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 overall association and linearity of ABP measurements are performed
- Present partial effect plots for each ABP-CVR outcome pair: effect of ABP holding all other covariates constant.
- 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 Sensitivity 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
Diff. in mean SBP, wake - sleep, self-reported periods	14.5 (10.5)	13.4 (9.4)	0.6075
systolic.post.wake.mean minus systolic.pre.wake.mean	11.1 (12.3)	12.3 (12.2)	0.4331
systolic.post.wake.1 minus systolic.pre.wake.1	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, determined by a1c, glucose, and/or rx			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, determined from variables in med hx			0.622
– Yes	4 (2%)	7 (4%)	
– No	158 (98%)	167 (96%)	
A-fib, determined by med hx and/or echo and/or cmr rhythm			1
– Yes	9 (6%)	10 (6%)	
– No	151 (93%)	164 (94%)	
LV hypertrophy, determined by sex and scaled LV mass			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:

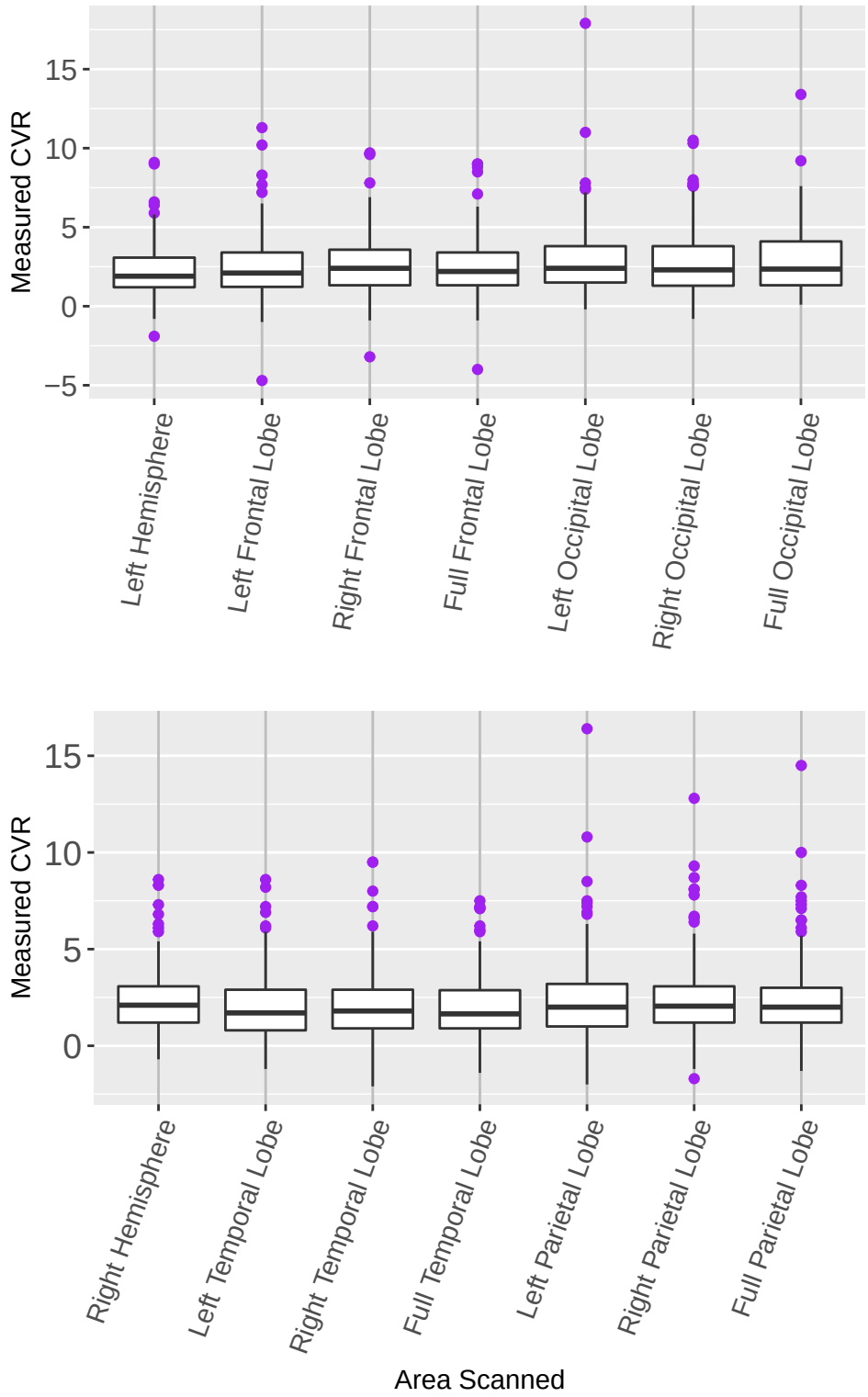
- Continuous variables have a mean (standard deviation), and discrete variables have a count (percentage).
- The p-value (significance < 0.05) for the univariate comparison of the each variable between the diagnosis groups is presented. Kruskal-Wallis tests are used for continuous variables and Chi-square 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.diff.sleep.self.reported	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, determined by a1c, glucose, and/or rx				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, determined from variables in med hx				0.6743
– Yes	5 (5%)	2 (3%)	0 (0%)	
– No	96 (95%)	60 (97%)	11 (100%)	
A-fib, determined by med hx and/or echo and/or cmr rhythm				0.1502
– Yes	4 (4%)	4 (6%)	2 (18%)	
– No	97 (96%)	58 (94%)	9 (82%)	
LV hypertrophy, determined by sex and scaled LV mass				0.576
– Yes	3 (3%)	3 (5%)	1 (9%)	
– No	97 (96%)	59 (95%)	10 (91%)	

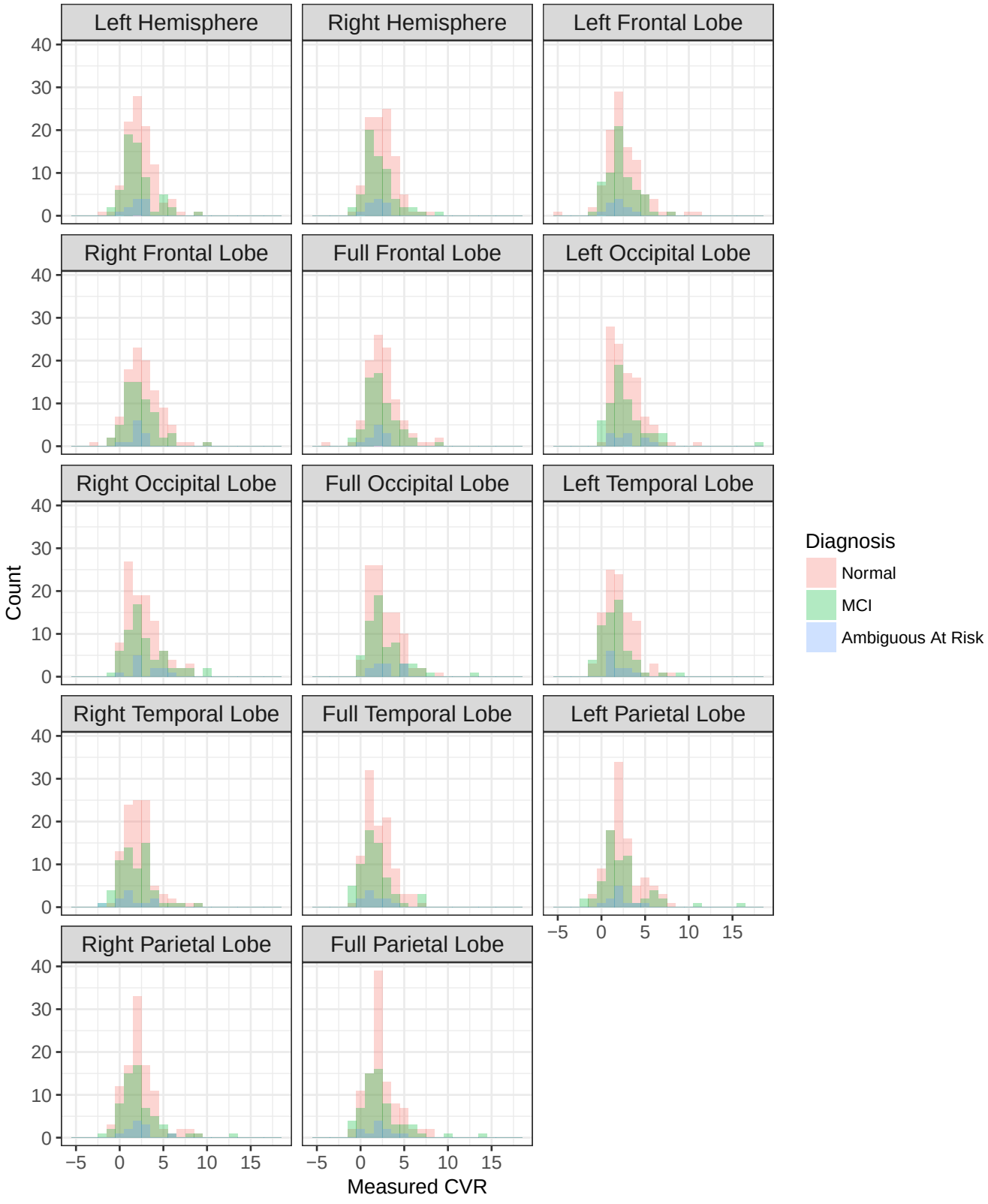
- Patients diagnosed with MCI appear to have some lower ABP measurements. However, these are all univariate relationships; these trends may not hold in the adjusted analyses.
- We also see a difference in education level, with the apparent ordering of highest average years of education to lowest being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

4.2 CVR Outcome Distribution



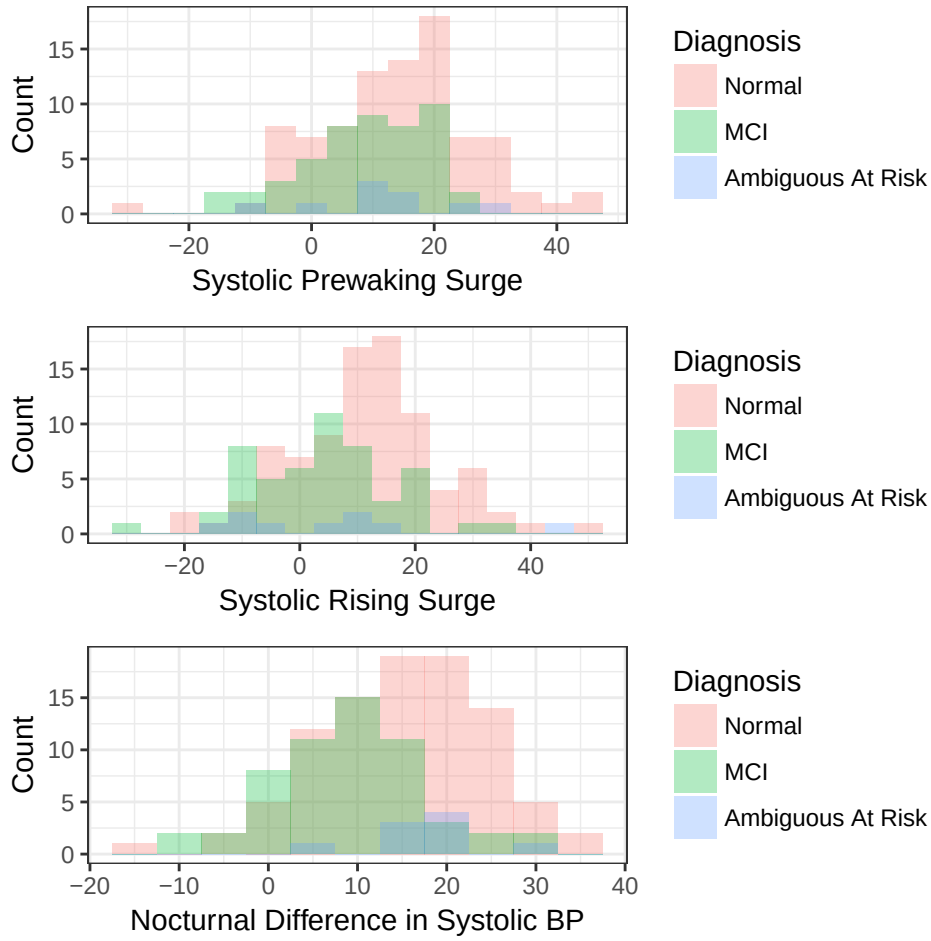
- Most of the outliers are for larger values of CVR.
- Outliers within each part of the brain are likely highly correlated. If a patient is an outlier for left frontal lobe, then she may be an outlier for the right side as well.
  - E.g. The low outliers of the frontal lobe regions: which are all from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

4.3 Distribution of CVR Outcomes by Diagnosis



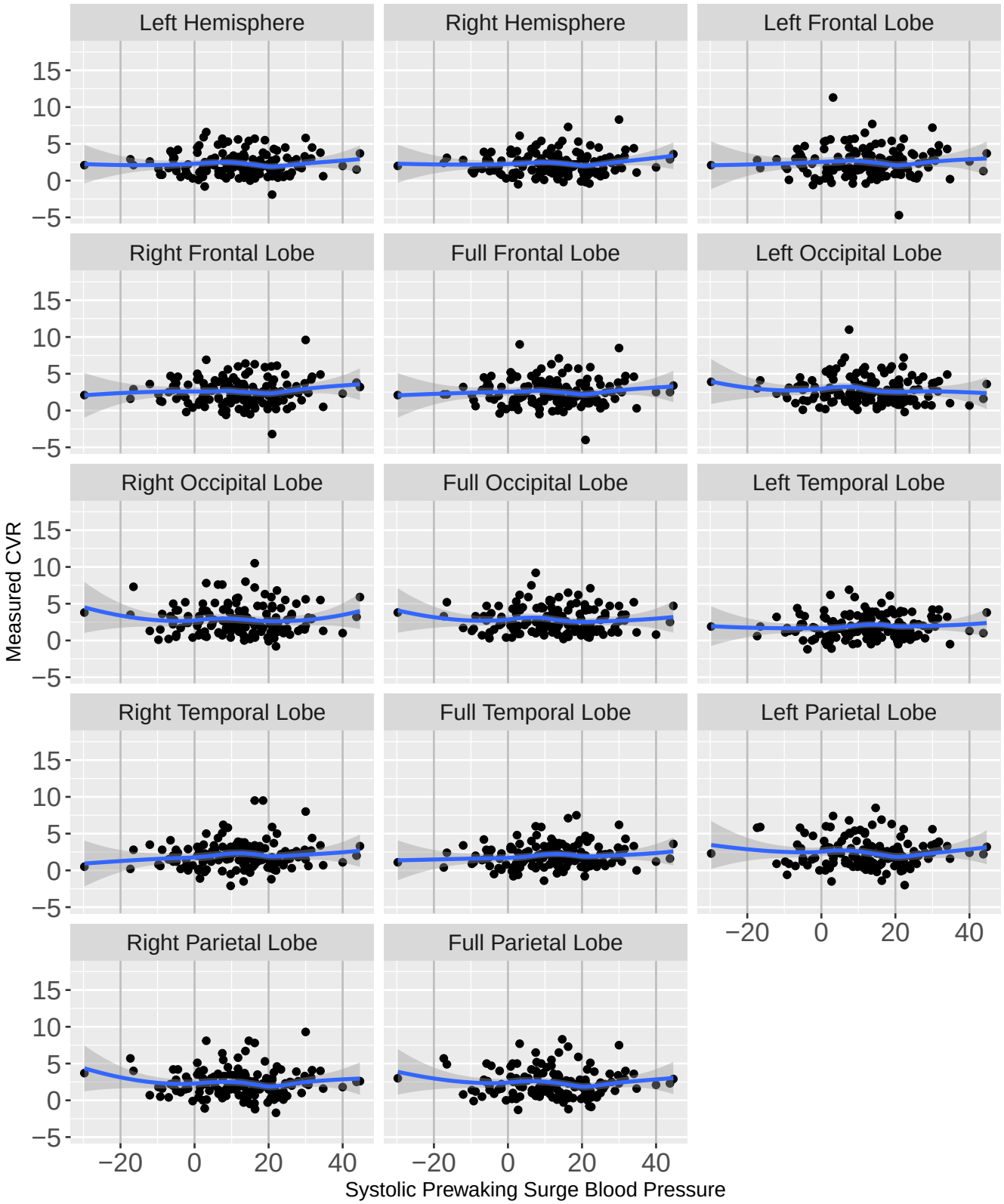
- Positive outliers in MCI group for some CVR outcomes.

4.4 ABP Measure Distribution by Diagnosis

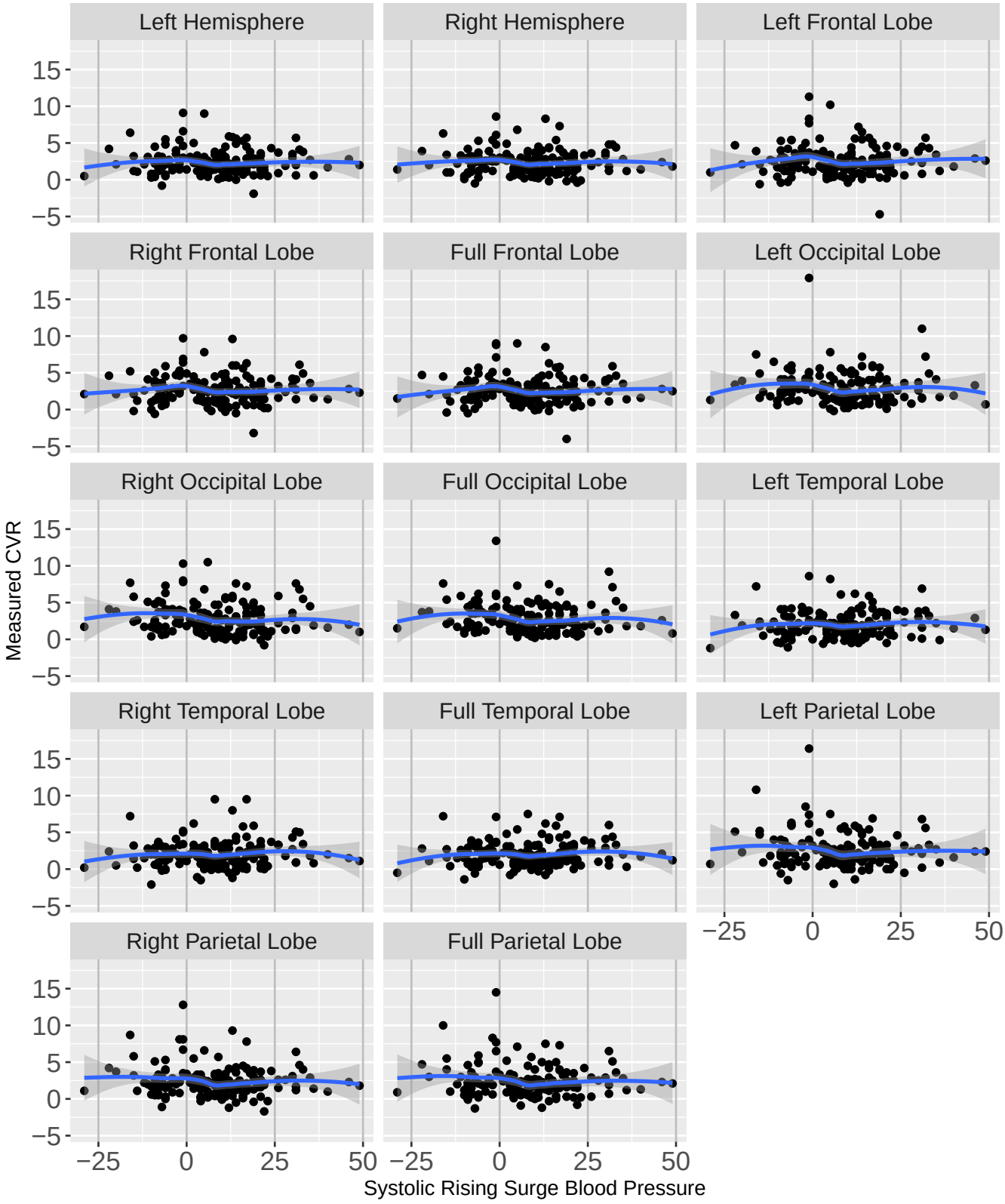


4.5 Unadjusted ABP-CVR Associations

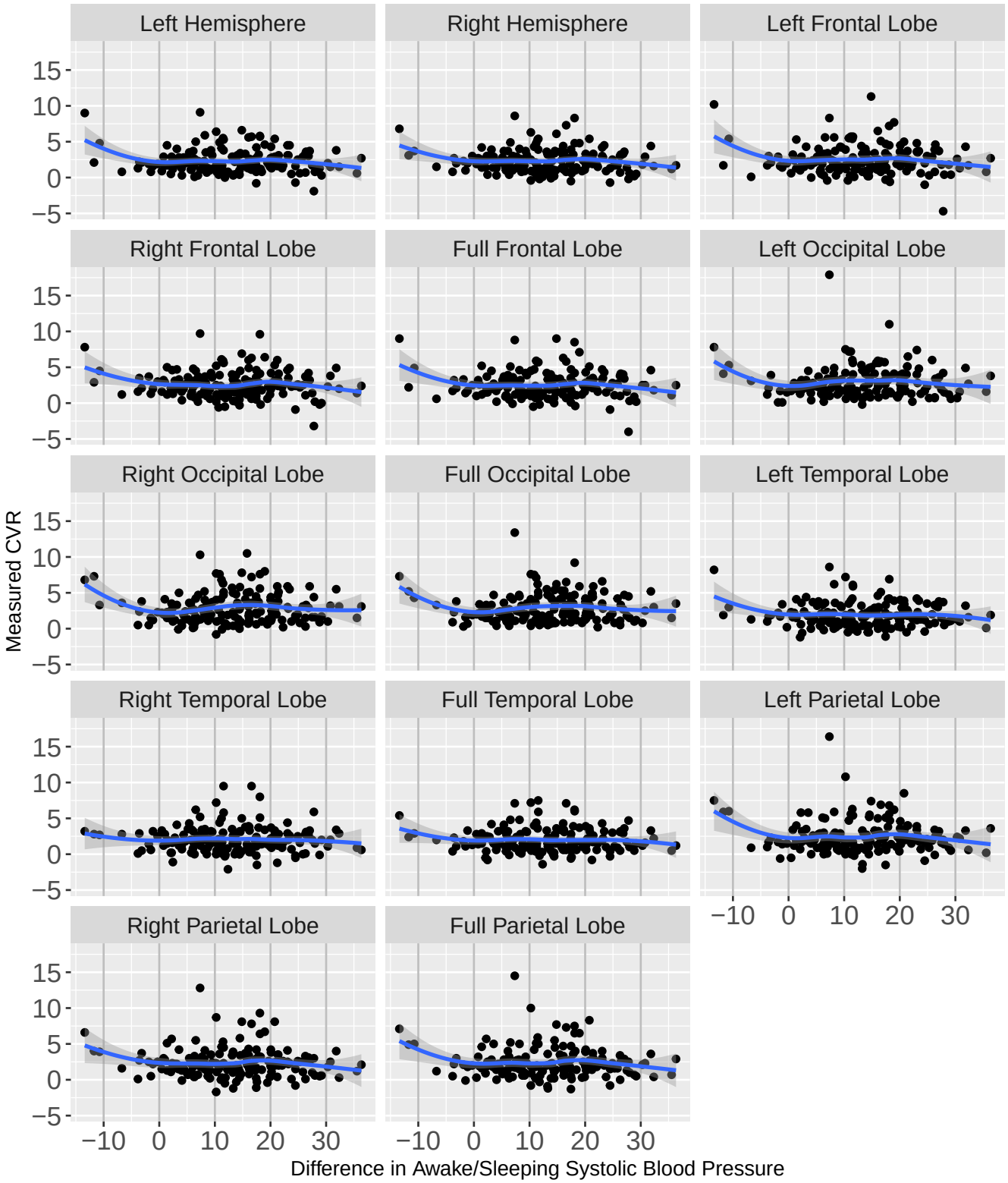
4.5.1 SBP Prewaking Surge



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.

5 Analysis Results

5.1 Missing Data

Table 3: Variables with Missing Observations

Variable	Missingness
LV hypertrophy, determined by sex and scaled LV mass	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

Table 4: 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	(-0.011,0.004)	(-0.023,0.03)	(-0.052, 0.033)
Right Hemisphere	(-0.017,0.023)	(-0.025,0.031)	(-0.041, 0.021)
Left Frontal Lobe	(-0.011,0.01)	(-0.026,0.038)	(-0.053, 0.031)
Right Frontal Lobe	(-0.023,0.037)	(-0.026,0.031)	(-0.056, 0.039)
Full Frontal Lobe	(-0.016,0.023)	(-0.025,0.034)	(-0.053, 0.034)
Left Occipital Lobe	(-0.008,-0.019)	(-0.044,0.053)	(-0.018, 0.005)
Right Occipital Lobe	(-0.021,0.02)	(-0.043,0.038)	(-0.03, 0.033)
Full Occipital Lobe	(-0.013,-0.001)	(-0.044,0.048)	(-0.024, 0.02)
Left Temporal Lobe	(0.007,-0.013)	(-0.009,0.019)	(-0.055, 0.044)
Right Temporal Lobe	(0.019,-0.019)	(-0.004,0.015)	(0.007, -0.027)
Full Temporal Lobe	(0.012,-0.015)	(-0.006,0.016)	(-0.023, 0.008)
Left Parietal Lobe	(-0.037,0.028)	(-0.058,0.067)	(-0.057, 0.041)
Right Parietal Lobe	(-0.042,0.045)	(-0.048,0.059)	(-0.056, 0.039)
Full Parietal Lobe	(-0.039,0.036)	(-0.054,0.064)	(-0.055, 0.038)

- 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:

- results for tests of overall association between ABP and CVR measurements ("overall" meaning using all coefficients affiliated with each ABP variable).
- partial effect plots as a visual representation of ABP effect on CVR for each model.

5.3 Test of Association between ABP and CVR

Table 5: P-values for Test of Association Between ABP and CVR

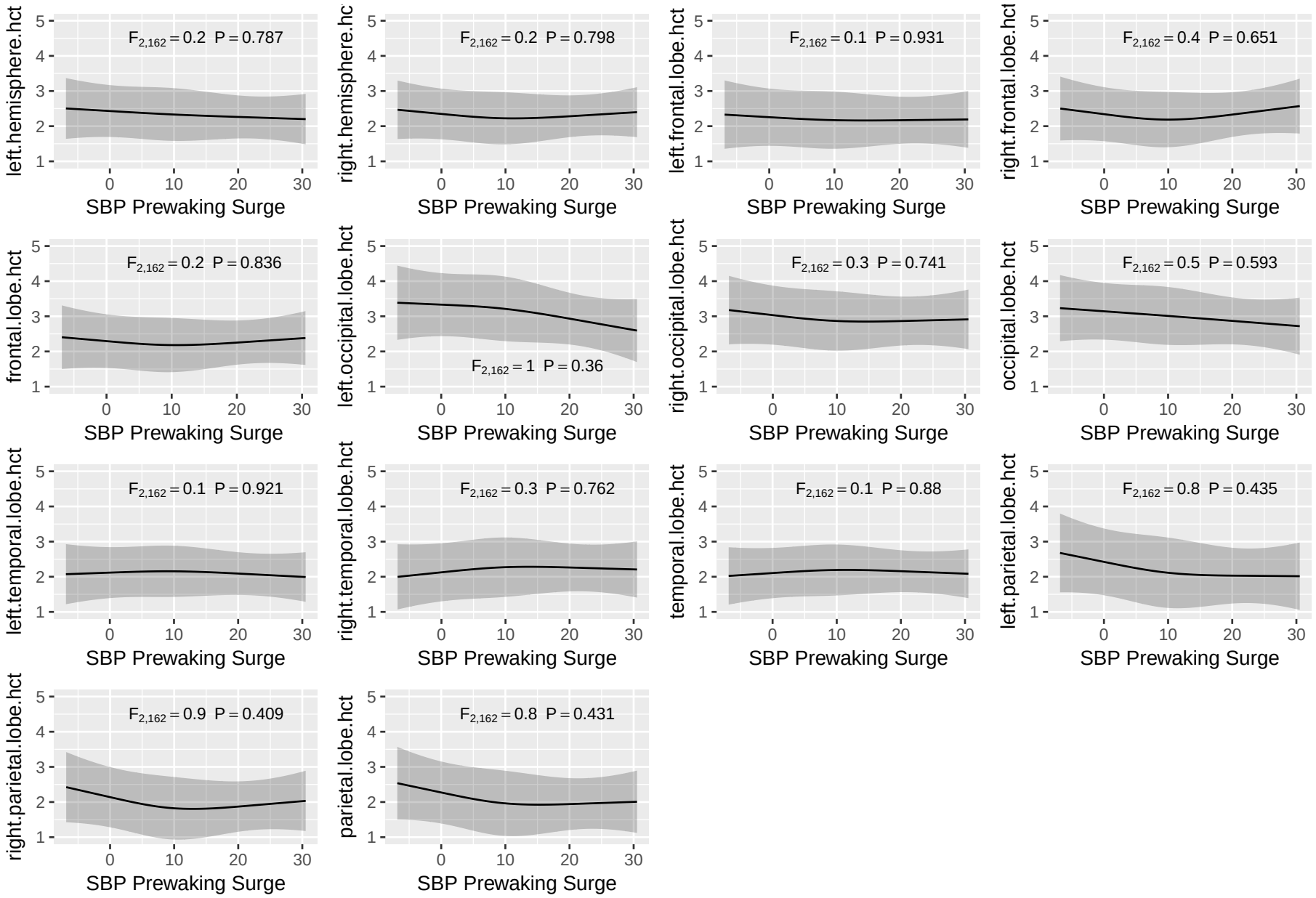
	SBP Prewaking Surge	SBP Rising Surge	Nocturnal SBP Difference
Left Hemisphere	0.787	0.494	0.215
Right Hemisphere	0.798	0.425	0.280
Left Frontal Lobe	0.931	0.495	0.243
Right Frontal Lobe	0.651	0.474	0.256
Full Frontal Lobe	0.836	0.481	0.246
Left Occipital Lobe	0.360	0.200	0.745
Right Occipital Lobe	0.741	0.148	0.808
Full Occipital Lobe	0.593	0.136	0.812
Left Temporal Lobe	0.921	0.791	0.250
Right Temporal Lobe	0.762	0.812	0.624
Full Temporal Lobe	0.880	0.793	0.537
Left Parietal Lobe	0.435	0.104	0.430
Right Parietal Lobe	0.409	0.124	0.314
Full Parietal Lobe	0.431	0.089	0.370

- 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 $\frac{.05}{42} = .0012$).

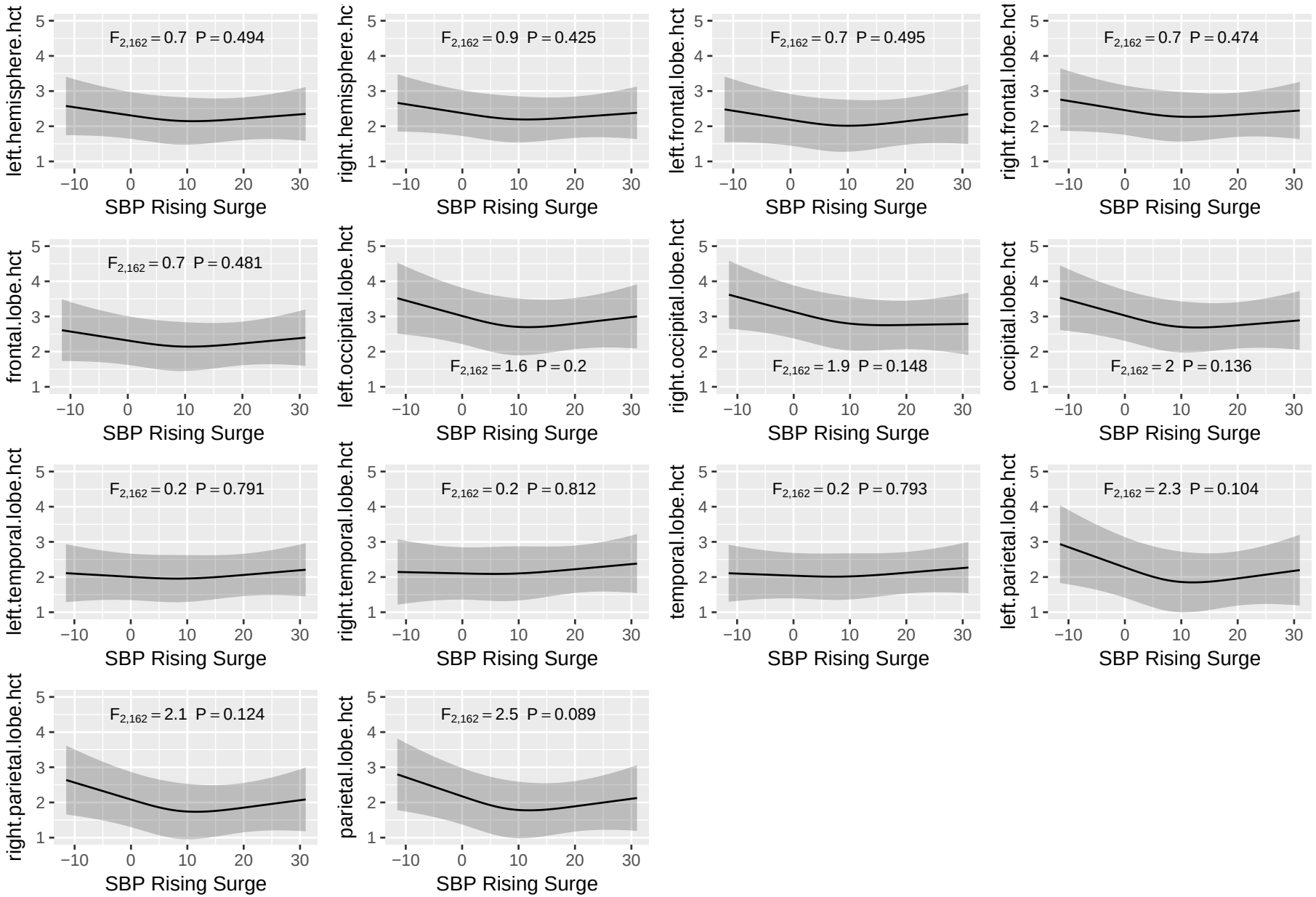
5.4 Partial Effect Plots

- Partial effect plots show the effect of each SBP measure on CVR outcome with other variables in the model fixed.
- 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.
- Generally, all curves have a slight decline for lower ABP values then tend to level off.
- Normal Cognition group tends to have the highest CVR more often.
- However, no consistent ordering of diagnosis group response across brain regions.

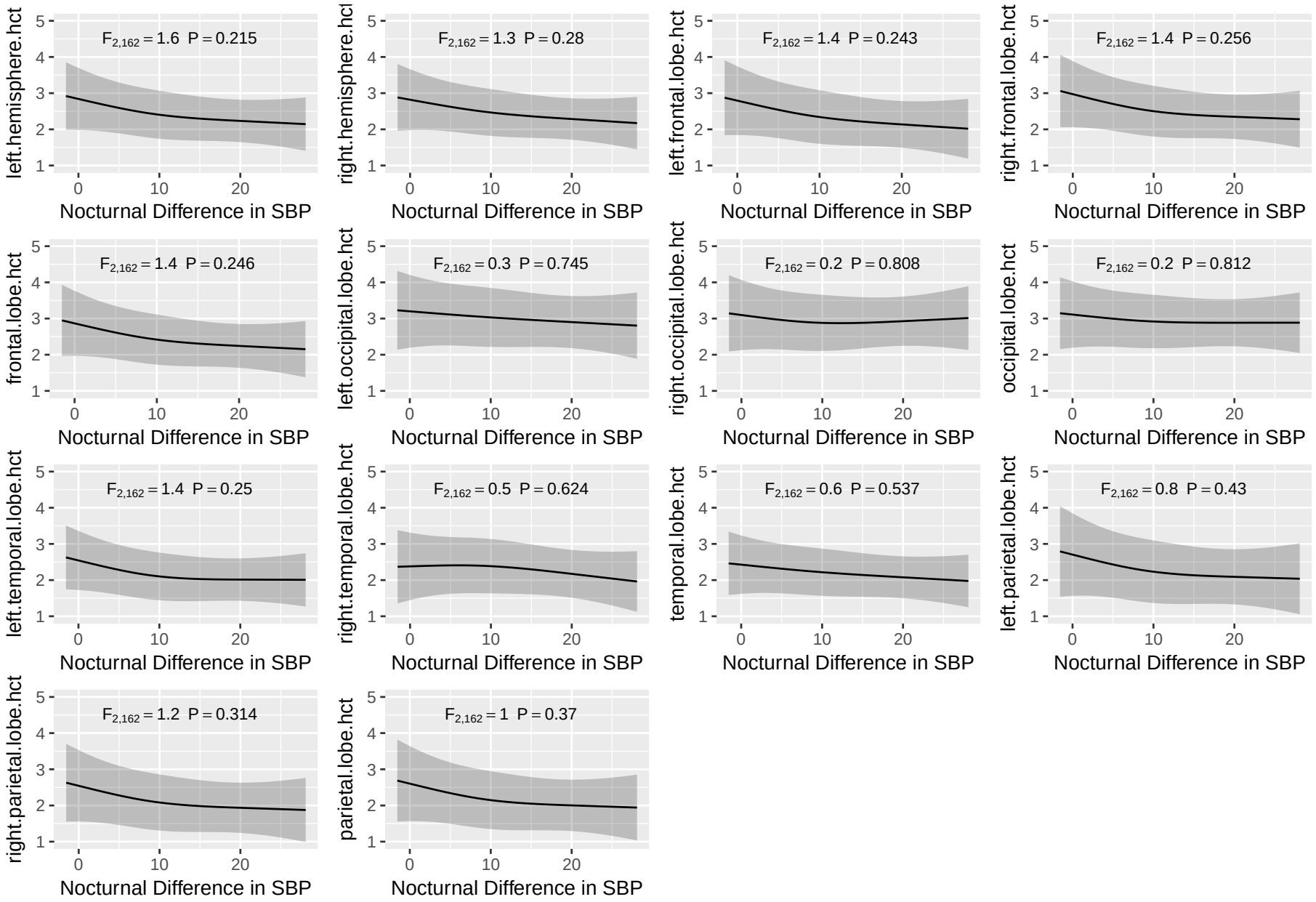
5.4.1 SBP Prewaking Surge



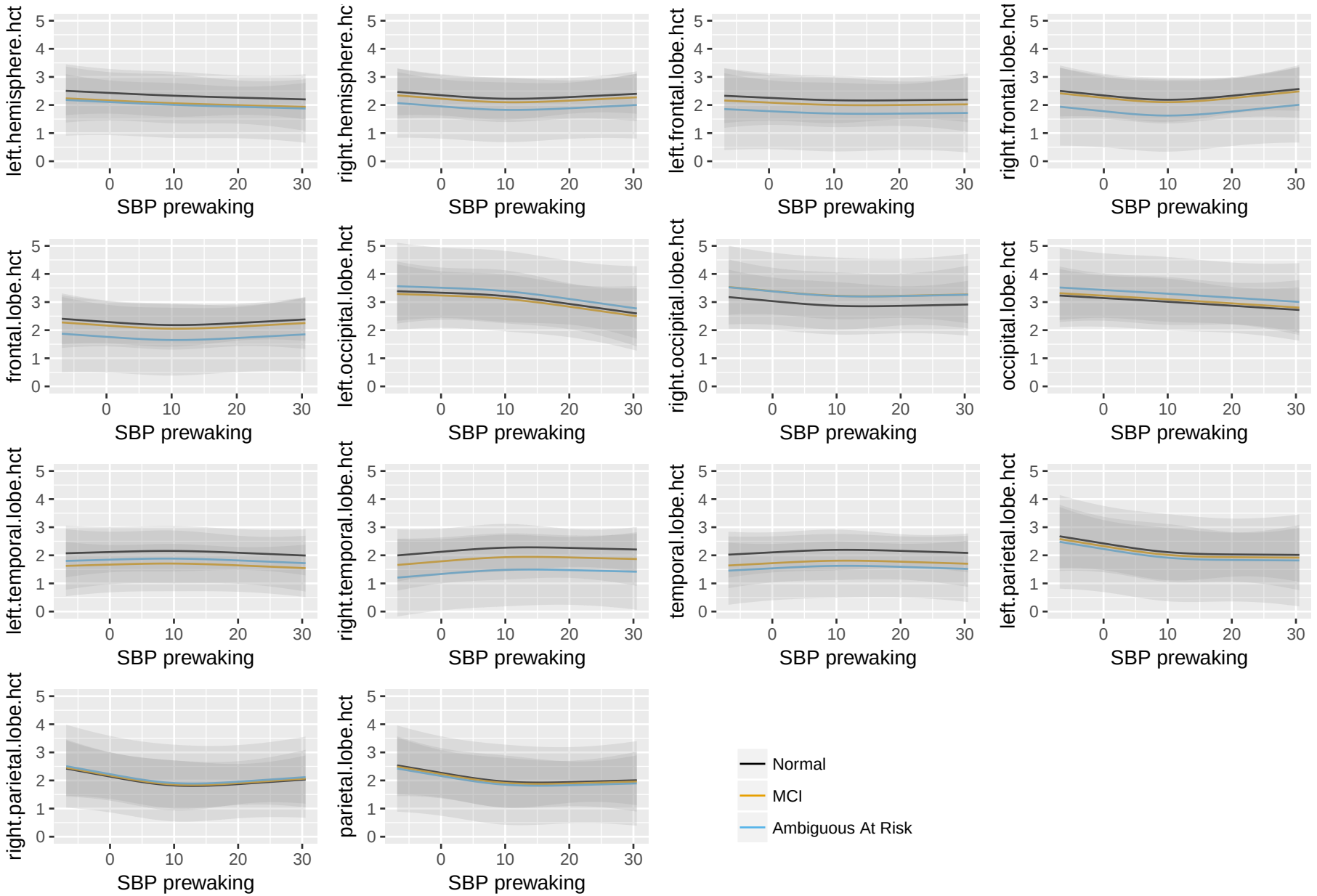
5.4.2 SBP Rising Surge



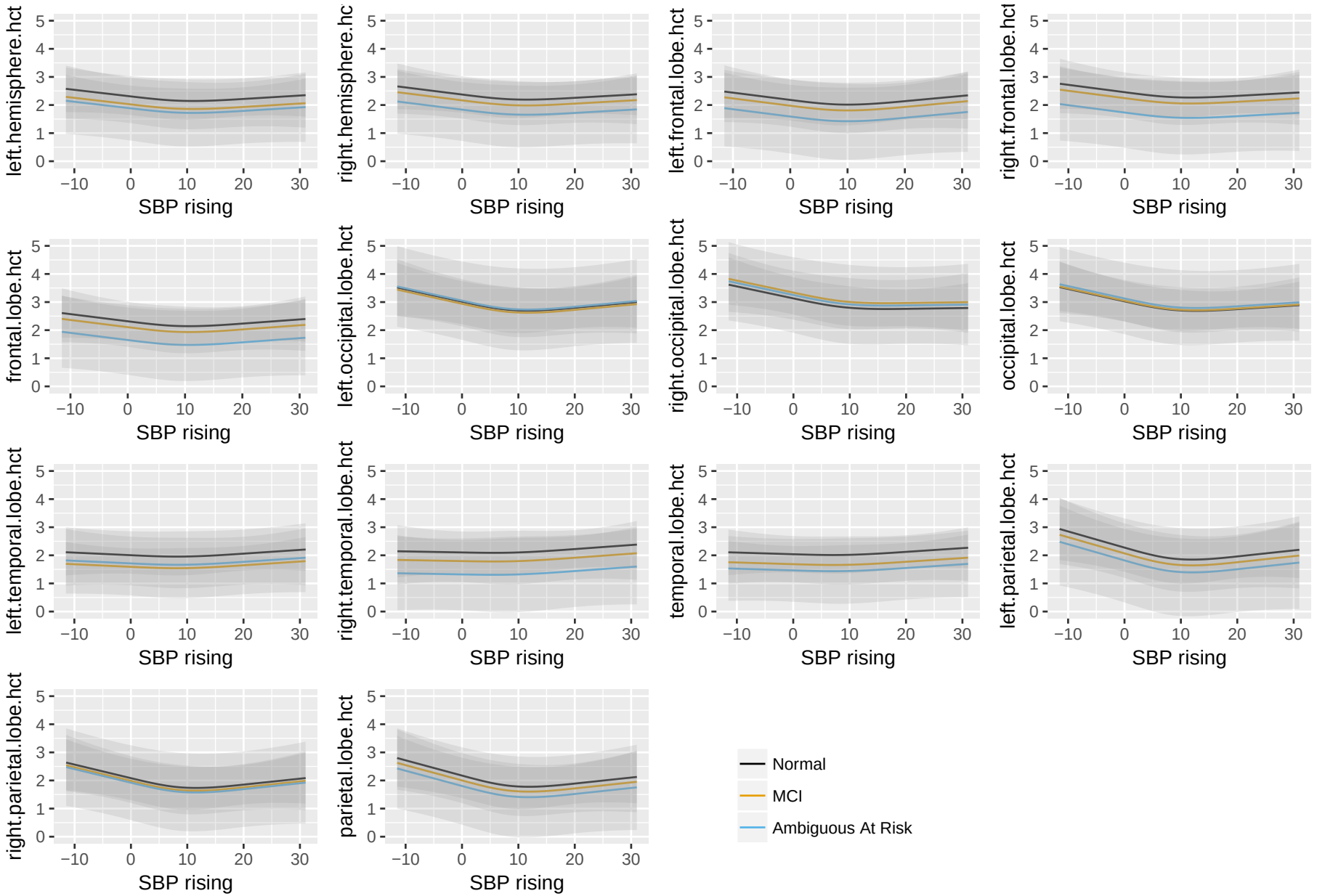
5.4.3 Nocturnal Decline in SBP



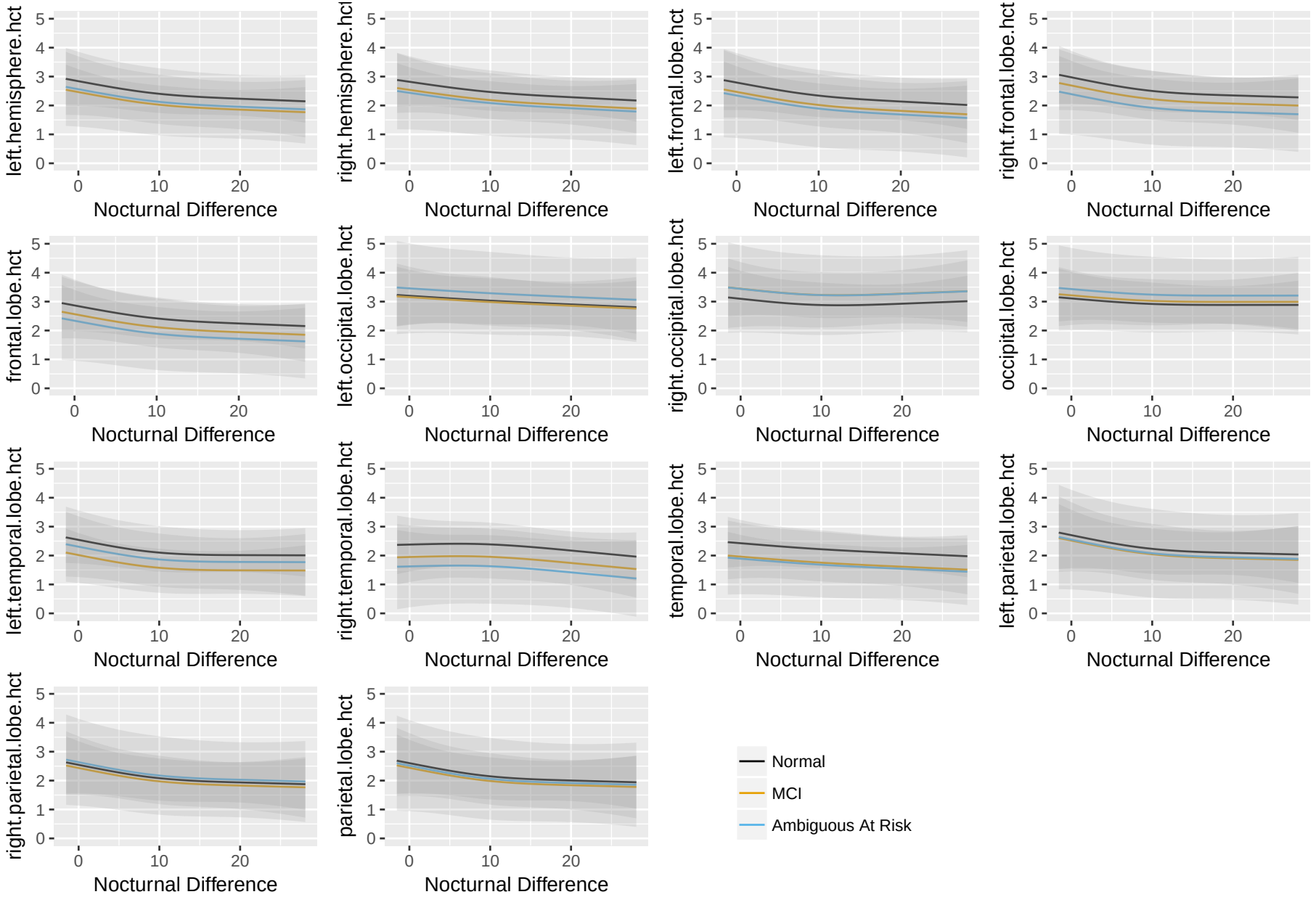
5.4.4 SBP Prewaking Surge by Diagnosis



5.4.5 SBP Rising Surge by Diagnosis



5.4.6 Nocturnal Decline in SBP by Diagnosis



5.5 Tests of Linearity for ABP Measures

Table 6: P-values for test of linearity for ABP predictors

	SBP Prewaking Surge	SBP Rising Surge	Nocturnal SBP Difference
Left Hemisphere	0.916	0.302	0.478
Right Hemisphere	0.534	0.278	0.649
Left Frontal Lobe	0.797	0.257	0.561
Right Frontal Lobe	0.356	0.326	0.451
Full Frontal Lobe	0.556	0.278	0.502
Left Occipital Lobe	0.678	0.141	0.930
Right Occipital Lobe	0.610	0.272	0.546
Full Occipital Lobe	0.979	0.143	0.698
Left Temporal Lobe	0.712	0.508	0.322
Right Temporal Lobe	0.621	0.668	0.605
Full Temporal Lobe	0.647	0.566	0.849
Left Parietal Lobe	0.592	0.095	0.522
Right Parietal Lobe	0.312	0.098	0.473
Full Parietal Lobe	0.455	0.082	0.507

- No evidence to suggest the effect is truly non-linear for any model

5.6 Secondary Aim

Table 7: R-squared for ABP predictor models

	SBP Prewaking Surge	SBP Rising Surge	Nocturnal SBP Difference
Left Hemisphere	0.058	0.062	0.076
Right Hemisphere	0.045	0.051	0.059
Left Frontal Lobe	0.070	0.075	0.086
Right Frontal Lobe	0.065	0.065	0.076
Full Frontal Lobe	0.069	0.074	0.085
Left Occipital Lobe	0.096	0.099	0.084
Right Occipital Lobe	0.058	0.077	0.056
Full Occipital Lobe	0.066	0.082	0.061
Left Temporal Lobe	0.055	0.056	0.070
Right Temporal Lobe	0.027	0.026	0.029
Full Temporal Lobe	0.037	0.037	0.043
Left Parietal Lobe	0.042	0.057	0.041
Right Parietal Lobe	0.059	0.069	0.059
Full Parietal Lobe	0.050	0.066	0.050

Table 8: 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.

6 Sensitivity Analyses

6.1 Model with Linear Effect of ABP Measures

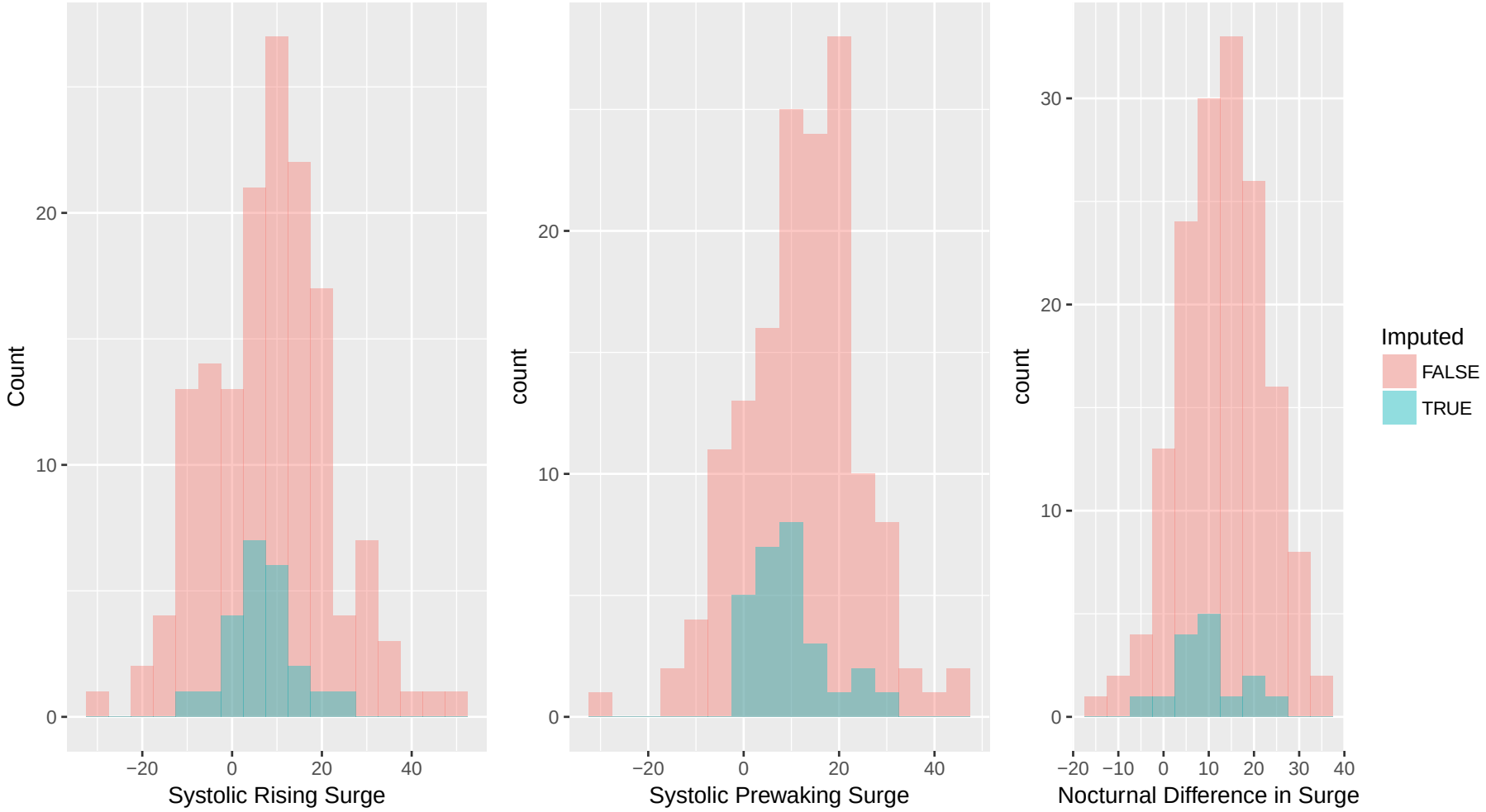
- No evidence of an association
- Coefficients are interpreted as the effect on CVR outcome for a one-mmHg increase in ABP measurement.
- Multiply coefficients by 10 to interpret the effect on CVR for a 10-mmHg increase in ABP measurement.
  - E.g. For a 10-mmHg increase in the systolic blood pressure prewaking surge, CVR in the left hemisphere is expected to decrease by .083, holding other model variables constant.

Table 9: 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

6.2 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
- Sensitivity analysis for linear effect
- Secondary aim

Brooklyn Stanley

- Data cleaning
- Application of inclusion/exclusion criteria
- Descriptive statistics
- Imputation and associated sensitivity analysis

9 Code Appendix

```
# 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                      #
```

```
########################################
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)
```

```
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)))]
########################################
#  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]))$p.value
    comparison <- rbind(comparison, c(label(cvrdata[,cat]),'','', round(pp,4)))
    for (lev in levels(cvrdata[,cat])){
      comparison <- rbind(comparison, c(paste("--",lev ),
                        paste(s <- sum(cvrdata[,cat]==lev, na.rm=T), " (", round(s*100/is),
                              "%)", sep=""),
                        paste(s <- sum(exclude[,cat]==lev, na.rm=T), " (", round(s*100/xs),
                              "%)", sep=""),""))
    }
    next
  }
  anovaData <- as.data.frame(rbind(cbind(cvrdata[,cat],rep("is", length(cvrdata[,cat]))),
                     cbind(exclude[,cat],rep("xs", length(exclude[,cat])))))
  anovaData[,1] <- as.numeric(as.character(anovaData[,1]))
  pp <- kruskal.test(anovaData[,1] ~ anovaData[,2])$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=""),
                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)
comparison.dx$Variable[grep("pre.wake.mean", comparison.dx$Variable)] <- predictors[1]
comparison.dx$Variable[grep("pre.wake.1", comparison.dx$Variable)] <- predictors[2]
comparison.dx$Variable[grep("Diff", comparison.dx$Variable)] <- predictors[3]


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")

#######################################
#  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]
```

```r
#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                       #
########################################
modelFit <- function(outcome, predictor, ma, knot){

  fit <- fit.mult.impute(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")),
                         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,
                       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)
}
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")

#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)


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                #
########################################
```

```
#Extract p-values for test of association

sys.prewaking.pval <- lapply(mod.sys.prewaking.surge,
                             function(x) anova(x)["systolic.prewaking.surge","P"])
sys.rising.pval <- lapply(mod.sys.rising.surge,
                             function(x) anova(x)["systolic.rising.surge","P"])
noc.sys.diff.pval <- lapply(mod.noc.sys.diff,
                             function(x) anova(x)["nocturnal.systolic.diff.sleep.self.reported","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$sformula[2])))
do.call(grid.arrange, sys.rising.PEP)
#Nocturnal difference
noc.sys.diff.PEP <- lapply(mod.noc.sys.diff,
                             function(x) ggplot(Predict(x, nocturnal.systolic.diff.sleep.self.reported),
                                                adj.subtitle = FALSE,
                                                anova = anova(x), size.anova = 3,
                                                pval = TRUE,
                                                ylim. = c(1,5),
                                                xlab = "Nocturnal Difference in SBP",
                                                ylab = gsub("asl.reac.", "", x$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,
                                                          ylim. = c(0,5),
                                                          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,
                                                       ylim. = c(0,5),
                                                       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(0,5),
                                                         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")
#Select R^2 values for each model
sys.prewaking.r2 <- lapply(mod.sys.prewaking.surge, function(x) x$stats["R2"])
sys.rising.r2 <- lapply(mod.sys.rising.surge, function(x) x$stats["R2"])
noc.sys.diff.r2 <- lapply(mod.noc.sys.diff, 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)
#######################################
#  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)
}


#Systolic prewaking surge
mod.sys.prewaking.surge.linear <- list()
```

```r
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"])))

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")
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)

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),
                           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]
```