)
raceethnicity.factor=Other	-0.864	0.501	(-1.85, 0.118)
education	0.095	0.067	(-0.0366, 0.226)
enrolled.dx.factor=MCI	0.328	0.363	(-0.383, 1.04)
enrolled.dx.factor=Ambiguous At Risk	0.320	0.662	(-0.978, 1.62)
apoe4pos.factor=No	-0.011	0.350	(-0.697, 0.674)
htnrx.factor=No	0.129	0.331	(-0.519, 0.777)

Table 15: Regression for ABP with CVR: SBP Prewaking Surge and Full Occipital Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	3.240	2.470	(-1.61, 8.08)
systolic.prewaking.surge	-0.014	0.017	(-0.0472, 0.02)
ma.occipital.lobe.vol	-0.000	0.000	(-5.37e-05, 1.27e-05)
age	0.017	0.022	(-0.0272, 0.0606)
sex.factor=Female	-0.740	0.349	(-1.42, -0.0553)*
raceethnicity.factor=Other	-0.632	0.475	(-1.56, 0.3)
education	0.038	0.063	(-0.0852, 0.162)
enrolled.dx.factor=MCI	0.088	0.340	(-0.58, 0.755)
enrolled.dx.factor=Ambiguous At Risk	0.281	0.621	(-0.937, 1.5)
apoe4pos.factor=No	-0.113	0.328	(-0.755, 0.53)
htnrx.factor=No	0.444	0.309	(-0.162, 1.05)

Table 16: Regression for ABP with CVR: SBP Prewaking Surge and Left Temporal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	3.430	2.190	(-0.851, 7.72)
systolic.prewaking.surge	-0.002	0.015	(-0.0311, 0.028)
ma.left.temporal.lobe.vol	-0.000	0.000	(-5.93e-05, 2.11e-05)
age	0.002	0.019	(-0.0362, 0.04)
sex.factor=Female	-0.338	0.316	(-0.957, 0.282)
raceethnicity.factor=Other	-0.562	0.411	(-1.37, 0.244)
education	-0.006	0.055	(-0.113, 0.102)
enrolled.dx.factor=MCI	-0.426	0.299	(-1.01, 0.16)
enrolled.dx.factor=Ambiguous At Risk	-0.262	0.543	(-1.33, 0.801)
apoe4pos.factor=No	-0.136	0.286	(-0.698, 0.425)
htnrx.factor=No	0.473	0.270	(-0.0555, 1)

Table 17: Regression for ABP with CVR: SBP Prewaking Surge and Right Temporal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	2.860	2.490	(-2.01, 7.73)
systolic.prewaking.surge	0.007	0.017	(-0.0269, 0.0401)
ma.right.temporal.lobe.vol	0.000	0.000	(-4.29e-05, 4.76e-05)
age	-0.011	0.022	(-0.054, 0.0314)
sex.factor=Female	-0.059	0.358	(-0.76, 0.642)
raceethnicity.factor=Other	-0.072	0.456	(-0.965, 0.822)
education	0.003	0.061	(-0.117, 0.123)
enrolled.dx.factor=MCI	-0.308	0.332	(-0.958, 0.342)
enrolled.dx.factor=Ambiguous At Risk	-0.766	0.601	(-1.94, 0.413)
apoe4pos.factor=No	-0.149	0.319	(-0.774, 0.477)
htnrx.factor=No	0.056	0.299	(-0.53, 0.642)

Table 18: Regression for ABP with CVR: SBP Prewaking Surge and Full Temporal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	3.110	2.170	(-1.14, 7.37)
systolic.prewaking.surge	0.002	0.015	(-0.0265, 0.0313)
ma.temporal.lobe.vol	-0.000	0.000	(-2.4e-05, 1.63e-05)
age	-0.005	0.019	(-0.0422, 0.0322)
sex.factor=Female	-0.202	0.311	(-0.812, 0.407)
raceethnicity.factor=Other	-0.338	0.399	(-1.12, 0.444)
education	-0.002	0.053	(-0.107, 0.102)
enrolled.dx.factor=MCI	-0.359	0.290	(-0.928, 0.21)
enrolled.dx.factor=Ambiguous At Risk	-0.552	0.526	(-1.58, 0.48)
apoe4pos.factor=No	-0.123	0.278	(-0.669, 0.423)
htnrx.factor=No	0.283	0.261	(-0.229, 0.796)

Table 19: Regression for ABP with CVR: SBP Prewaking Surge and Left Parietal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.440	2.670	(-3.8, 6.68)
systolic.prewaking.surge	-0.019	0.021	(-0.0603, 0.0225)
ma.left.parietal.lobe.vol	0.000	0.000	(-4.85e-05, 4.94e-05)
age	0.021	0.026	(-0.0301, 0.0726)
sex.factor=Female	-0.319	0.399	(-1.1, 0.462)
raceethnicity.factor=Other	-0.033	0.557	(-1.13, 1.06)
education	-0.015	0.074	(-0.162, 0.131)
enrolled.dx.factor=MCI	-0.138	0.405	(-0.931, 0.655)
enrolled.dx.factor=Ambiguous At Risk	-0.233	0.736	(-1.68, 1.21)
apoe4pos.factor=No	-0.296	0.388	(-1.06, 0.465)
htnrx.factor=No	0.697	0.365	(-0.0188, 1.41)

Table 20: Regression for ABP with CVR: SBP Prewaking Surge and Right Parietal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.350	2.430	(-3.41, 6.12)
systolic.prewaking.surge	-0.013	0.018	(-0.0483, 0.0234)
ma.right.parietal.lobe.vol	0.000	0.000	(-4.35e-05, 4.44e-05)
age	0.008	0.023	(-0.0372, 0.0536)
sex.factor=Female	-0.187	0.366	(-0.905, 0.53)
raceethnicity.factor=Other	-0.349	0.490	(-1.31, 0.61)
education	0.036	0.065	(-0.0914, 0.164)
enrolled.dx.factor=MCI	-0.032	0.357	(-0.731, 0.667)
enrolled.dx.factor=Ambiguous At Risk	0.025	0.648	(-1.25, 1.3)
apoe4pos.factor=No	-0.344	0.343	(-1.02, 0.328)
htnrx.factor=No	0.705	0.324	(0.0704, 1.34)*

Table 21: Regression for ABP with CVR: SBP Prewaking Surge and Full Parietal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.320	2.520	(-3.61, 6.25)
systolic.prewaking.surge	-0.016	0.019	(-0.0534, 0.022)
ma.parietal.lobe.vol	0.000	0.000	(-2.19e-05, 2.47e-05)
age	0.015	0.024	(-0.0327, 0.0618)
sex.factor=Female	-0.242	0.374	(-0.975, 0.49)
raceethnicity.factor=Other	-0.182	0.511	(-1.18, 0.819)
education	0.006	0.068	(-0.127, 0.14)
enrolled.dx.factor=MCI	-0.101	0.372	(-0.83, 0.627)
enrolled.dx.factor=Ambiguous At Risk	-0.158	0.676	(-1.48, 1.17)
apoe4pos.factor=No	-0.330	0.357	(-1.03, 0.369)
htnrx.factor=No	0.708	0.336	(0.0491, 1.37)*

Table 22: Regression for ABP with CVR: SBP Rising Surge and Left Hemisphere

	Coefficient	StdError	95% Conf. Int.
Intercept	4.160	2.420	(-0.585, 8.9)
systolic.rising.surge	-0.006	0.015	(-0.0362, 0.0246)
ma.left.hemisphere	-0.000	0.000	(-8.67e-06, 1.44e-06)
age	-0.002	0.019	(-0.0396, 0.0366)
sex.factor=Female	-0.327	0.321	(-0.955, 0.302)
raceethnicity.factor=Other	-0.122	0.409	(-0.923, 0.68)
education	0.041	0.054	(-0.0655, 0.148)
enrolled.dx.factor=MCI	-0.272	0.295	(-0.85, 0.306)
enrolled.dx.factor=Ambiguous At Risk	-0.357	0.537	(-1.41, 0.696)
apoe4pos.factor=No	-0.116	0.282	(-0.669, 0.437)
htnrx.factor=No	0.575	0.265	(0.0547, 1.1)*

Table 23: Regression for ABP with CVR: SBP Rising Surge and Right Hemisphere

	Coefficient	StdError	95% Conf. Int.
Intercept	3.190	2.430	(-1.57, 7.95)
systolic.rising.surge	-0.007	0.015	(-0.0366, 0.0224)
ma.right.hemisphere	-0.000	0.000	(-7.05e-06, 3.25e-06)
age	-0.007	0.019	(-0.044, 0.0304)
sex.factor=Female	-0.211	0.322	(-0.842, 0.42)
raceethnicity.factor=Other	-0.137	0.397	(-0.914, 0.64)
education	0.063	0.053	(-0.0403, 0.167)
enrolled.dx.factor=MCI	-0.194	0.287	(-0.756, 0.369)
enrolled.dx.factor=Ambiguous At Risk	-0.469	0.524	(-1.5, 0.557)
apoe4pos.factor=No	-0.103	0.275	(-0.643, 0.436)
htnrx.factor=No	0.380	0.259	(-0.128, 0.888)

Table 24: Regression for ABP with CVR: SBP Rising Surge and Left Frontal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	2.650	2.200	(-1.65, 6.96)
systolic.rising.surge	-0.004	0.018	(-0.0386, 0.031)
ma.left.frontal.lobe.vol	-0.000	0.000	(-3.14e-05, 1e-05)
age	-0.004	0.022	(-0.0471, 0.0394)
sex.factor=Female	0.008	0.334	(-0.647, 0.663)
raceethnicity.factor=Other	-0.004	0.469	(-0.924, 0.916)
education	0.070	0.062	(-0.0521, 0.192)
enrolled.dx.factor=MCI	-0.189	0.342	(-0.859, 0.481)
enrolled.dx.factor=Ambiguous At Risk	-0.507	0.630	(-1.74, 0.729)
apoe4pos.factor=No	-0.055	0.327	(-0.696, 0.587)
htnrx.factor=No	0.821	0.309	(0.216, 1.43)*

Table 25: Regression for ABP with CVR: SBP Rising Surge and Right Frontal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.970	2.190	(-2.32, 6.25)
systolic.rising.surge	-0.008	0.017	(-0.0411, 0.0254)
ma.right.frontal.lobe.vol	-0.000	0.000	(-2.66e-05, 1.74e-05)
age	-0.004	0.021	(-0.0449, 0.0377)
sex.factor=Female	-0.069	0.323	(-0.701, 0.564)
raceethnicity.factor=Other	0.123	0.445	(-0.75, 0.996)
education	0.087	0.059	(-0.029, 0.203)
enrolled.dx.factor=MCI	-0.197	0.325	(-0.835, 0.44)
enrolled.dx.factor=Ambiguous At Risk	-0.656	0.601	(-1.83, 0.521)
apoe4pos.factor=No	-0.086	0.311	(-0.696, 0.524)
htnrx.factor=No	0.615	0.293	(0.0398, 1.19)*

Table 26: Regression for ABP with CVR: SBP Rising Surge and Full Frontal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	2.490	2.110	(-1.65, 6.63)
systolic.rising.surge	-0.006	0.017	(-0.0384, 0.0273)
ma.frontal.lobe.vol	-0.000	0.000	(-1.46e-05, 6.13e-06)
age	-0.005	0.021	(-0.0454, 0.0359)
sex.factor=Female	-0.041	0.316	(-0.661, 0.578)
raceethnicity.factor=Other	0.038	0.440	(-0.824, 0.9)
education	0.078	0.059	(-0.0367, 0.192)
enrolled.dx.factor=MCI	-0.194	0.321	(-0.823, 0.436)
enrolled.dx.factor=Ambiguous At Risk	-0.592	0.592	(-1.75, 0.569)
apoe4pos.factor=No	-0.075	0.307	(-0.678, 0.527)
htnrx.factor=No	0.709	0.290	(0.142, 1.28)*

Table 27: Regression for ABP with CVR: SBP Rising Surge and Left Occipital Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	4.130	2.760	(-1.27, 9.54)
systolic.rising.surge	-0.013	0.019	(-0.0497, 0.0236)
ma.left.occipital.lobe.vol	-0.000	0.000	(-0.00014, 8.91e-06)
age	0.027	0.025	(-0.021, 0.0749)
sex.factor=Female	-0.992	0.383	(-1.74, -0.241)*
raceethnicity.factor=Other	-0.514	0.523	(-1.54, 0.51)
education	0.004	0.068	(-0.13, 0.138)
enrolled.dx.factor=MCI	-0.054	0.371	(-0.781, 0.673)
enrolled.dx.factor=Ambiguous At Risk	0.154	0.674	(-1.17, 1.47)
apoe4pos.factor=No	-0.223	0.356	(-0.921, 0.475)
htnrx.factor=No	0.754	0.335	(0.0972, 1.41)*

Table 28: Regression for ABP with CVR: SBP Rising Surge and Right Occipital Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.420	2.470	(-3.42, 6.27)
systolic.rising.surge	-0.020	0.018	(-0.0557, 0.0154)
ma.right.occipital.lobe.vol	-0.000	0.000	(-7.53e-05, 4.9e-05)
age	0.012	0.024	(-0.0344, 0.0585)
sex.factor=Female	-0.473	0.365	(-1.19, 0.243)
raceethnicity.factor=Other	-0.865	0.501	(-1.85, 0.117)
education	0.093	0.067	(-0.0382, 0.224)
enrolled.dx.factor=MCI	0.225	0.363	(-0.486, 0.935)
enrolled.dx.factor=Ambiguous At Risk	0.204	0.662	(-1.09, 1.5)
apoe4pos.factor=No	0.011	0.350	(-0.674, 0.696)
htnrx.factor=No	0.128	0.331	(-0.521, 0.776)

Table 29: Regression for ABP with CVR: SBP Rising Surge and Full Occipital Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	2.920	2.470	(-1.93, 7.76)
systolic.rising.surge	-0.016	0.017	(-0.0495, 0.0177)
ma.occipital.lobe.vol	-0.000	0.000	(-5.17e-05, 1.48e-05)
age	0.018	0.022	(-0.0257, 0.062)
sex.factor=Female	-0.708	0.349	(-1.39, -0.023)*
raceethnicity.factor=Other	-0.637	0.475	(-1.57, 0.294)
education	0.038	0.063	(-0.0853, 0.162)
enrolled.dx.factor=MCI	0.044	0.340	(-0.623, 0.711)
enrolled.dx.factor=Ambiguous At Risk	0.208	0.621	(-1.01, 1.43)
apoe4pos.factor=No	-0.107	0.328	(-0.75, 0.536)
htnrx.factor=No	0.448	0.309	(-0.158, 1.05)

Table 30: Regression for ABP with CVR: SBP Rising Surge and Left Temporal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	3.380	2.190	(-0.899, 7.67)
systolic.rising.surge	0.002	0.015	(-0.0276, 0.0315)
ma.left.temporal.lobe.vol	-0.000	0.000	(-5.92e-05, 2.11e-05)
age	0.002	0.019	(-0.0363, 0.04)
sex.factor=Female	-0.320	0.316	(-0.94, 0.299)
raceethnicity.factor=Other	-0.562	0.411	(-1.37, 0.244)
education	-0.005	0.055	(-0.112, 0.102)
enrolled.dx.factor=MCI	-0.406	0.299	(-0.992, 0.18)
enrolled.dx.factor=Ambiguous At Risk	-0.250	0.543	(-1.31, 0.813)
apoe4pos.factor=No	-0.145	0.286	(-0.706, 0.416)
htnrx.factor=No	0.473	0.270	(-0.0557, 1)

Table 31: Regression for ABP with CVR: SBP Rising Surge and Right Temporal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	3.010	2.490	(-1.86, 7.88)
systolic.rising.surge	0.005	0.017	(-0.0281, 0.0389)
ma.right.temporal.lobe.vol	0.000	0.000	(-4.39e-05, 4.66e-05)
age	-0.012	0.022	(-0.0546, 0.0308)
sex.factor=Female	-0.084	0.358	(-0.785, 0.617)
raceethnicity.factor=Other	-0.064	0.456	(-0.957, 0.83)
education	0.003	0.061	(-0.118, 0.123)
enrolled.dx.factor=MCI	-0.303	0.332	(-0.953, 0.347)
enrolled.dx.factor=Ambiguous At Risk	-0.744	0.601	(-1.92, 0.434)
apoe4pos.factor=No	-0.149	0.319	(-0.775, 0.477)
htnrx.factor=No	0.054	0.299	(-0.532, 0.64)

Table 32: Regression for ABP with CVR: SBP Rising Surge and Full Temporal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	3.160	2.170	(-1.1, 7.41)
systolic.rising.surge	0.004	0.015	(-0.0253, 0.0324)
ma.temporal.lobe.vol	-0.000	0.000	(-2.42e-05, 1.61e-05)
age	-0.005	0.019	(-0.0425, 0.0319)
sex.factor=Female	-0.205	0.311	(-0.815, 0.404)
raceethnicity.factor=Other	-0.335	0.399	(-1.12, 0.447)
education	-0.002	0.053	(-0.107, 0.102)
enrolled.dx.factor=MCI	-0.347	0.290	(-0.915, 0.222)
enrolled.dx.factor=Ambiguous At Risk	-0.537	0.526	(-1.57, 0.494)
apoe4pos.factor=No	-0.128	0.278	(-0.674, 0.417)
htnrx.factor=No	0.282	0.261	(-0.23, 0.795)

Table 33: Regression for ABP with CVR: SBP Rising Surge and Left Parietal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.100	2.670	(-4.13, 6.34)
systolic.rising.surge	-0.018	0.021	(-0.0599, 0.0229)
ma.left.parietal.lobe.vol	0.000	0.000	(-4.63e-05, 5.17e-05)
age	0.023	0.026	(-0.0287, 0.074)
sex.factor=Female	-0.271	0.399	(-1.05, 0.511)
raceethnicity.factor=Other	-0.049	0.557	(-1.14, 1.04)
education	-0.015	0.074	(-0.161, 0.131)
enrolled.dx.factor=MCI	-0.175	0.405	(-0.969, 0.618)
enrolled.dx.factor=Ambiguous At Risk	-0.315	0.736	(-1.76, 1.13)
apoe4pos.factor=No	-0.293	0.388	(-1.05, 0.468)
htnrx.factor=No	0.707	0.365	(-0.00965, 1.42)

Table 34: Regression for ABP with CVR: SBP Rising Surge and Right Parietal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.160	2.430	(-3.61, 5.92)
systolic.rising.surge	-0.014	0.018	(-0.0498, 0.0218)
ma.right.parietal.lobe.vol	0.000	0.000	(-4.21e-05, 4.58e-05)
age	0.009	0.023	(-0.0362, 0.0546)
sex.factor=Female	-0.160	0.366	(-0.878, 0.557)
raceethnicity.factor=Other	-0.362	0.490	(-1.32, 0.597)
education	0.037	0.065	(-0.091, 0.165)
enrolled.dx.factor=MCI	-0.069	0.357	(-0.768, 0.63)
enrolled.dx.factor=Ambiguous At Risk	-0.038	0.648	(-1.31, 1.23)
apoe4pos.factor=No	-0.340	0.343	(-1.01, 0.333)
htnrx.factor=No	0.712	0.324	(0.0774, 1.35)*

Table 35: Regression for ABP with CVR: SBP Rising Surge and Full Parietal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.050	2.520	(-3.88, 5.98)
systolic.rising.surge	-0.017	0.019	(-0.0546, 0.0207)
ma.parietal.lobe.vol	0.000	0.000	(-2.09e-05, 2.57e-05)
age	0.016	0.024	(-0.0314, 0.063)
sex.factor=Female	-0.206	0.374	(-0.939, 0.526)
raceethnicity.factor=Other	-0.197	0.511	(-1.2, 0.804)
education	0.007	0.068	(-0.127, 0.141)
enrolled.dx.factor=MCI	-0.143	0.372	(-0.872, 0.586)
enrolled.dx.factor=Ambiguous At Risk	-0.235	0.676	(-1.56, 1.09)
apoe4pos.factor=No	-0.325	0.357	(-1.03, 0.375)
htnrx.factor=No	0.716	0.336	(0.0573, 1.38)*

Table 36: Regression for ABP with CVR: SBP Nocturnal Difference and Left Hemisphere

	Coefficient	StdError	95% Conf. Int.
Intercept	4.500	2.420	(-0.239, 9.24)
nocturnal.systolic.diff.sleep.self.reported	-0.026	0.015	(-0.0565, 0.0042)
ma.left.hemisphere	-0.000	0.000	(-8.57e-06, 1.53e-06)
age	-0.002	0.019	(-0.04, 0.0362)
sex.factor=Female	-0.427	0.321	(-1.06, 0.201)
raceethnicity.factor=Other	-0.083	0.409	(-0.885, 0.718)
education	0.039	0.054	(-0.0679, 0.145)
enrolled.dx.factor=MCI	-0.386	0.295	(-0.965, 0.192)
enrolled.dx.factor=Ambiguous At Risk	-0.275	0.537	(-1.33, 0.778)
apoe4pos.factor=No	-0.074	0.282	(-0.627, 0.479)
htnrx.factor=No	0.587	0.265	(0.0664, 1.11)*

Table 37: Regression for ABP with CVR: SBP Nocturnal Difference and Right Hemisphere

	Coefficient	StdError	95% Conf. Int.
Intercept	3.480	2.430	(-1.28, 8.24)
nocturnal.systolic.diff.sleep.self.reported	-0.024	0.015	(-0.0535, 0.00554)
ma.right.hemisphere	-0.000	0.000	(-6.96e-06, 3.34e-06)
age	-0.007	0.019	(-0.0444, 0.03)
sex.factor=Female	-0.294	0.322	(-0.925, 0.336)
raceethnicity.factor=Other	-0.102	0.397	(-0.879, 0.675)
education	0.061	0.053	(-0.0422, 0.165)
enrolled.dx.factor=MCI	-0.286	0.287	(-0.848, 0.277)
enrolled.dx.factor=Ambiguous At Risk	-0.382	0.524	(-1.41, 0.645)
apoe4pos.factor=No	-0.068	0.275	(-0.608, 0.471)
htnrx.factor=No	0.391	0.259	(-0.117, 0.899)

Table 38: Regression for ABP with CVR: SBP Nocturnal Difference and Left Frontal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	3.030	2.200	(-1.27, 7.34)
nocturnal.systolic.diff.sleep.self.reported	-0.029	0.018	(-0.0637, 0.00586)
ma.left.frontal.lobe.vol	-0.000	0.000	(-3.04e-05, 1.1e-05)
age	-0.004	0.022	(-0.0475, 0.039)
sex.factor=Female	-0.115	0.334	(-0.77, 0.54)
raceethnicity.factor=Other	0.040	0.469	(-0.88, 0.96)
education	0.067	0.062	(-0.0554, 0.189)
enrolled.dx.factor=MCI	-0.332	0.342	(-1, 0.338)
enrolled.dx.factor=Ambiguous At Risk	-0.443	0.630	(-1.68, 0.793)
apoe4pos.factor=No	-0.003	0.327	(-0.645, 0.638)
htnrx.factor=No	0.835	0.309	(0.23, 1.44)*

Table 39: Regression for ABP with CVR: SBP Nocturnal Difference and Right Frontal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	2.190	2.190	(-2.09, 6.48)
nocturnal.systolic.diff.sleep.self.reported	-0.026	0.017	(-0.0595, 0.007)
ma.right.frontal.lobe.vol	-0.000	0.000	(-2.52e-05, 1.88e-05)
age	-0.004	0.021	(-0.0452, 0.0373)
sex.factor=Female	-0.155	0.323	(-0.787, 0.478)
raceethnicity.factor=Other	0.164	0.445	(-0.709, 1.04)
education	0.085	0.059	(-0.0317, 0.201)
enrolled.dx.factor=MCI	-0.295	0.325	(-0.932, 0.343)
enrolled.dx.factor=Ambiguous At Risk	-0.574	0.601	(-1.75, 0.603)
apoe4pos.factor=No	-0.047	0.311	(-0.657, 0.563)
htnrx.factor=No	0.629	0.293	(0.0535, 1.2)*

Table 40: Regression for ABP with CVR: SBP Nocturnal Difference and Full Frontal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	2.790	2.110	(-1.36, 6.93)
nocturnal.systolic.diff.sleep.self.reported	-0.027	0.017	(-0.0596, 0.00602)
ma.frontal.lobe.vol	-0.000	0.000	(-1.4e-05, 6.69e-06)
age	-0.005	0.021	(-0.0457, 0.0355)
sex.factor=Female	-0.144	0.316	(-0.763, 0.476)
raceethnicity.factor=Other	0.079	0.440	(-0.783, 0.941)
education	0.075	0.059	(-0.0397, 0.19)
enrolled.dx.factor=MCI	-0.311	0.321	(-0.94, 0.318)
enrolled.dx.factor=Ambiguous At Risk	-0.522	0.592	(-1.68, 0.639)
apoe4pos.factor=No	-0.031	0.307	(-0.633, 0.571)
htnrx.factor=No	0.723	0.290	(0.156, 1.29)*

Table 41: Regression for ABP with CVR: SBP Nocturnal Difference and Left Occipital Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	4.160	2.760	(-1.25, 9.57)
nocturnal.systolic.diff.sleep.self.reported	-0.014	0.019	(-0.051, 0.0223)
ma.left.occipital.lobe.vol	-0.000	0.000	(-0.000138, 1.09e-05)
age	0.027	0.025	(-0.0212, 0.0747)
sex.factor=Female	-0.999	0.383	(-1.75, -0.247)*
raceethnicity.factor=Other	-0.488	0.523	(-1.51, 0.536)
education	0.003	0.068	(-0.131, 0.137)
enrolled.dx.factor=MCI	-0.048	0.371	(-0.776, 0.679)
enrolled.dx.factor=Ambiguous At Risk	0.258	0.674	(-1.06, 1.58)
apoe4pos.factor=No	-0.219	0.356	(-0.917, 0.479)
htnrx.factor=No	0.760	0.335	(0.103, 1.42)*

Table 42: Regression for ABP with CVR: SBP Nocturnal Difference and Right Occipital Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.460	2.470	(-3.38, 6.31)
nocturnal.systolic.diff.sleep.self.reported	-0.004	0.018	(-0.0399, 0.0312)
ma.right.occipital.lobe.vol	-0.000	0.000	(-7.91e-05, 4.52e-05)
age	0.011	0.024	(-0.0353, 0.0576)
sex.factor=Female	-0.420	0.365	(-1.14, 0.297)
raceethnicity.factor=Other	-0.865	0.501	(-1.85, 0.117)
education	0.095	0.067	(-0.0362, 0.226)
enrolled.dx.factor=MCI	0.339	0.363	(-0.372, 1.05)
enrolled.dx.factor=Ambiguous At Risk	0.344	0.662	(-0.954, 1.64)
apoe4pos.factor=No	-0.017	0.350	(-0.702, 0.668)
htnrx.factor=No	0.134	0.331	(-0.514, 0.782)

Table 43: Regression for ABP with CVR: SBP Nocturnal Difference and Full Occipital Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	2.950	2.470	(-1.9, 7.79)
nocturnal.systolic.diff.sleep.self.reported	-0.009	0.017	(-0.0424, 0.0248)
ma.occipital.lobe.vol	-0.000	0.000	(-5.21e-05, 1.44e-05)
age	0.018	0.022	(-0.0263, 0.0614)
sex.factor=Female	-0.684	0.349	(-1.37, 0.000357)
raceethnicity.factor=Other	-0.627	0.475	(-1.56, 0.305)
education	0.038	0.063	(-0.085, 0.162)
enrolled.dx.factor=MCI	0.101	0.340	(-0.566, 0.768)
enrolled.dx.factor=Ambiguous At Risk	0.323	0.621	(-0.894, 1.54)
apoe4pos.factor=No	-0.119	0.328	(-0.762, 0.524)
htnrx.factor=No	0.453	0.309	(-0.154, 1.06)

Table 44: Regression for ABP with CVR: SBP Nocturnal Difference and Left Temporal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	3.580	2.190	(-0.704, 7.86)
nocturnal.systolic.diff.sleep.self.reported	-0.021	0.015	(-0.0503, 0.00881)
ma.left.temporal.lobe.vol	-0.000	0.000	(-5.64e-05, 2.39e-05)
age	0.002	0.019	(-0.0361, 0.0401)
sex.factor=Female	-0.413	0.316	(-1.03, 0.206)
raceethnicity.factor=Other	-0.528	0.411	(-1.33, 0.278)
education	-0.009	0.055	(-0.116, 0.0987)
enrolled.dx.factor=MCI	-0.538	0.299	(-1.12, 0.0479)
enrolled.dx.factor=Ambiguous At Risk	-0.231	0.543	(-1.29, 0.832)
apoe4pos.factor=No	-0.100	0.286	(-0.661, 0.462)
htnrx.factor=No	0.481	0.270	(-0.0475, 1.01)

Table 45: Regression for ABP with CVR: SBP Nocturnal Difference and Right Temporal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	3.340	2.490	(-1.54, 8.21)
nocturnal.systolic.diff.sleep.self.reported	-0.014	0.017	(-0.0475, 0.0195)
ma.right.temporal.lobe.vol	0.000	0.000	(-4.38e-05, 4.66e-05)
age	-0.012	0.022	(-0.0547, 0.0308)
sex.factor=Female	-0.177	0.358	(-0.878, 0.524)
raceethnicity.factor=Other	-0.048	0.456	(-0.942, 0.845)
education	0.001	0.061	(-0.12, 0.121)
enrolled.dx.factor=MCI	-0.425	0.332	(-1.08, 0.225)
enrolled.dx.factor=Ambiguous At Risk	-0.758	0.601	(-1.94, 0.421)
apoe4pos.factor=No	-0.111	0.319	(-0.736, 0.515)
htnrx.factor=No	0.060	0.299	(-0.526, 0.646)

Table 46: Regression for ABP with CVR: SBP Nocturnal Difference and Full Temporal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	3.390	2.170	(-0.867, 7.65)
nocturnal.systolic.diff.sleep.self.reported	-0.017	0.015	(-0.0453, 0.0124)
ma.temporal.lobe.vol	-0.000	0.000	(-2.34e-05, 1.68e-05)
age	-0.005	0.019	(-0.0424, 0.032)
sex.factor=Female	-0.293	0.311	(-0.902, 0.317)
raceethnicity.factor=Other	-0.311	0.399	(-1.09, 0.471)
education	-0.005	0.053	(-0.11, 0.0995)
enrolled.dx.factor=MCI	-0.468	0.290	(-1.04, 0.101)
enrolled.dx.factor=Ambiguous At Risk	-0.534	0.526	(-1.57, 0.497)
apoe4pos.factor=No	-0.089	0.278	(-0.635, 0.457)
htnrx.factor=No	0.289	0.261	(-0.223, 0.802)

Table 47: Regression for ABP with CVR: SBP Nocturnal Difference and Left Parietal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.290	2.670	(-3.95, 6.52)
nocturnal.systolic.diff.sleep.self.reported	-0.025	0.021	(-0.0668, 0.016)
ma.left.parietal.lobe.vol	0.000	0.000	(-4.52e-05, 5.28e-05)
age	0.022	0.026	(-0.0294, 0.0733)
sex.factor=Female	-0.312	0.399	(-1.09, 0.469)
raceethnicity.factor=Other	-0.010	0.557	(-1.1, 1.08)
education	-0.016	0.074	(-0.162, 0.13)
enrolled.dx.factor=MCI	-0.197	0.405	(-0.99, 0.597)
enrolled.dx.factor=Ambiguous At Risk	-0.151	0.736	(-1.59, 1.29)
apoe4pos.factor=No	-0.277	0.388	(-1.04, 0.484)
htnrx.factor=No	0.718	0.365	(0.00171, 1.43)*

Table 48: Regression for ABP with CVR: SBP Nocturnal Difference and Right Parietal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.220	2.430	(-3.54, 5.98)
nocturnal.systolic.diff.sleep.self.reported	-0.025	0.018	(-0.0612, 0.0104)
ma.right.parietal.lobe.vol	0.000	0.000	(-3.86e-05, 4.94e-05)
age	0.009	0.023	(-0.0366, 0.0542)
sex.factor=Female	-0.205	0.366	(-0.922, 0.512)
raceethnicity.factor=Other	-0.322	0.490	(-1.28, 0.638)
education	0.035	0.065	(-0.0934, 0.162)
enrolled.dx.factor=MCI	-0.118	0.357	(-0.817, 0.581)
enrolled.dx.factor=Ambiguous At Risk	0.094	0.648	(-1.18, 1.36)
apoe4pos.factor=No	-0.317	0.343	(-0.989, 0.356)
htnrx.factor=No	0.726	0.324	(0.0914, 1.36)*

Table 49: Regression for ABP with CVR: SBP Nocturnal Difference and Full Parietal Lobe

	Coefficient	StdError	95% Conf. Int.
Intercept	1.160	2.520	(-3.77, 6.09)
nocturnal.systolic.diff.sleep.self.reported	-0.025	0.019	(-0.0628, 0.0126)
ma.parietal.lobe.vol	0.000	0.000	(-1.97e-05, 2.69e-05)
age	0.015	0.024	(-0.032, 0.0624)
sex.factor=Female	-0.246	0.374	(-0.978, 0.487)
raceethnicity.factor=Other	-0.156	0.511	(-1.16, 0.845)
education	0.005	0.068	(-0.129, 0.139)
enrolled.dx.factor=MCI	-0.172	0.372	(-0.9, 0.557)
enrolled.dx.factor=Ambiguous At Risk	-0.085	0.676	(-1.41, 1.24)
apoe4pos.factor=No	-0.307	0.357	(-1.01, 0.392)
htnrx.factor=No	0.729	0.336	(0.0695, 1.39)*

6.2 Restricted Cubic Spline Model Output

The following table presents coefficient results for the models originally fit with ABP predictors modeled as restricted cubic splines.

Table 50: Coefficients for ABP with CVR: ABP Modeled as Restricted Cubic Spline with 3 Knots

	Systolic Prewaking Surge	Systolic Rising Surge	Nocturnal SBP Difference
Left Hemisphere	(-0.013,0.006)	(-0.027,0.024)	(-0.107, 0.098)
Right Hemisphere	(-0.015,0.021)	(-0.023,0.02)	(-0.078, 0.069)
Left Frontal Lobe	(-0.019,0.015)	(-0.039,0.039)	(-0.115, 0.102)
Right Frontal Lobe	(-0.03,0.044)	(-0.027,0.023)	(-0.11, 0.103)
Full Frontal Lobe	(-0.024,0.029)	(-0.034,0.031)	(-0.111, 0.101)
Left Occipital Lobe	(0.001,-0.032)	(-0.026,0.03)	(-0.063, 0.058)
Right Occipital Lobe	(-0.012,0.009)	(-0.042,0.043)	(-0.051, 0.059)
Full Occipital Lobe	(-0.004,-0.013)	(-0.034,0.037)	(-0.057, 0.058)
Left Temporal Lobe	(-0.009,0)	(-0.017,0.019)	(-0.122, 0.119)
Right Temporal Lobe	(0.018,-0.016)	(0.003,0.003)	(0.016, -0.039)
Full Temporal Lobe	(0.005,-0.008)	(-0.005,0.009)	(-0.049, 0.038)
Left Parietal Lobe	(-0.023,0.016)	(-0.06,0.065)	(-0.067, 0.062)
Right Parietal Lobe	(-0.032,0.037)	(-0.06,0.067)	(-0.095, 0.097)
Full Parietal Lobe	(-0.028,0.027)	(-0.06,0.065)	(-0.081, 0.079)

- Since we are using 3 knots, each ABP variable has 2 associated coefficients

Note: Coefficients from fitting a restricted cubic spline are not directly interpretable regarding effect on the CVR measurements in each region of interest. Rather than interpreting the table above, we provide partial effect plots as a visual representation of ABP effect on CVR for each model.

6.3 Partial Effect Plots

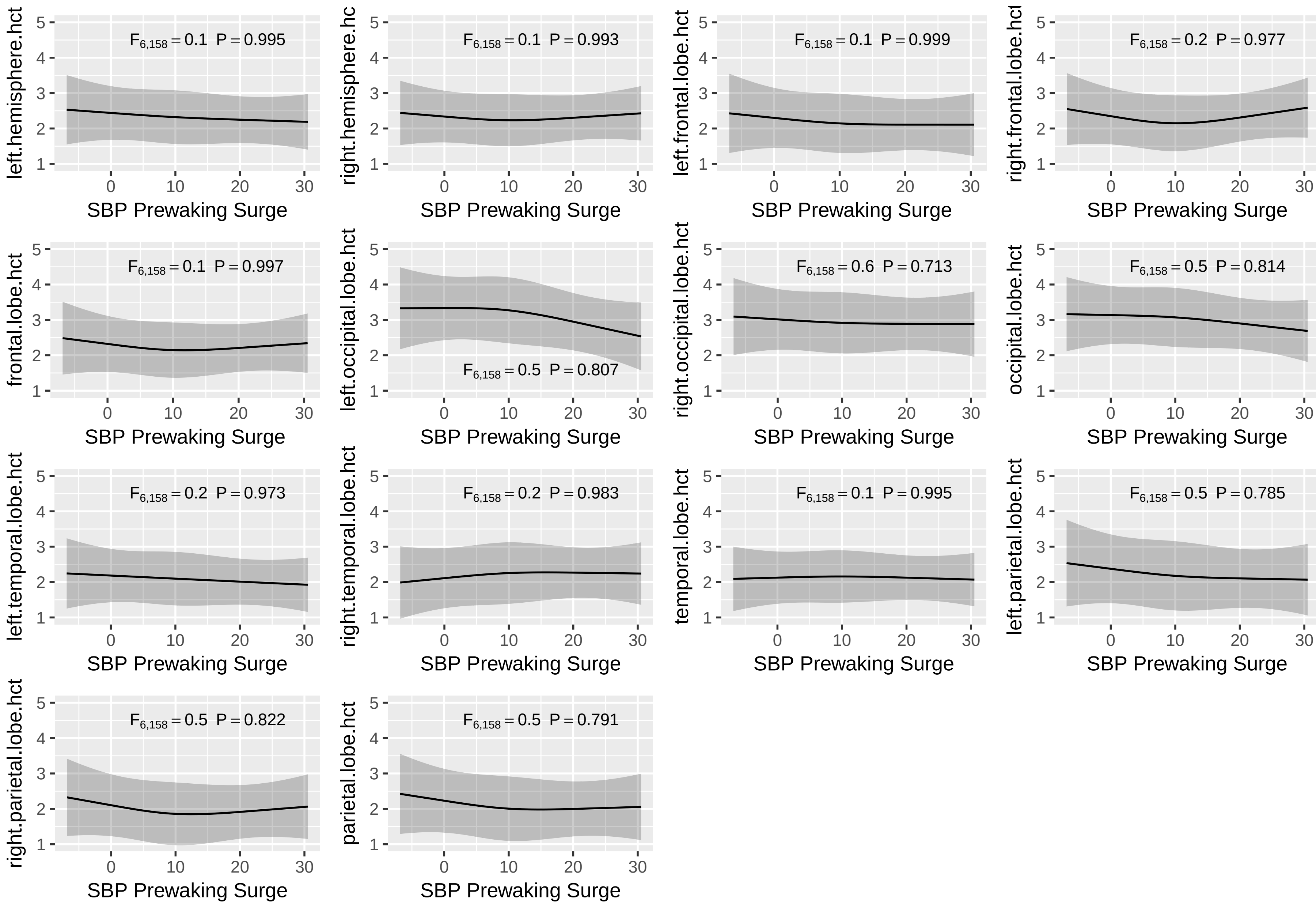
Partial effect plots show the effect of each ABP measure on CVR outcome with other variables in the model fixed. Due to the exploratory nature of this analysis, these plots are presented for the models in which ABP predictors were represented as restricted cubic splines. This is to allow effects to differ at different values of the systolic blood pressure measurement distributions.

- ABP:diagnosis interactions were included in these models to make the stratified partial effect plots more informative.
- A single plot is presented from each model for the predictor of interest against the CVR outcome for the specified region of interest, overall and stratified by diagnosis.
- By default, continuous variables are fixed at their median and categorical variables are fixed at their mode.

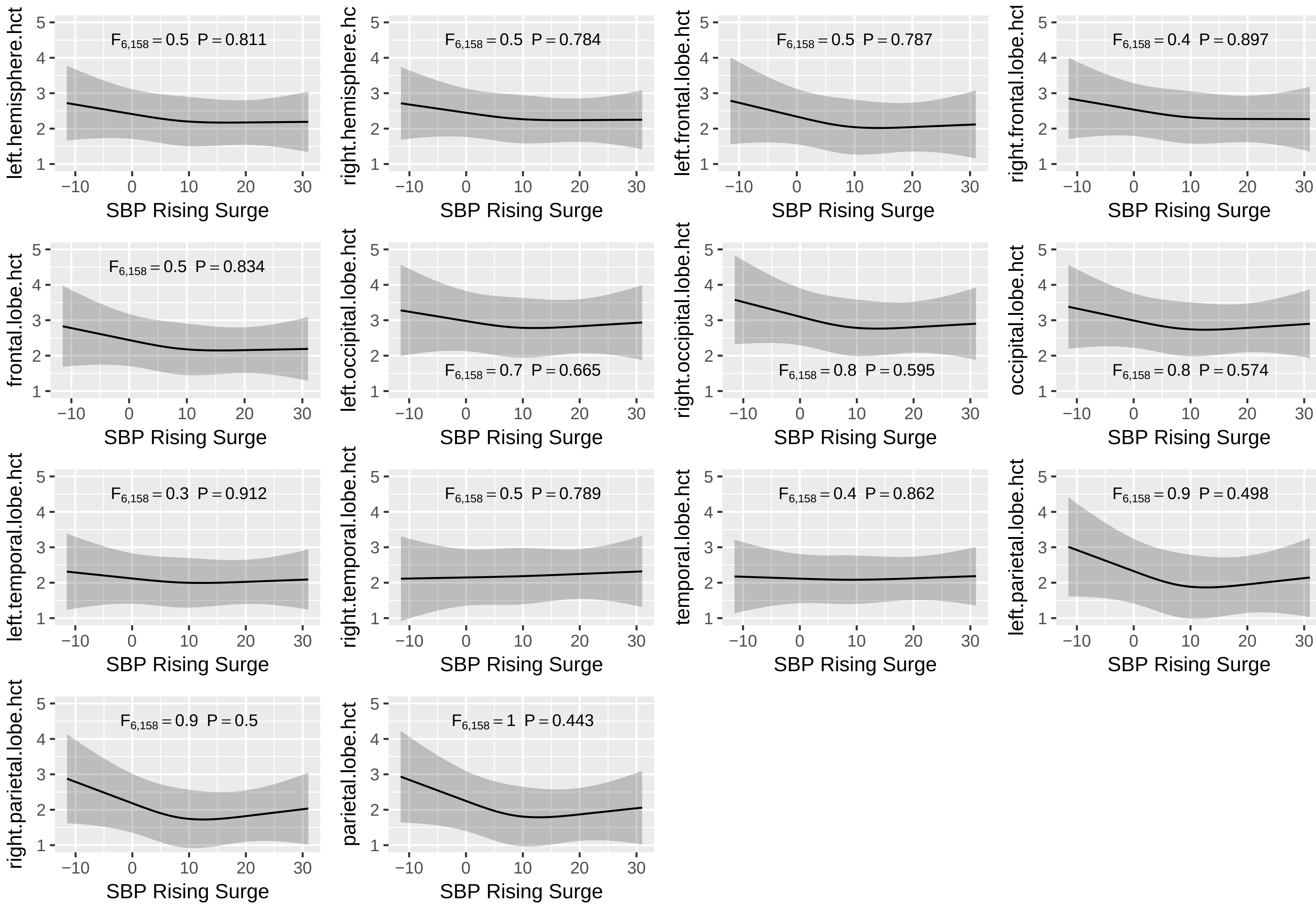
Plot comments:

- Generally, all curves have a slight decline for lower ABP values then tend to level off.
- No consistent ordering of diagnosis group response across brain regions, and curves for all diagnosis groups are highly similar.
- The Ambiguous At Risk group had the largest variability for Nocturnal Difference in SBP. However, since there are only 11 patients in this group, this may be spurious.

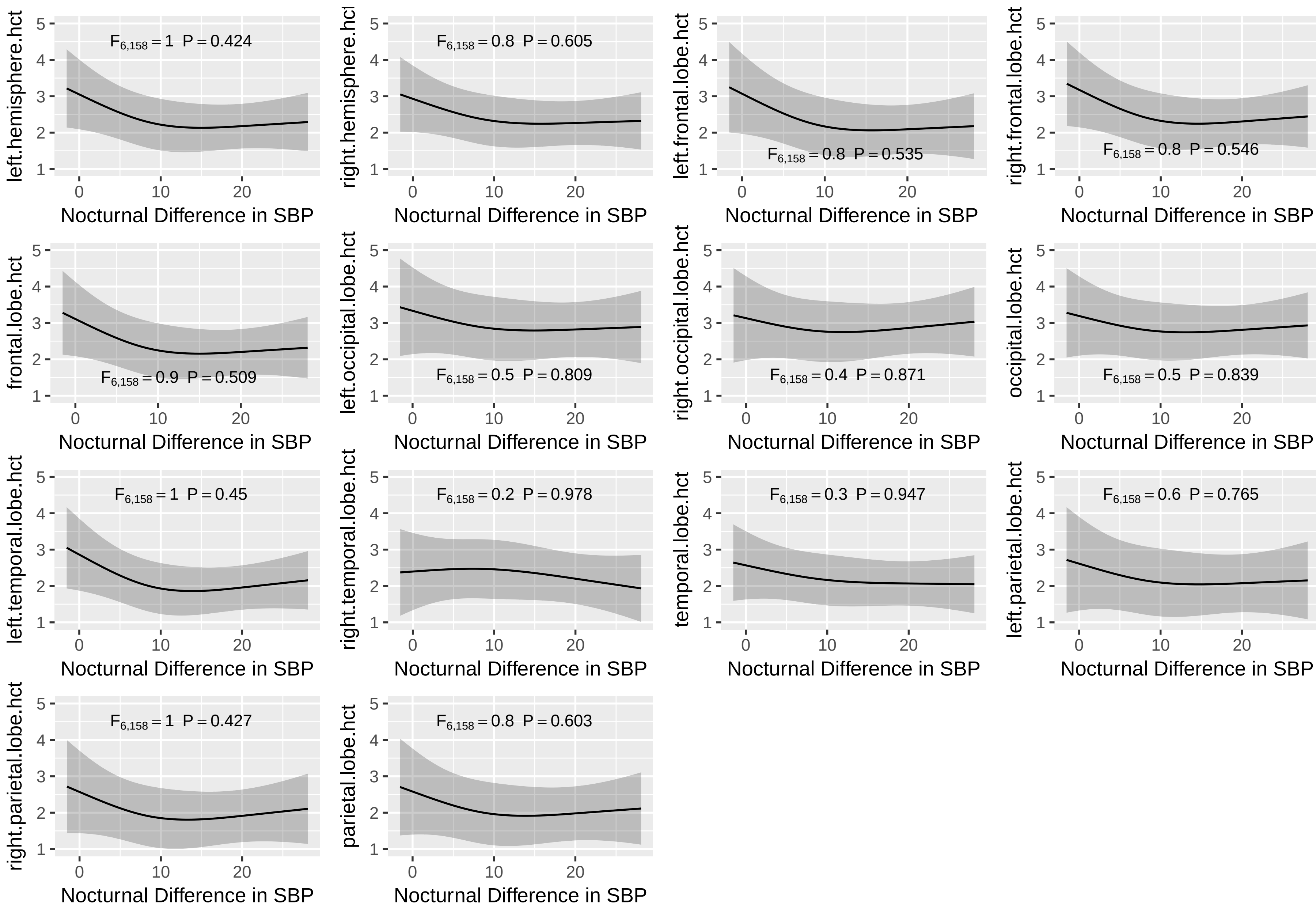
6.3.1 SBP Prewaking Surge



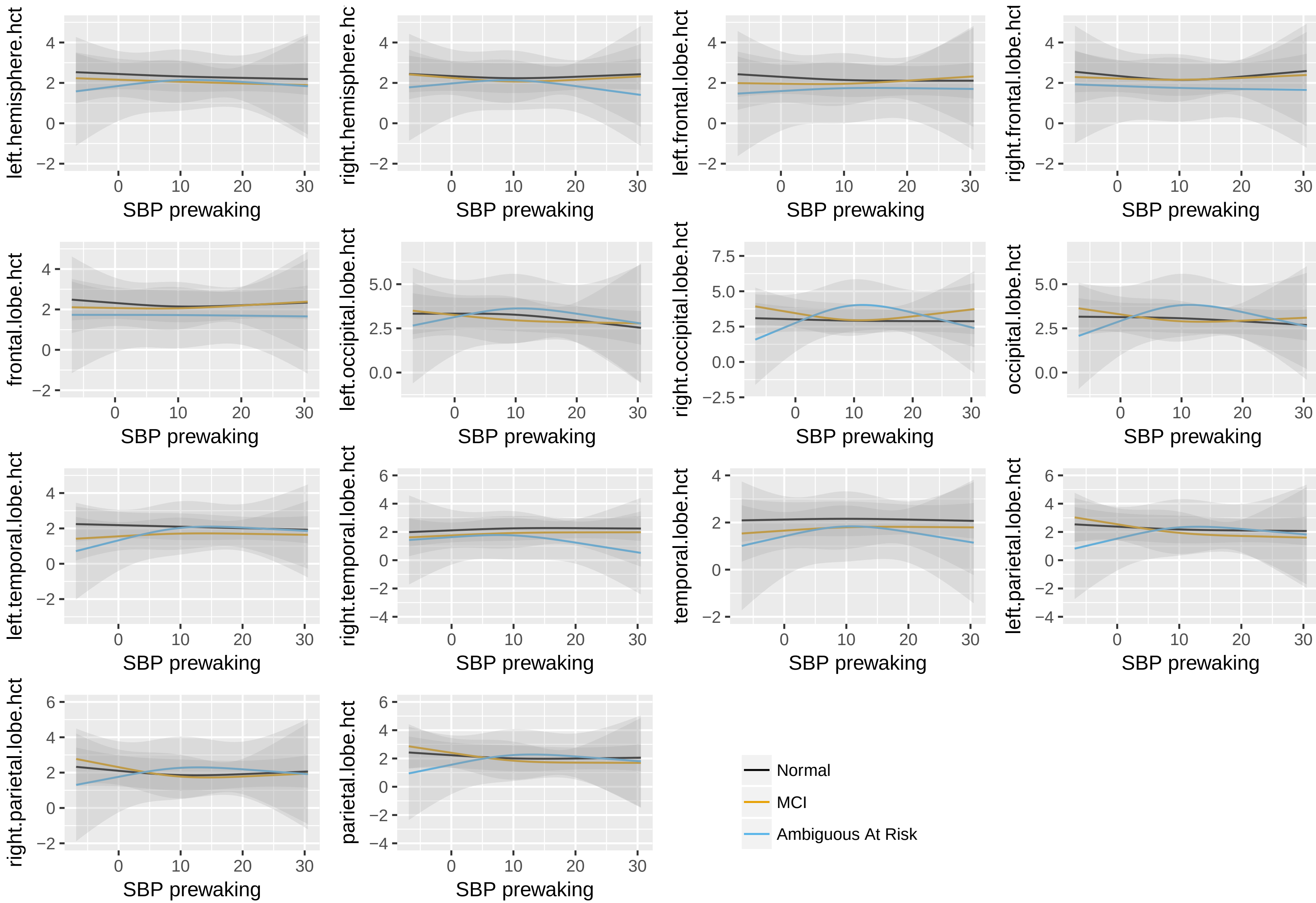
6.3.2 SBP Rising Surge



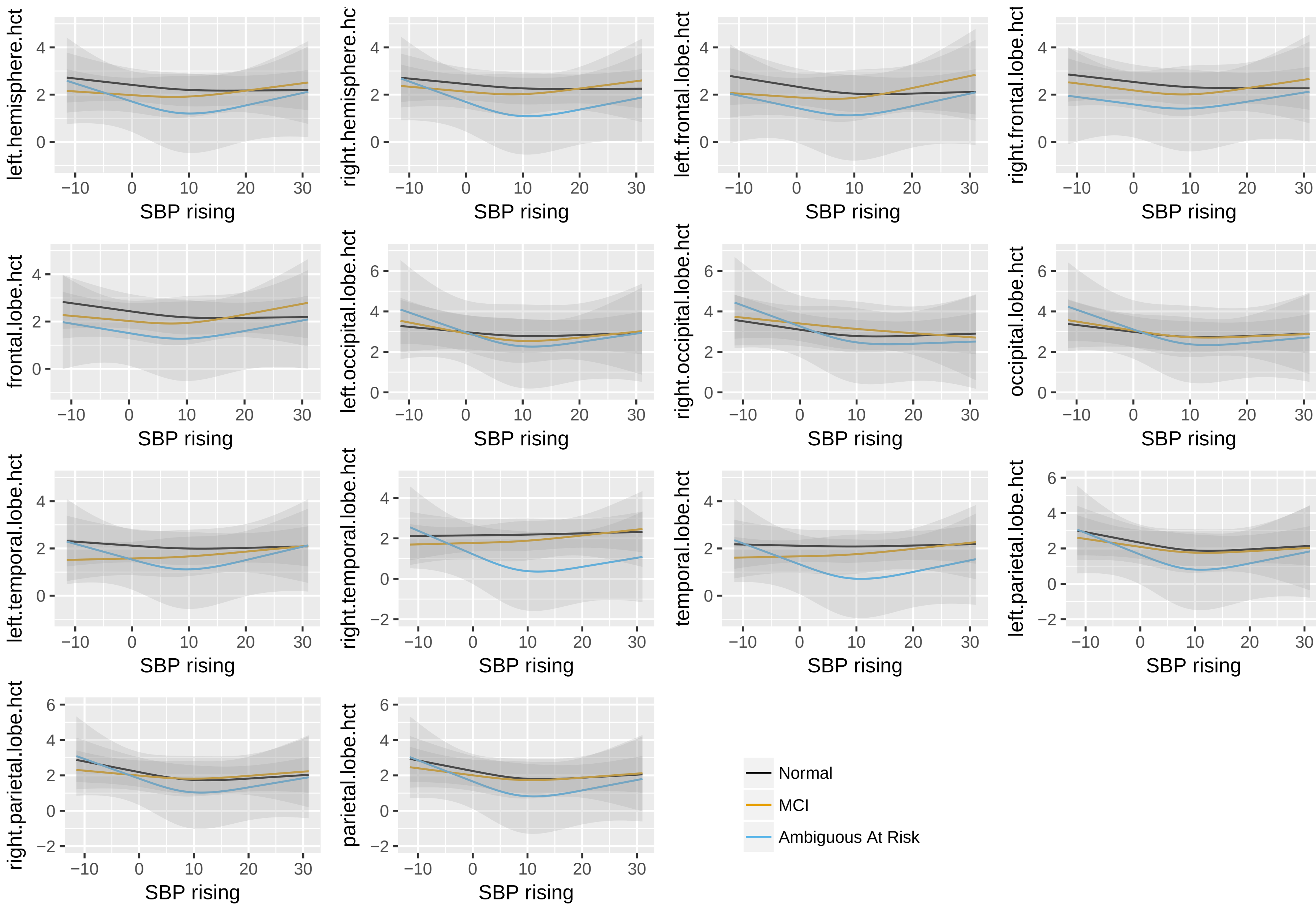
6.3.3 Nocturnal Decline in SBP



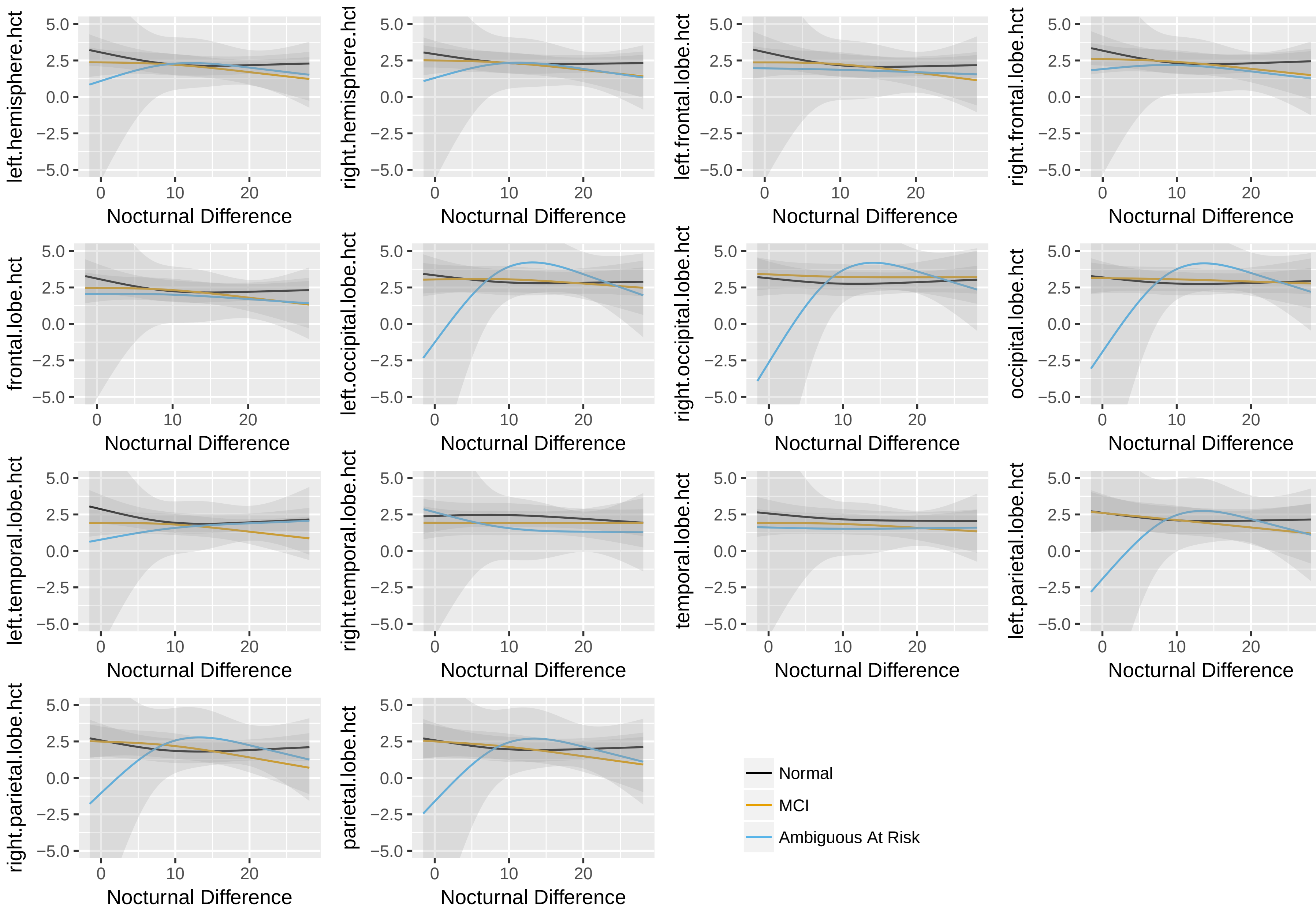
6.3.4 SBP Prewaking Surge by Diagnosis



6.3.5 SBP Rising Surge by Diagnosis



6.3.6 Nocturnal Decline in SBP by Diagnosis



6.4 Tests of Linearity for ABP Measures

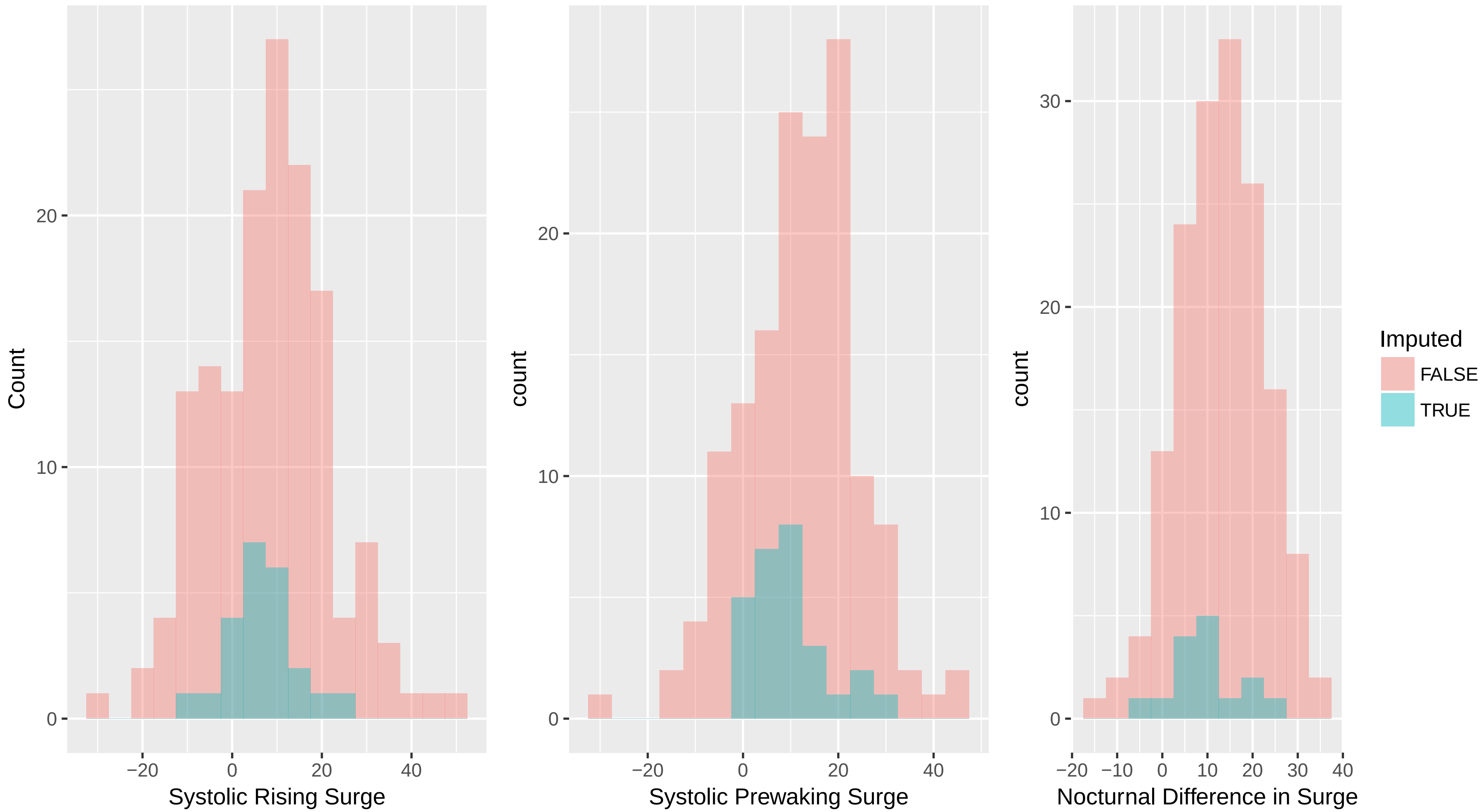
- The following table represents results for tests of linearity of the ABP measurements, when each ABP measure is modeled as a restricted cubic spline with three knots.
- No evidence to suggest the effect is truly non-linear for any model. (All p-values are greater than 0.05.)

Table 51: P-values for test of linearity for ABP predictors

	SBP Prewaking Surge	SBP Rising Surge	Nocturnal SBP Difference
Left Hemisphere	0.931	0.686	0.302
Right Hemisphere	0.850	0.622	0.465
Left Frontal Lobe	0.980	0.903	0.375
Right Frontal Lobe	0.951	0.894	0.408
Full Frontal Lobe	0.976	0.907	0.364
Left Occipital Lobe	0.842	0.750	0.327
Right Occipital Lobe	0.267	0.811	0.425
Full Occipital Lobe	0.526	0.847	0.352
Left Temporal Lobe	0.831	0.667	0.235
Right Temporal Lobe	0.930	0.507	0.902
Full Temporal Lobe	0.872	0.543	0.809
Left Parietal Lobe	0.768	0.763	0.518
Right Parietal Lobe	0.765	0.768	0.237
Full Parietal Lobe	0.751	0.749	0.364

6.5 Imputation Validity

- Distribution of each of the predictors with the distribution of the imputed values overlayed in blue.
- This is to display that the imputations are consistent with the observed data.



7 R session information

```
R version 3.3.2 (2016-10-31)
Packages:
          Version
Formula     1.2-1
ggplot2     2.2.1
gridExtra   2.2.1
Hmisc       4.0-2
knitr      1.15.1
rms         5.1-0
SparseM      1.72
xtable      1.8-2
                                                                             Depends
Formula                                                        R (>= 2.0.0), stats
ggplot2                                                                 R (>= 3.1)
gridExtra                                                                     <NA>
Hmisc                        lattice, survival (>= 2.40-1), Formula, ggplot2 (>= 2.2)
knitr                                                                 R (>= 3.1.0)
rms       Hmisc (>= 4.0-2), survival (>= 2.40-1), lattice, ggplot2 (>=\n2.2), SparseM
SparseM                                                       R (>= 2.15), methods
xtable                                                               R (>= 2.10.0)
```

8 Roles and Responsibilities

Hannah Weeks

- Project overview and statistical analysis plan
- Model fitting and partial effect plots
- Tests of association and linearity
- Interaction analysis
- Secondary aim

Brooklyn Stanley

- Data cleaning
- Application of inclusion/exclusion criteria
- Descriptive statistics
- Imputation and associated sensitivity analysis
- Tables for full regression output of linear models

9 Code Appendix

```r
# R options
#options(scipen= 8)
library(knitr)
# options for knitr
opts_chunk$set(tidy= FALSE)
opts_chunk$set(highlight= TRUE)
opts_chunk$set(comment= NA)
opts_chunk$set(
    fig.path   = 'figure/graphics-',
    cache.path = 'cache/graphics-',
    fig.align  = 'center',
    #dev        = 'postscript',
    dev        = 'pdf',
    fig.width  = 5,
    fig.height = 5,
    fig.show   = 'hold',
    cache      = FALSE,
    par        = TRUE
    )
opts_chunk$set(echo= FALSE)
opts_chunk$set(warning= FALSE)
opts_chunk$set(message= FALSE)
#opts_chunk$set(results= 'hide')

knit_hooks$set(
    par= function(before, options, envir){
        if (before && options$fig.show != 'none') {
            par(
                mar      = c(4, 4, 2.1, .1),
                cex.lab  = .95,
                cex.axis = .9,
                mgp      = c(2, .7, 0),
                tcl      = -.3)
        }
    }
)

knit_hooks$set(inline = function(x) {
   if (is.numeric(x)) round(x, 3) else x})
# Setting up R
rm(list= ls())
options(datadist= NULL)

# So that rms functions will work correctly with ordered factors
options(contrasts=c("contr.treatment","contr.treatment"))


# other libraries
library(Hmisc)
library(rms)
library(xtable)
library(ggplot2)
library(grid)
library(gridExtra) # for grid.arrange

set.seed(20170215)
runPlot=TRUE
runAnalyses=TRUE
#######################################
#  File Directory                     #
```

```r
########################################
proj.dir <- file.path("~", "Documents", "BIOS7352", "Project1")
data.dir <- file.path(proj.dir, "dataForABP_CBF_2017-01-11.rds")

datfile  <- file.path(data.dir)

########################################
#  Variables                           #
########################################

# Descriptive and Adjusting Variables
cov.con <- Cs(age, education)
cov.cat <- Cs(enrolled.dx.factor, sex.factor, raceethnicity.factor,
              apoe4pos.factor, enrolled.dx.factor,
              htnrx.factor, diabetes.factor, currentsmoking.factor, cvd.factor, afib.factor,  echo.lvh.factor)

desc.cov <- c(cov.cat,
              cov.con)

#covariates for model
model.cov <- Cs(age, raceethnicity.factor, education, enrolled.dx.factor, apoe4pos.factor)

#Predictors
predictors <- Cs(
    systolic.prewaking.surge,
    systolic.rising.surge,
    nocturnal.systolic.diff.sleep.self.reported
)

#Outcomes
outcomes.reac <- Cs(asl.reac.left.hemisphere,
                    asl.reac.right.hemisphere,
                    asl.reac.left.frontal.lobe,
                    asl.reac.right.frontal.lobe,
                    asl.reac.frontal.lobe,
                    asl.reac.left.occipital.lobe,
                    asl.reac.right.occipital.lobe,
                    asl.reac.occipital.lobe,
                    asl.reac.left.temporal.lobe,
                    asl.reac.right.temporal.lobe,
                    asl.reac.temporal.lobe,
                    asl.reac.left.parietal.lobe,
                    asl.reac.right.parietal.lobe,
                    asl.reac.parietal.lobe)
outcomes.reac=paste0(outcomes.reac, '.hct')

ma.vars <- Cs(     ma.left.hemisphere,
                   ma.right.hemisphere,
                   ma.left.frontal.lobe.vol,
                   ma.right.frontal.lobe.vol,
                   ma.frontal.lobe.vol,
                   ma.left.occipital.lobe.vol,
                   ma.right.occipital.lobe.vol,
                   ma.occipital.lobe.vol,
                   ma.left.temporal.lobe.vol,
                   ma.right.temporal.lobe.vol,
                   ma.temporal.lobe.vol,
                   ma.left.parietal.lobe.vol,
                   ma.right.parietal.lobe.vol,
                   ma.parietal.lobe.vol)

outcomes.list=vector("list", 1)
```

```r
names(outcomes.list)=c("ASL.Reac")
outcomes.list[['ASL.Reac']]=outcomes.reac

outcomes=unlist(outcomes.list)

# Exclusion Criteria Variables
excl.var <- Cs(time.reading.indicator, asl.reac.usable)

#Read in the data
totalData <- readRDS(datfile)
#######################################
#  Inclusion/Exclusion                #
#######################################

#Dementia
cvrdata <- totalData[totalData$enrolled.dx.factor != "Dementia",
                     c(1:18, grep("asl.reac", names(totalData)),
                       grep("ma.", names(totalData)))]
#Quality check
cvrdata <- totalData[totalData$asl.reac.usable == 1,]
#At least 39 readings
cvrdata <- cvrdata[cvrdata$time.reading.indicator == 'Yes' &
                     !is.na(cvrdata$time.reading.indicator),]

#Excluded patients
exclude <- totalData[!(totalData$map.id %in% cvrdata$map.id),
                     c(1:18, 61, grep("asl.reac", names(totalData)),
                       grep("ma.", names(totalData)))]

label(cvrdata$echo.lvh.factor) <- "LV Hypertrophy"
label(cvrdata$afib.factor) <- "A-fib"
label(cvrdata$cvd.factor) <- "CVD"
label(cvrdata$diabetes.factor) <- "Diabetic"
label(cvrdata$systolic.prewaking.surge) <- "Systolic Prewaking Surge"
label(cvrdata$systolic.rising.surge) <- "Systolic Rising Surge"
label(cvrdata$nocturnal.systolic.diff.sleep.self.reported) <- "Nocturnal Systolic Difference"


#######################################
#  Inclusion/Exclusion Comparison     #
#######################################

cats <- names(cvrdata)[3:18]
comparison <- c(c(), c(), c(),c())
is <- length(cvrdata$map.id)
xs <- length(exclude$map.id)
for (cat in cats){
  if (is.factor(cvrdata[,cat])){
    chiData <- rbind(cbind(cvrdata[,cat],rep("is", length(cvrdata[,cat]))),
                     cbind(exclude[,cat],rep("xs", length(exclude[,cat]))))
    pp <- chisq.test(table(chiData[,1], chiData[,2]))$p.value
    comparison <- rbind(comparison, c(label(cvrdata[,cat]),'','', round(pp,4)))
    for (lev in levels(cvrdata[,cat])){
      comparison <- rbind(comparison, c(paste("--",lev ),
                      paste(s <- sum(cvrdata[,cat]==lev, na.rm=T), " (", round(s*100/is),
                            "%)", sep=""),
                      paste(s <- sum(exclude[,cat]==lev, na.rm=T), " (", round(s*100/xs),
                            "%)", sep=""),""))
    }
    next
  }
```

```r
  anovaData <- as.data.frame(rbind(cbind(cvrdata[,cat],rep("is", length(cvrdata[,cat]))),
                   cbind(exclude[,cat],rep("xs", length(exclude[,cat])))))
  anovaData[,1] <- as.numeric(as.character(anovaData[,1]))
  pp <- kruskal.test(anovaData[,1] ~ anovaData[,2])$p.value
  comparison <- rbind(c(label(cvrdata[,cat]),
              paste(round(mean(cvrdata[,cat], na.rm=T),1)," (",
                    round(sd(cvrdata[,cat],na.rm=T),1), ")",sep=""),
              paste(round(mean(exclude[,cat], na.rm=T),1)," (",
                    round(sd(exclude[,cat],na.rm=T),1), ")",sep=""),
              round(pp,4)), comparison)
}
comparison <- as.data.frame(comparison[,c(1,3,2,4)])

colnames(comparison) <- c("Variable",
                          paste0("\\parbox{.5in}{Excluded N=", nrow(exclude), "}"),
                          paste0("\\parbox{.9in}{Analyzed Data N=", nrow(cvrdata), "}"),
                          "P-Value")

print(xtable(comparison,
      caption="Comparison of Demographics for Excluded and Included Data"),
      include.rownames = FALSE,
      caption.placement = "top", table.placement = "ht",
      sanitize.colnames.function = force, booktabs = TRUE)
#######################################
#  Table of Covariates by dx Group    #
#######################################

cats <- names(cvrdata)[3:18][-4]
comparison.dx <- c(c(), c(), c(),c())
mciData <- cvrdata[cvrdata$enrolled.dx.factor=="MCI",]
normData <- cvrdata[cvrdata$enrolled.dx.factor=="Normal",]
abData <- cvrdata[cvrdata$enrolled.dx.factor=="Ambiguous At Risk",]
ms <- length(mciData$map.id)
ns <- length(normData$map.id)
as <- length(abData$map.id)
for (cat in cats){
  if (is.factor(cvrdata[,cat])){
    chiData <- rbind(cbind(normData[,cat],rep("ns", length(normData[,cat]))),
                   cbind(mciData[,cat],rep("ms", length(mciData[,cat]))),
                   cbind(abData[,cat],rep("as", length(abData[,cat]))))
    pp <- chisq.test(table(chiData[,1], chiData[,2]))$p.value
    comparison.dx <- rbind(comparison.dx, c(label(cvrdata[,cat]),'','','', round(pp,4)))
    for (lev in levels(cvrdata[,cat])){
      comparison.dx <- rbind(comparison.dx, c(paste("--",lev ),
                    paste(s <- sum(normData[,cat]==lev, na.rm=T), " (", round(s*100/ns),
                          "%)", sep=""),
                    paste(s <- sum(mciData[,cat]==lev, na.rm=T), " (", round(s*100/ms),
                          "%)", sep=""),
                    paste(s <- sum(abData[,cat]==lev, na.rm=T), " (", round(s*100/as),
                          "%)", sep=""), ''))
    }
    next
  }
  anovaData <- as.data.frame(rbind(cbind(normData[,cat],rep("ns", length(normData[,cat]))),
                   cbind(mciData[,cat],rep("ms", length(mciData[,cat]))),
                   cbind(abData[,cat],rep("as", length(abData[,cat])))))
  anovaData[,1] <- as.numeric(as.character(anovaData[,1]))
  pp <- kruskal.test(anovaData[,1] ~ anovaData[,2])$p.value
  comparison.dx <- rbind(c(label(cvrdata[,cat]),
              paste(round(mean(normData[,cat], na.rm=T),1)," (",
                    round(sd(normData[,cat],na.rm=T),1), ")",sep=""),
```

```r
                paste(round(mean(mciData[,cat], na.rm=T),1)," (",
                      round(sd(mciData[,cat],na.rm=T),1), ")",sep=""),
                paste(round(mean(abData[,cat], na.rm=T),1)," (",
                      round(sd(abData[,cat],na.rm=T),1), ")",sep=""),
                round(pp, 4)), comparison.dx)
}
comparison.dx <- as.data.frame(comparison.dx)
colnames(comparison.dx) <- c("Variable",
                             paste0("\\parbox{.5in}{Normal N=", nrow(normData), "}"),
                             paste0("\\parbox{.41in}{MCI    N=", nrow(mciData), "}"),
                             paste0("\\parbox{.61in}{Ambiguous At-Risk      N=", nrow(abData), "}"),
                             "P-value")

comparison.dx$Variable <- as.character(comparison.dx$Variable)


print(xtable(comparison.dx, caption =
               paste0("Comparison of Demographics by Consensus Diagnosis (N = ",
                      nrow(cvrdata), ")")),
      caption.placement = "top", include.rownames = FALSE,
      sanitize.colnames.function = force, booktabs = TRUE)
all.predictors <- cvrdata[,c(predictors, model.cov)]
all.outcomes <- cvrdata[, outcomes.reac]

outlong <- c()
for (out in names(all.outcomes)){
  lab <- rep(out, length(all.outcomes[,out]))
  temp <- cbind(all.outcomes[, out], lab, all.predictors)
  outlong <- rbind(outlong, temp)
}

names(outlong)[1] <- "outcome"
levels(outlong$lab) <- c("Left Hemisphere", "Right Hemisphere", "Left Frontal Lobe",
                         "Right Frontal Lobe", "Full Frontal Lobe", "Left Occipital Lobe",
                         "Right Occipital Lobe", "Full Occipital Lobe", "Left Temporal Lobe",
                         "Right Temporal Lobe", "Full Temporal Lobe", "Left Parietal Lobe",
                         "Right Parietal Lobe", "Full Parietal Lobe")

#######################################
#  Outcome Boxplots                   #
#######################################

#Left hemisphere, frontal lobe, occipital lobe
box1 <- ggplot(outlong[c(1:174,349:1392),], aes(factor(lab), outcome)) +
  geom_boxplot(outlier.colour = "purple") +
  theme(legend.position="none", strip.text = element_text(size=12),
        axis.text.x = element_text(size=11, angle = 80, hjust = 1),
        axis.text.y  = element_text(size=12),
        panel.grid.major.x=element_line(colour='grey')) +
  ylab("Measured CVR") + xlab("")

#Right hemisphere, temporal lobe, parietal lobe
box2 <- ggplot(outlong[c(175:348,1393:2436),], aes(factor(lab), outcome)) +
  geom_boxplot(outlier.colour = "purple") +
  theme(legend.position="none", strip.text = element_text(size=12),
        axis.text.x = element_text(size=11, angle = 70, hjust = 1),
        axis.text.y  = element_text(size=14),
        panel.grid.major.x=element_line(colour='grey')) +
  ylab("Measured CVR") + xlab("Area Scanned")

grid.arrange(box1, box2, ncol = 1)
```

```
########################################
#  Outcome Histograms                  #
########################################

ggplot(outlong, aes(x=outcome, fill = enrolled.dx.factor)) +
  geom_histogram(alpha=0.3, position="identity", binwidth = 1) + facet_wrap(~lab, ncol=3) +
  theme_bw() + theme(strip.text = element_text(size=12),
          axis.text.x = element_text(size=10), axis.text.y  = element_text(size=10)) +
  ylab("Count") + xlab("Measured CVR") + scale_fill_discrete(name = "Diagnosis")
########################################
#  Predictor Histograms                #
########################################

hist1 <- ggplot(cvrdata, aes(x=systolic.prewaking.surge, fill = enrolled.dx.factor)) +
  geom_histogram(alpha=0.3, position="identity", binwidth = 5) + theme_bw() +
  xlab("Systolic Prewaking Surge") + ylab("Count") + scale_fill_discrete(name = "Diagnosis")

hist2 <- ggplot(cvrdata, aes(x=systolic.rising.surge, fill = enrolled.dx.factor)) +
  geom_histogram(alpha=0.3, position="identity", binwidth = 5) + theme_bw() +
  xlab("Systolic Rising Surge") + ylab("Count") + scale_fill_discrete(name = "Diagnosis")

hist3 <- ggplot(cvrdata, aes(x=nocturnal.systolic.diff.sleep.self.reported, fill = enrolled.dx.factor)) +
  geom_histogram(alpha=0.3, position="identity", binwidth = 5) + theme_bw() +
  xlab("Nocturnal Difference in Systolic BP") + ylab("Count") + scale_fill_discrete(name = "Diagnosis")

grid.arrange(hist1, hist2, hist3, ncol = 1)
########################################
#  Unadjusted Association              #
########################################

ggplot(outlong, aes(systolic.prewaking.surge, outcome, group=1)) +
  geom_point() + geom_smooth() + facet_wrap(~lab, ncol=3) +
  theme(legend.position="none", strip.text = element_text(size=12),
        axis.text.x = element_text(size=14), axis.text.y  = element_text(size=14),
        panel.grid.major.x=element_line(colour='grey')) +
  ylab("Measured CVR") + xlab("Systolic Prewaking Surge Blood Pressure")
ggplot(outlong, aes(systolic.rising.surge, outcome)) +
  geom_point() + geom_smooth() + facet_wrap(~lab, ncol=3) +
  theme(legend.position="none", strip.text = element_text(size=12),
        axis.text.x = element_text(size=14), axis.text.y  = element_text(size=14),
        panel.grid.major.x=element_line(colour='grey')) +
  ylab("Measured CVR") + xlab("Systolic Rising Surge Blood Pressure")
ggplot(outlong, aes(nocturnal.systolic.diff.sleep.self.reported, outcome, group=1)) +
  geom_point() + geom_smooth() + facet_wrap(~lab, ncol=3) +
  theme(legend.position="none", strip.text = element_text(size=12),
        axis.text.x = element_text(size=14), axis.text.y  = element_text(size=14),
        panel.grid.major.x=element_line(colour='grey')) +
  ylab("Measured CVR") + xlab("Difference in Awake/Sleeping Systolic Blood Pressure")

outlong.interaction <- outlong[outlong$enrolled.dx.factor != "Ambiguous at Risk",]
ggplot(outlong.interaction, aes(systolic.prewaking.surge, outcome, color = enrolled.dx.factor)) +
  geom_point(alpha=0.4) + geom_smooth(se = FALSE) + facet_wrap(~lab, ncol=3) +
  theme(strip.text = element_text(size=12),
        axis.text.x = element_text(size=14), axis.text.y  = element_text(size=14),
        panel.grid.major.x=element_line(colour='grey')) + scale_colour_discrete(name = "Diagnosis") +
  ylab("Measured CVR") + xlab("Systolic Prewaking Surge Blood Pressure")
ggplot(outlong.interaction, aes(systolic.rising.surge, outcome, color = enrolled.dx.factor)) +
  geom_point(alpha=0.4) + geom_smooth(se = FALSE) + facet_wrap(~lab, ncol=3) +
  theme(strip.text = element_text(size=12),
        axis.text.x = element_text(size=14), axis.text.y  = element_text(size=14),
        panel.grid.major.x=element_line(colour='grey')) + scale_colour_discrete(name = "Diagnosis") +
  ylab("Measured CVR") + xlab("Systolic Rising Surge Blood Pressure")
```

```
ggplot(outlong.interaction, aes(nocturnal.systolic.diff.sleep.self.reported, outcome,
                                color = enrolled.dx.factor)) +
  geom_point(alpha=0.4) + geom_smooth(se = FALSE) + facet_wrap(~lab, ncol=3) +
  theme(strip.text = element_text(size=12),
        axis.text.x = element_text(size=14), axis.text.y  = element_text(size=14),
        panel.grid.major.x=element_line(colour='grey')) + scale_colour_discrete(name = "Diagnosis") +
  ylab("Measured CVR") + xlab("Difference in Awake/Sleeping Systolic Blood Pressure")
#######################################
#  Missing Data                      #
#######################################

missing <- c(c(), c())
#comparison[,c("Variable", "Analyzed Data")]
for (cat in cats){
    missing <- rbind(missing, c(label(cvrdata[,cat]),
                                paste(s <- sum(is.na(cvrdata[,cat])),
                                      " (", round(s*100/is, 2), "%)", sep="")))
 }

missing <- as.data.frame(missing)
colnames(missing) <- c("Variable", "Missingness")
missing$Variable <- as.character(missing$Variable)

missing$Variable[grep("pre.wake.mean", missing$Variable)] <- predictors[1]
missing$Variable[grep("pre.wake.1", missing$Variable)] <- predictors[2]
missing$Variable[grep("Diff", missing$Variable)] <- predictors[3]

#Only print variables that actually have values missing
print(xtable(missing[missing$Missingness != "0 (0%)",],
             caption= "Variables with Missing Observations"),
      caption.placement = "top", include.rownames = FALSE)
#######################################
#  Multiple-Imputation               #
#######################################

#Need to re-factor since we removed patients with dementia
cvrdata$enrolled.dx.factor <-factor(cvrdata$enrolled.dx.factor)

#Use ICV and just left and right hemisphere
#  since we don't have the degrees of freedom to control for ROI all volumes
impute.data <- aregImpute(~ systolic.rising.surge + systolic.prewaking.surge +
                            nocturnal.systolic.diff.sleep.self.reported +
                            enrolled.dx.factor + sex.factor + raceethnicity.factor +
                            apoe4pos.factor + education + age +
                            htnrx.factor + icv +
                            asl.reac.left.hemisphere.hct +
                            asl.reac.right.hemisphere.hct,
                          data = cvrdata)
#######################################
#  Model Fitting: Linear Effect      #
#######################################

modelFitLinear <- function(outcome, predictor, ma){

  fit <- fit.mult.impute(as.formula(paste0(outcome, "~", predictor, "+", ma, "+",
"age + sex.factor + raceethnicity.factor + education",
"+ enrolled.dx.factor + apoe4pos.factor + htnrx.factor")),
                         fitter = ols, xtrans = impute.data, data = cvrdata)

  return(fit)
}
```

```r
#Systolic prewaking surge
mod.sys.prewaking.surge.linear <- list()
for(i in seq_along(outcomes.reac)){
  mod.sys.prewaking.surge.linear[[i]] <- modelFitLinear(outcome = outcomes.reac[i],
                                                  predictor = predictors[1],
                                                  ma = ma.vars[i])
}

#Systolic rising surge
mod.sys.rising.surge.linear <- list()
for(i in seq_along(outcomes.reac)){
  mod.sys.rising.surge.linear[[i]] <- modelFitLinear(outcome = outcomes.reac[i],
                                          predictor = predictors[2],
                                          ma = ma.vars[i])
}

#Nocturnal Difference
mod.noc.sys.diff.linear <- list()
for(i in seq_along(outcomes.reac)){
  mod.noc.sys.diff.linear[[i]] <- modelFitLinear(outcome = outcomes.reac[i],
                                          predictor = predictors[3],
                                          ma = ma.vars[i])
}

sys.prewaking.lin.coef <- do.call(rbind, lapply(mod.sys.prewaking.surge.linear,
                             function(x) c(x$coef[grep("prewaking", names(x$coef))],
                                           sqrt(x$var[grep("prewaking", names(x$coef)),
                                                      grep("prewaking", names(x$coef))]),
                                           anova(x)["systolic.prewaking.surge","P"])))


sys.rising.lin.coef <- do.call(rbind, lapply(mod.sys.rising.surge.linear,
                             function(x) c(x$coef[grep("rising", names(x$coef))],
                                           sqrt(x$var[grep("rising", names(x$coef)),
                                                      grep("rising", names(x$coef))]),
                                           anova(x)["systolic.rising.surge","P"])))


noc.diff.lin.coef <- do.call(rbind, lapply(mod.noc.sys.diff.linear,
                             function(x) c(x$coef[grep("noc", names(x$coef))],
                                           sqrt(x$var[grep("noc", names(x$coef)),
                                                      grep("noc", names(x$coef))]),
                                           anova(x)["nocturnal.systolic.diff.sleep.self.reported","P"])))
outcomeNames <- c("Left Hemisphere", "Right Hemisphere", "Left Frontal Lobe",
                  "Right Frontal Lobe", "Full Frontal Lobe", "Left Occipital Lobe",
                  "Right Occipital Lobe", "Full Occipital Lobe", "Left Temporal Lobe",
                  "Right Temporal Lobe", "Full Temporal Lobe", "Left Parietal Lobe",
                  "Right Parietal Lobe", "Full Parietal Lobe")

prewaking.coef.table <- as.data.frame(sys.prewaking.lin.coef, row.names = outcomeNames)

rising.coef.table <- as.data.frame(sys.rising.lin.coef, row.names = outcomeNames)

noc.diff.coef.table <- as.data.frame(noc.diff.lin.coef, row.names = outcomeNames)

addtorow <- list()
addtorow$pos <- list()
addtorow$pos[[1]] <- 0
addtorow$pos[[2]] <- 0
addtorow$command <- c('& \\multicolumn{3}{c}{SBP Prewaking Surge} &
```

```
                      \\multicolumn{3}{c}{SBP Rising Surge} &
                      \\multicolumn{3}{c}{Nocturnal Decline in SBP} \\\\',
                      c('& Coefficient & Standard Error & P-value
                        & Coefficient & Standard Error & P-value
                        & Coefficient & Standard Error & P-value \\\\'))

full.table <- cbind(prewaking.coef.table, rising.coef.table, noc.diff.coef.table)
names(full.table) <- NULL
print(xtable(full.table, align = c("l", rep("r", 9)), digits = 4,
             caption = paste0("Coefficients for Linear ABP with CVR")),
      caption.placement = "top", booktabs = TRUE, add.to.row = addtorow,
      sanitize.text.function = force, table.placement = "ht")
#######################################
#  Model Fitting: Interaction         #
#######################################

modelFitInter <- function(outcome, predictor, ma){

  fit <- fit.mult.impute(as.formula(paste0(outcome, "~", predictor, "*enrolled.dx.factor +", ma, "+",
"age + sex.factor + raceethnicity.factor + education",
" + apoe4pos.factor + htnrx.factor")),
                         fitter = ols, xtrans = impute.data,
data = cvrdata[cvrdata$enrolled.dx.factor != "Ambiguous At Risk",])

  return(fit)
}


#Systolic prewaking surge
mod.sys.prewaking.surge.int <- list()
for(i in seq_along(outcomes.reac)){
  mod.sys.prewaking.surge.int[[i]] <- modelFitInter(outcome = outcomes.reac[i],
                                                    predictor = predictors[1],
                                                    ma = ma.vars[i])
}

#Systolic rising surge
mod.sys.rising.surge.int <- list()
for(i in seq_along(outcomes.reac)){
  mod.sys.rising.surge.int[[i]] <- modelFitInter(outcome = outcomes.reac[i],
                                            predictor = predictors[2],
                                            ma = ma.vars[i])
}

#Nocturnal Difference
mod.noc.sys.diff.int <- list()
for(i in seq_along(outcomes.reac)){
  mod.noc.sys.diff.int[[i]] <- modelFitInter(outcome = outcomes.reac[i],
                                            predictor = predictors[3],
                                            ma = ma.vars[i])
}
#Grab coefficients associated with interaction
sys.prewaking.int.coef <- do.call(rbind, lapply(mod.sys.prewaking.surge.int,
                              function(x) c(x$coef[length(x$coef)],
                                            sqrt(x$var[length(x$coef),
                                                       length(x$coef)]),
                                            anova(x)[" All Interactions","P"])))


sys.rising.int.coef <- do.call(rbind, lapply(mod.sys.rising.surge.int,
                              function(x) c(x$coef[length(x$coef)],
```

```
                                        sqrt(x$var[length(x$coef),
                                                   length(x$coef)]),
                                        anova(x)[" All Interactions","P"]))


noc.diff.int.coef <- do.call(rbind, lapply(mod.noc.sys.diff.int,
                             function(x) c(x$coef[length(x$coef)],
                                        sqrt(x$var[length(x$coef),
                                                   length(x$coef)]),
                                        anova(x)[" All Interactions","P"]))


prewaking.int.table <- as.data.frame(sys.prewaking.int.coef, row.names = outcomeNames)

rising.int.table <- as.data.frame(sys.rising.int.coef, row.names = outcomeNames)

noc.diff.int.table <- as.data.frame(noc.diff.int.coef, row.names = outcomeNames)

addtorow <- list()
addtorow$pos <- list()
addtorow$pos[[1]] <- 0
addtorow$pos[[2]] <- 0
addtorow$command <- c('& \\multicolumn{3}{c}{SBP Prewaking Surge} &
                      \\multicolumn{3}{c}{SBP Rising Surge} &
                      \\multicolumn{3}{c}{Nocturnal Decline in SBP} \\\\',
                      c('& Coefficient & Standard Error & P-value
                        & Coefficient & Standard Error & P-value
                        & Coefficient & Standard Error & P-value \\\\'))

int.table <- cbind(prewaking.int.table, rising.int.table, noc.diff.int.table)
names(int.table) <- NULL
print(xtable(int.table, align = c("l", rep("r", 9)), digits = 4,
             caption = paste0("Coefficients for ABP:CVR Interaction")),
      caption.placement = "top", booktabs = TRUE, add.to.row = addtorow,
      sanitize.text.function = force, table.placement = "ht")
#Select R^2 values for each model
sys.prewaking.r2 <- lapply(mod.sys.prewaking.surge.linear, function(x) x$stats["R2"])
sys.rising.r2 <- lapply(mod.sys.rising.surge.linear, function(x) x$stats["R2"])
noc.sys.diff.r2 <- lapply(mod.noc.sys.diff.linear, function(x) x$stats["R2"])

r2.table <- data.frame("SBP Prewaking Surge" = unlist(sys.prewaking.r2),
                          "SBP Rising Surge" = unlist(sys.rising.r2),
                          "Nocturnal SBP Difference" = unlist(noc.sys.diff.r2),
                          row.names = outcomeNames,
                          check.names = FALSE)

print(xtable(r2.table, digits = 3,
             caption = "R-squared for ABP predictor models"),
      caption.placement = "top")
corMat <- as.data.frame(cor(cvrdata[,outcomes.reac], !is.na(cvrdata[,predictors])),
                        row.names = outcomeNames)
names(corMat) <- c("SBP Prewaking Surge", "SBP Rising Surge", "Nocturnal Decline in SBP")

print(xtable(corMat, digits = 3, caption = "Correlation Matrix for ABP Predictors and CVR Outcomes"),
      caption.placement = "top", booktabs = TRUE)
for (i in 1:14){
  coef <- mod.sys.prewaking.surge.linear[[i]]$coefficients
  se <- sqrt(diag(mod.noc.sys.diff.linear[[i]]$var))
  confUp <- coef + qnorm(0.975)*se
  confLow <- coef - qnorm(0.975)*se
  confInt <- paste("(", signif(confLow,3), ", ", signif(confUp,3), ")",
```

```
                 ifelse(0 < confUp & 0 > confLow, "", "*"), sep="")
  results <- data.frame(Coefficient = signif(coef,3), StdError = signif(se,3), ConfInt=confInt)
  colnames(results)[3] <- "95% Conf. Int."
  print(xtable(results, align = c("l", rep("r", 3)), digits = 3,
           caption = paste0("Regression for ABP with CVR: SBP Prewaking Surge and ", levels(outlong$lab)[i])),
      caption.placement = "top", booktabs = TRUE)
}
for (i in 1:14){
  coef <- mod.sys.rising.surge.linear[[i]]$coefficients
  se <- sqrt(diag(mod.noc.sys.diff.linear[[i]]$var))
  confUp <- coef + qnorm(0.975)*se
  confLow <- coef - qnorm(0.975)*se
  confInt <- paste("(", signif(confLow,3), ", ", signif(confUp,3), ")",
                 ifelse(0 < confUp & 0 > confLow, "", "*"), sep="")
  results <- data.frame(Coefficient = signif(coef,3), StdError = signif(se,3), ConfInt=confInt)
  colnames(results)[3] <- "95% Conf. Int."
  print(xtable(results, align = c("l", rep("r", 3)), digits = 3,
           caption = paste0("Regression for ABP with CVR: SBP Rising Surge and ", levels(outlong$lab)[i])),
      caption.placement = "top", booktabs = TRUE)
}
for (i in 1:14){
  coef <- mod.noc.sys.diff.linear[[i]]$coefficients
  se <- sqrt(diag(mod.noc.sys.diff.linear[[i]]$var))
  confUp <- coef + qnorm(0.975)*se
  confLow <- coef - qnorm(0.975)*se
  confInt <- paste("(", signif(confLow,3), ", ", signif(confUp,3), ")",
                 ifelse(0 < confUp & 0 > confLow, "", "*"), sep="")
  results <- data.frame(Coefficient = signif(coef,3), StdError = signif(se,3), ConfInt=confInt)
  colnames(results)[3] <- "95% Conf. Int."
  print(xtable(results, align = c("l", rep("r", 3)), digits = 3,
           caption = paste0("Regression for ABP with CVR: SBP Nocturnal Difference and ", levels(outlong$lab)[i])),
      caption.placement = "top", booktabs = TRUE)
}
########################################
#  Model Fitting                       #
########################################
modelFit <- function(outcome, predictor, ma, knot){

  fit <- fit.mult.impute(as.formula(paste0(outcome, "~ rcs(", predictor, ", c(",
                                           knot[1],",", knot[2],",",
                                           knot[3],"))*enrolled.dx.factor +",
                                           ma, "+",
"age + sex.factor + raceethnicity.factor + education",
"+ apoe4pos.factor + htnrx.factor")),
                         fitter = ols, xtrans = impute.data, data = cvrdata)

  return(fit)
}

#Knot locations for each predictor
prewaking.knot <- c(0,
                   quantile(subset(cvrdata, systolic.prewaking.surge > 0)$systolic.prewaking.surge,
                            probs = c(.25, .75), na.rm = T))

rising.knot <- c(0,
                quantile(subset(cvrdata, systolic.rising.surge > 0)$systolic.rising.surge,
                         probs = c(.25, .75), na.rm = T))

noc.knot <- c(0,
             quantile(subset(cvrdata,
       nocturnal.systolic.diff.sleep.self.reported > 0)$nocturnal.systolic.diff.sleep.self.reported,
```

```r
                        probs = c(.25, .75), na.rm = T))

#Print to see knot values
knots <- rbind(prewaking.knot, rising.knot, noc.knot); colnames(knots) = NULL

#Define datadist for model fitting
dd <- datadist(cvrdata)
options(datadist = "dd")

#Systolic prewaking surge
mod.sys.prewaking.surge <- list()
for(i in seq_along(outcomes.reac)){
  mod.sys.prewaking.surge[[i]] <- modelFit(outcome = outcomes.reac[i],
                                            predictor = predictors[1],
                                            ma = ma.vars[i],
                                            knot = prewaking.knot)
}

#Systolic rising surge
mod.sys.rising.surge <- list()
for(i in seq_along(outcomes.reac)){
  mod.sys.rising.surge[[i]] <- modelFit(outcome = outcomes.reac[i],
                                            predictor = predictors[2],
                                            ma = ma.vars[i],
                                         knot = rising.knot)
}

#Nocturnal Difference
mod.noc.sys.diff <- list()
for(i in seq_along(outcomes.reac)){
  mod.noc.sys.diff[[i]] <- modelFit(outcome = outcomes.reac[i],
                                            predictor = predictors[3],
                                            ma = ma.vars[i],
                                     knot = noc.knot)
}

#Extract coefficients associated with ABP measures
sys.prewaking.coef <- do.call(rbind, lapply(mod.sys.prewaking.surge,
                             function(x) x$coef[grep("prewaking", names(x$coef))]))
sys.prewaking.coef.vec <- apply(sys.prewaking.coef, MARGIN = 1,
                                function(x) paste0("(", round(x[1], 3), ",",
                                                   round(x[2], 3),")"))

sys.rising.coef <- do.call(rbind, lapply(mod.sys.rising.surge,
                             function(x) x$coef[grep("rising", names(x$coef))]))
sys.rising.coef.vec <- apply(sys.rising.coef, MARGIN = 1,
                             function(x) paste0("(", round(x[1], 3), ",",
                                                round(x[2], 3),")"))

noc.diff.coef <- do.call(rbind, lapply(mod.noc.sys.diff,
                             function(x) x$coef[grep("noc", names(x$coef))]))
noc.diff.coef.vec <- apply(noc.diff.coef, MARGIN = 1,
                           function(x) paste0("(", round(x[1], 3), ",  ",
                                              round(x[2], 3),")"))


coef.table <- data.frame("Systolic Prewaking Surge" = sys.prewaking.coef.vec,
                         "Systolic Rising Surge" = sys.rising.coef.vec,
                         "Nocturnal SBP Difference" = noc.diff.coef.vec,
                          row.names = outcomeNames, check.names = FALSE)
```

```r
print(xtable(coef.table, align = c("l", rep("r", 3)),
             caption = paste0("Coefficients for ABP with CVR: ABP Modeled as Restricted Cubic Spline with 3 Knots")),
      caption.placement = "top", booktabs = TRUE)
############################################
#  Tests of Association for RCS Models  #
############################################
#Not printed since primary results were based on linear model,
#  but this is how the test results would be extracted if needed
#  in the future

#Extract p-values for test of association

sys.prewaking.pval <- lapply(mod.sys.prewaking.surge,
                             function(x) anova(x)[1,"P"])
sys.rising.pval <- lapply(mod.sys.rising.surge,
                             function(x) anova(x)[1,"P"])
noc.sys.diff.pval <- lapply(mod.noc.sys.diff,
                             function(x) anova(x)[1,"P"])

assoc.table <- data.frame("SBP Prewaking Surge" = unlist(sys.prewaking.pval),
                          "SBP Rising Surge" = unlist(sys.rising.pval),
                          "Nocturnal SBP Difference" = unlist(noc.sys.diff.pval),
                          row.names = outcomeNames,
                          check.names = FALSE)

# print(xtable(assoc.table, digits = 3,
#              caption = "P-values for Test of Association Between ABP and CVR"),
#       caption.placement = "top", booktabs = TRUE)
#Default plotting values for partial effect plots
subset_cvrdata <- subset(cvrdata, select = c(age, education, sex.factor,
                                             enrolled.dx.factor, raceethnicity.factor,
                                             apoe4pos.factor, htnrx.factor))

adj_tab <- xtable(datadist(subset_cvrdata)$limits["Adjust to",],
                           caption = "Default Partial Effect Plot Covariate Values")
#######################################
#  Partial Effect Plots               #
#######################################

#Systolic prewaking surge
sys.prewaking.PEP <- lapply(mod.sys.prewaking.surge,
                             function(x) ggplot(Predict(x, systolic.prewaking.surge),
                                                adj.subtitle = FALSE,
                                                anova = anova(x), size.anova = 3,
                                                pval = TRUE,
                                                ylim. = c(1,5),
                                                xlab = "SBP Prewaking Surge",
                                                ylab = gsub("asl.reac.", "", x$sformula[2])))



do.call(grid.arrange, sys.prewaking.PEP)
#Systolic rising surge
sys.rising.PEP <- lapply(mod.sys.rising.surge,
                             function(x) ggplot(Predict(x, systolic.rising.surge),
                                                adj.subtitle = FALSE,
                                                anova = anova(x), size.anova = 3,
                                                pval = TRUE,
                                                ylim. = c(1,5),
                                                xlab = "SBP Rising Surge",
                                                ylab = gsub("asl.reac.", "", x$sformula[2])))
```

```r
do.call(grid.arrange, sys.rising.PEP)
#Nocturnal difference
noc.sys.diff.PEP <- lapply(mod.noc.sys.diff,
                            function(x) ggplot(Predict(x, nocturnal.systolic.diff.sleep.self.reported),
                                               adj.subtitle = FALSE,
                                               anova = anova(x), size.anova = 3,
                                               pval = TRUE,
                                               ylim. = c(1,5),
                                               xlab = "Nocturnal Difference in SBP",
                                               ylab = gsub("asl.reac.", "", x$sformula[2])))
do.call(grid.arrange, noc.sys.diff.PEP)
#######################################
#  Partial Effect Plots by Diagnosis  #
#######################################

#Function obtained from:
# http://stackoverflow.com/questions/11883844/inserting-a-table-under-the-legend-in-a-ggplot2-histogram

#create common legend for stratified plots
g_legend<-function(a.gplot){
  tmp <- ggplot_gtable(ggplot_build(a.gplot))
  leg <- which(sapply(tmp$grobs, function(x) x$name) == "guide-box")
  legend <- tmp$grobs[[leg]]
  return(legend)}

legend.dx <- g_legend(ggplot(Predict(mod.noc.sys.diff[[1]],
                                     nocturnal.systolic.diff.sleep.self.reported,
                 enrolled.dx = c("Normal", "MCI", "Ambiguous At Risk"))))
#Systolic prewaking surge
sys.prewaking.PEP.dx <- lapply(mod.sys.prewaking.surge,
                            function(x) ggplot(Predict(x, systolic.prewaking.surge,
                                               enrolled.dx.factor = c("Normal",
                                                                       "MCI",
                                                                       "Ambiguous At Risk")),
                                               colfill = "grey60",
                                               adj.subtitle = FALSE,
                                               xlab = "SBP prewaking",
                                               ylab = gsub("asl.reac.", "", x$sformula[2])) +
  theme(legend.position = "none"))

sys.prewaking.PEP.dx[[15]] <- legend.dx
do.call(grid.arrange, sys.prewaking.PEP.dx)
#Systolic rising surge
sys.rising.PEP.dx <- lapply(mod.sys.rising.surge,
                            function(x) ggplot(Predict(x, systolic.rising.surge,
                                               enrolled.dx.factor = c("Normal",
                                                                        "MCI",
                                                                        "Ambiguous At Risk")),
                                               colfill = "grey60",
                                               adj.subtitle = FALSE,
                                               xlab = "SBP rising",
                                               ylab = gsub("asl.reac.", "", x$sformula[2])) +
  theme(legend.position = "none"))

sys.rising.PEP.dx[[15]] <- legend.dx
do.call(grid.arrange, sys.rising.PEP.dx)
#Nocturnal difference
noc.sys.diff.PEP.dx <- lapply(mod.noc.sys.diff,
                            function(x) ggplot(Predict(x, nocturnal.systolic.diff.sleep.self.reported,
                                               enrolled.dx.factor = c("Normal",
                                                                        "MCI",
```

```
                                                                                "Ambiguous At Risk")),
                                                       colfill = "grey60",
                                                       adj.subtitle = FALSE,
                                                       ylim. = c(-5,5),
                                                       xlab = "Nocturnal Difference",
                                                       ylab = gsub("asl.reac.", "", x$sformula[2])) +
  theme(legend.position = "none"))


noc.sys.diff.PEP.dx[[15]] <- legend.dx
do.call(grid.arrange, noc.sys.diff.PEP.dx)
#######################################
#  Tests of Linearity                 #
#######################################

#Select p-values for test of linearity
sys.prewaking.nonlin <- lapply(mod.sys.prewaking.surge,
                             function(x) anova(x)[" Nonlinear","P"])
sys.rising.nonlin <- lapply(mod.sys.rising.surge,
                             function(x) anova(x)[" Nonlinear","P"])
noc.sys.diff.nonlin <- lapply(mod.noc.sys.diff,
                             function(x) anova(x)[" Nonlinear","P"])


linear.table <- data.frame("SBP Prewaking Surge" = unlist(sys.prewaking.nonlin),
                          "SBP Rising Surge" = unlist(sys.rising.nonlin),
                          "Nocturnal SBP Difference" = unlist(noc.sys.diff.nonlin),
                          row.names = outcomeNames,
                          check.names = FALSE)

print(xtable(linear.table, digits = 3,
             caption = "P-values for test of linearity for ABP predictors"),
      caption.placement = "top")
cvrdata$sys.rising.impute <- cvrdata$systolic.rising.surge
cvrdata$sys.prewaking.impute <- cvrdata$systolic.prewaking.surge
cvrdata$noc.diff.impute <- cvrdata$nocturnal.systolic.diff.sleep.self.reported

cvrdata$noc.diff.impute[is.na(cvrdata$noc.diff.impute)] <-
  rowMeans(impute.data$imputed$nocturnal.systolic.diff.sleep.self.reported[,])
cvrdata$sys.rising.impute[is.na(cvrdata$sys.rising.impute)] <-
  rowMeans(impute.data$imputed$systolic.rising.surge[,])
cvrdata$sys.prewaking.impute[is.na(cvrdata$sys.prewaking.impute)] <-
  rowMeans(impute.data$imputed$systolic.prewaking.surge[,])

sens1 <- ggplot(cvrdata, aes(x=sys.rising.impute, fill = is.na(systolic.rising.surge))) +
  geom_histogram(alpha=0.4, position="identity", binwidth = 5) +
  ylab("Count") + theme(legend.position = "none") +
  xlab("Systolic Rising Surge") + scale_fill_discrete(name = "Imputed")

sens2 <- ggplot(cvrdata, aes(x=sys.prewaking.impute, fill = is.na(systolic.prewaking.surge))) +
  geom_histogram(alpha=0.4, position="identity", binwidth = 5) +
  theme(legend.position = "none") +
  xlab("Systolic Prewaking Surge") + scale_fill_discrete(name = "Imputed")

sens3 <- ggplot(cvrdata, aes(x=noc.diff.impute, fill = is.na(nocturnal.systolic.diff.sleep.self.reported))) +
  geom_histogram(alpha=0.4, position="identity", binwidth = 5) +
  xlab("Nocturnal Difference in Surge") + scale_fill_discrete(name = "Imputed")

grid.arrange(sens1, sens2, sens3, ncol = 3)
#########################################
#  Model Fitting: Complete Observations #
```

```
#  (ignoring missing data)              #
#########################################

#Results available if desired but suppressed since conclusions do not change
#  (results still not significant at 0.05 level)
#Models with restricted cubic splines

modelFitComplete <- function(outcome, predictor, ma, knot){

  fit <- ols(as.formula(paste0(outcome, "~ rcs(", predictor, ", c(",
                                          knot[1],",", knot[2],",",
                                          knot[3],")) +",
                                          ma, "+",
"age + sex.factor + raceethnicity.factor + education",
"+ enrolled.dx.factor + apoe4pos.factor + htnrx.factor")), data = cvrdata)

  return(fit)
}


#Systolic prewaking surge
mod.sys.prewaking.surge.comp <- list()
for(i in seq_along(outcomes.reac)){
  mod.sys.prewaking.surge.comp[[i]] <- modelFitComplete(outcome = outcomes.reac[i],
                                                  predictor = predictors[1],
                                                  ma = ma.vars[i],
                                                  knot = prewaking.knot)
}

#Systolic rising surge
mod.sys.rising.surge.comp <- list()
for(i in seq_along(outcomes.reac)){
  mod.sys.rising.surge.comp[[i]] <- modelFitComplete(outcome = outcomes.reac[i],
                                                  predictor = predictors[2],
                                                  ma = ma.vars[i],
                                                  knot = rising.knot)
}

#Nocturnal Difference
mod.noc.sys.diff.comp <- list()
for(i in seq_along(outcomes.reac)){
  mod.noc.sys.diff.comp[[i]] <- modelFitComplete(outcome = outcomes.reac[i],
                                                  predictor = predictors[3],
                                                  ma = ma.vars[i],
                                                  knot = noc.knot)
}

sys.prewaking.comp <- lapply(mod.sys.prewaking.surge.comp,
                             function(x) anova(x)["systolic.prewaking.surge","P"])


sys.rising.comp <- lapply(mod.sys.rising.surge.linear,
                             function(x) anova(x)["systolic.rising.surge","P"])


noc.diff.comp <- lapply(mod.noc.sys.diff.linear,
                             function(x) anova(x)["nocturnal.systolic.diff.sleep.self.reported","P"])
#Summary of analysis results if we had ignored missing values for each predictor
complete.table <- data.frame(unlist(sys.prewaking.comp),
                             unlist(sys.rising.comp),
                             unlist(noc.diff.comp),
```

```r
                          row.names = outcomeNames, check.names = FALSE)

names(complete.table) <- c(paste0("SBP Prewaking (N = ",
                                   nrow(cvrdata[!is.na(cvrdata$systolic.prewaking.surge),]),
                                   ")"),
                           paste0("SBP Rising (N = ",
                                  nrow(cvrdata[!is.na(cvrdata$systolic.rising.surge),]),
                                   ")"),
                           paste0("Nocturnal Diff. (N = ",
                                  nrow(cvrdata[!is.na(cvrdata$nocturnal.systolic.diff.sleep.self.reported),]),
                                   ")"))

print(xtable(complete.table, digits = 3,
             caption = "Complete Observation Associations for ABP and CVR"),
      caption.placement = "top", booktabs = TRUE)
#######################################
#  Session Information                #
#######################################

    cat(version['version.string'][[1]], "\n")
    pack <- installed.packages()
    pack.out <- pack[, c('Package', 'Version', 'Priority',
        'Depends')]
    pack.in.session <- (.packages())
    pack.out2 <- data.frame(pack.out[pack.out[, 1] %in%
        pack.in.session, ])[, -1]
    cat("Packages:\n")
    pack.out2[!pack.out2$Priority%in%c('base','recommended'),-2,
        drop=FALSE]
```