Oral Qualifying Exam

Effect Sizes in Neuroimaging

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Overview

- Background
  - Effect sizes vs. *p* values
  - Neuroimaging context
- RESI R Package
- Multivariate Neuroimaging
  - Predictive accuracy
  - Semiparametric Theory
- Current and Future Directions

Background

Effect Sizes and *p* Values

P Values

- Significance testing
- Existence of association
- Sample size dependent

Effect Sizes

- Magnitude of association
- Clinically meaningful
- Parameter not dependent on sample size

Effect Sizes and *p* Values

Effect Sizes

- Magnitude of association
- Clinically meaningful
- Parameter not dependent on sample size

Unstandardized

- Units interpreted in context
- E.g., Beta coefficients

Standardized

- Unitless
- Comparable across different contexts
- E.g., Cohen's *d*, odds ratio

Effect Sizes

- An increased call for reporting effect sizes in place of or alongside *p* values[1-11]
  - ASA Statement on Statistical Significance and *p* Values (Wasserstein and Lazar, 2016)
- Challenges to reporting standardized effect sizes (Vandekar et al., 2020)
  - Many choices available, but most defined in the context of a specific population parameter
  - Often do not accommodate nuisance parameters
  - Lack of confidence interval procedures
  - Lack of user-friendly software

Neuroimaging Background (Soares et al., 2016)

- Focusing on functional magnetic resonance imaging (fMRI)
- Measure blood-oxygen-level dependent (BOLD) signal
- Collect 3D images, comprised of tens of thousands to over a million voxels, of brain over time
- Preprocessing steps
- Can fit subject-level models to voxel time series to generate individual 3D maps or 2D summaries

fMRI Analysis

fMRI data

Univariate Analysis

- Analyze each voxel/region separately
- Threshold and control for errors
- Group-level, associational

Multivariate Analysis

- Include all voxels/regions in model
- Generate individual predictions
- Machine learning

Mass Univariate Analysis

- Typically use cluster-extent thresholding (Vandekar and Stephens, 2021)
- First, threshold on *p* value (e.g., <0.01 or <0.001)
- Then, compute cluster *p* values based on null distribution of cluster size
- With increasing sample sizes, more and more “significant” voxels
  - Null hypothesis fallacy (Bowring et al., 2019)
  - Becoming a more prevalent problem with access to large scale datasets (e.g., Human Connectome Project, UK Biobank) (Bowring et al., 2019)

Using Effect Sizes

- Colorized maps based on effect size more informative than maps based on test statistics (Chen et al., 2017)
- Using an initial threshold based on a standardized effect size can produce more stable results (Vandekar and Stephens, 2021)

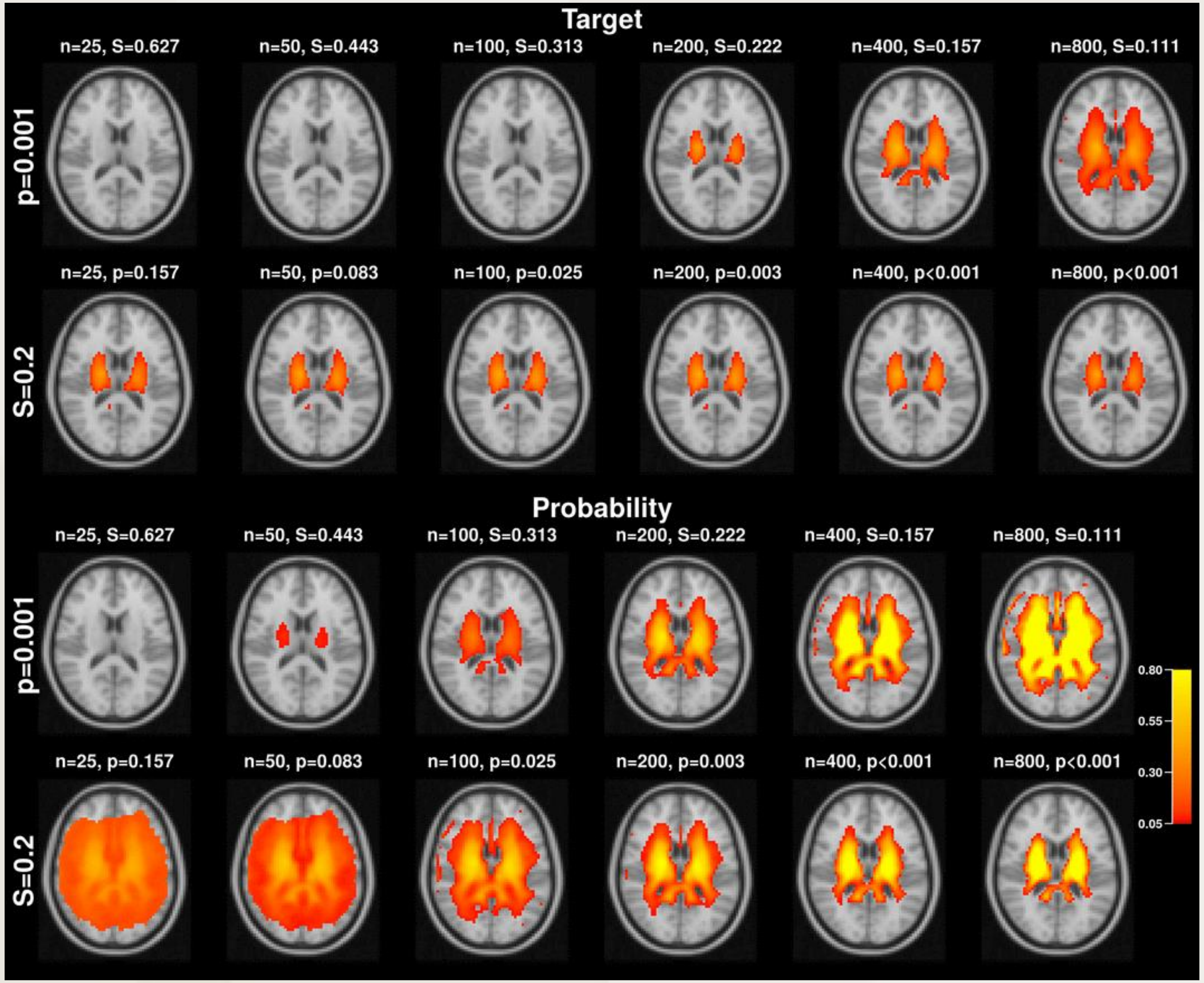

Figure 2 of Vandekar and Stephens (2021)

RESI: An R Package for Robust Effect Sizes

Jones et al., in press

RESI: A New Effect Size Index

- The Robust Effect Size Index (RESI) was recently introduced to address the challenges in using and reporting effect sizes (Vandekar et al., 2020)
- Uses M-estimation, so is broadly applicable and easy to compare across model types
- Robust to model misspecification when using a robust test statistic

RESI (S) Definition

- Consider a Wald statistic, T^2, for $H_0: \beta = \beta_0 \in \mathbb{R}^m$ in a dataset with n independent observations.
- Under known variance, T^2 follows a Chi-square distribution with m degrees of freedom and noncentrality parameter

$$n(\beta - \beta_0)^T \Sigma_\beta^{-1} (\beta - \beta_0)$$

- We can easily compute estimator $\hat{S}_\beta$ from Chi-square, F, Z, and t test statistics.

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- Under known variance, T^2 follows a Chi-square distribution with m degrees of freedom and noncentrality parameter

$$n\boldsymbol{(\beta - \beta_0)^T \Sigma_\beta^{-1} (\beta - \beta_0)} = n\boldsymbol{S_\beta^2}$$

- We can easily compute estimator $\hat{S}_\beta$ from Chi-square, F, Z, and t test statistics.

Absolute vs. Signed RESI

- Chi-square and F statistics are non-negative
  - Represent absolute effect size
- Z and t statistics can be positive or negative
  - Able to compute a signed RESI
  - Communicates direction of effect
  - Alternative estimator available based on squaring and using Chi-square or F estimator

Guidelines for Interpretation

- Under setting of comparing difference in means assuming equal sample proportions and equal variance, Cohen’s *d* is equal to twice the RESI
- Can use Cohen’s guidelines as a rule of thumb, but should always be interpreted within context

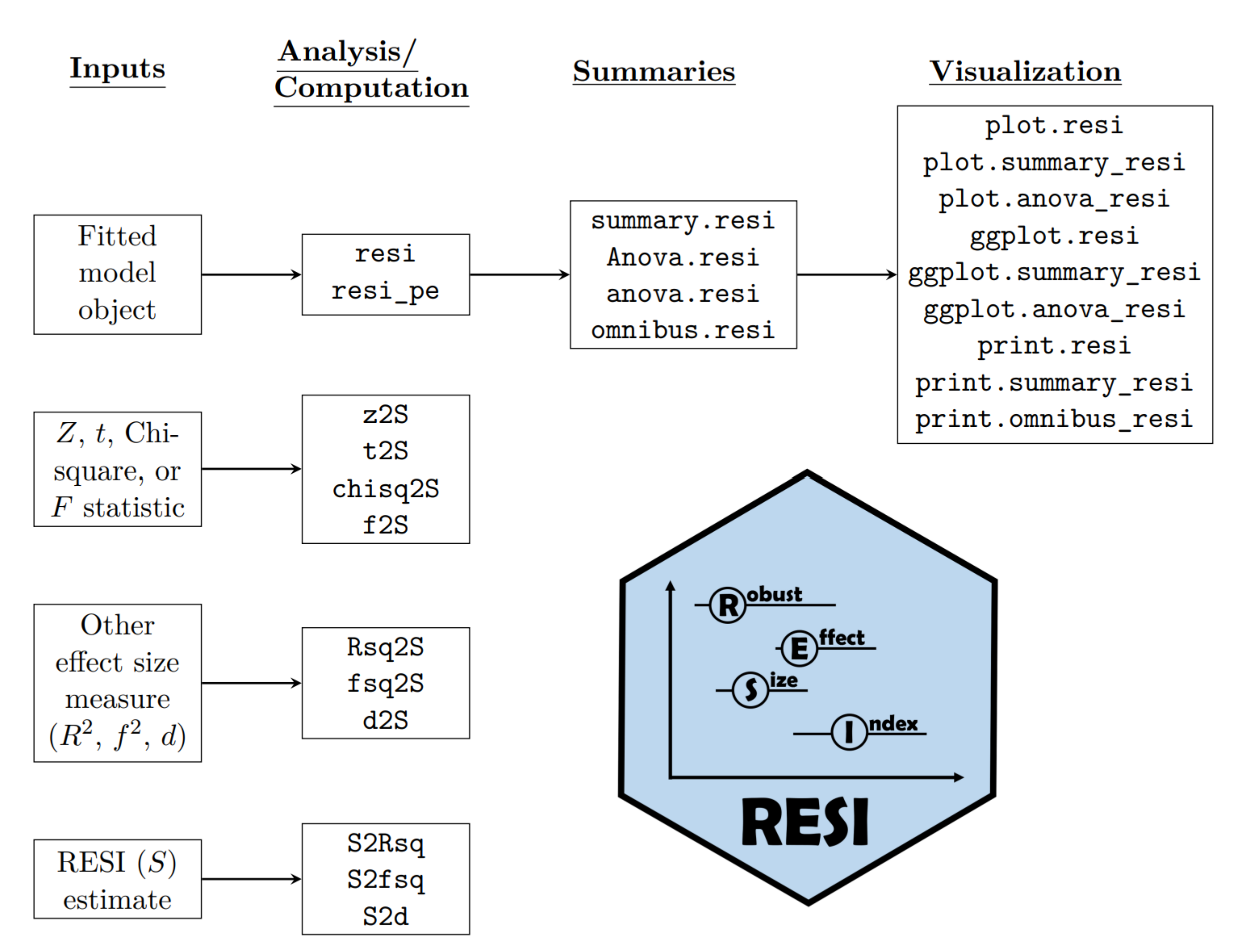
Cohen’s *d*	**RESI**	**“Rule of Thumb” Interpretation**
[0, 0.2]	[0, 0.1]	No effect - small
(0.2, 0.5]	(0.1, 0.25]	Small - medium
(0.5, 0.8]	(0.25, 0.4]	Medium - large
> 0.8	> 0.4	Large

Confidence Intervals

- When using a robust covariance estimator, the Chi-square and F distributions fail to produce confidence intervals with the nominal coverage level (Kang et al., 2023)
- RESI confidence interval procedure is based on a nonparametric bootstrap
  - Bayesian bootstrap is an alternative

RESI R Package Introduction

- `RESI` available on CRAN
- **Goal**: Provide user-friendly and customizable tools to estimate RESI and confidence intervals alongside common model outputs
- Main function (`resi()`) designed to take fitted model objects and perform RESI estimation for 3 elements:
  - Coefficients table – each non-reference level of each variable (univariate)
  - ANOVA table – each variable (multivariate)
  - Overall Wald test – comparing full model to intercept-only or other reduced model



RESI Package Structure and Logo

Model Type	Package	Coefficients Table?	ANOVA Table?	Overall Wald Test?
`lm`	`stats`[17]	✓	✓	✓
`glm`	`stats`[17]	✓	✓	✓
`nls`	`stats`[17]	✓		✓
`survreg`	`survival`[18]	✓	✓	✓
`coxph`	`survival`[18]	✓	✓	✓
`hurdle`	`pscl`[19]	✓		✓
`zeroinfl`	`pscl`[19]	✓		✓
`gee`	`gee`[20]	✓		
`geeglm`	`geepack`[21]	✓	✓	✓
`lme`	`nlme`[22]	✓	✓	
`lmerMod`	`lme4`[23]	✓	✓	

Supported Model Types and Outputs

Example

- Load RESI package and fit a model using `lm` in R:

```
set.seed(987)

library(RESI)

fit <- lm(charges ~ age + sex + bmi + region, data = RESI::insurance)

summary(fit)
```

```
Call:
lm(formula = charges ~ age + sex + bmi + region, data = RESI::insurance)

Residuals:
   Min     1Q Median     3Q    Max
-15350  -6994  -4932   6455  46682

Coefficients:
                Estimate Std. Error t value Pr(>|t|)
(Intercept)     -6076.00    1831.49  -3.318 0.000933 ***
age               244.21      22.28  10.960  < 2e-16 ***
sexmale          1335.70     622.27   2.146 0.032014 *
bmi               316.06      53.60   5.896  4.7e-09 ***
regionnorthwest  -969.34     892.16  -1.087 0.277451
regionsoutheast    65.88     896.63   0.073 0.941440
regionsouthwest -1552.80     895.38  -1.734 0.083105 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 11360 on 1331 degrees of freedom
Multiple R-squared:  0.1234, Adjusted R-squared:  0.1194
F-statistic: 31.22 on 6 and 1331 DF,  p-value: < 2.2e-16
```

RESI Estimation (Default Arguments)

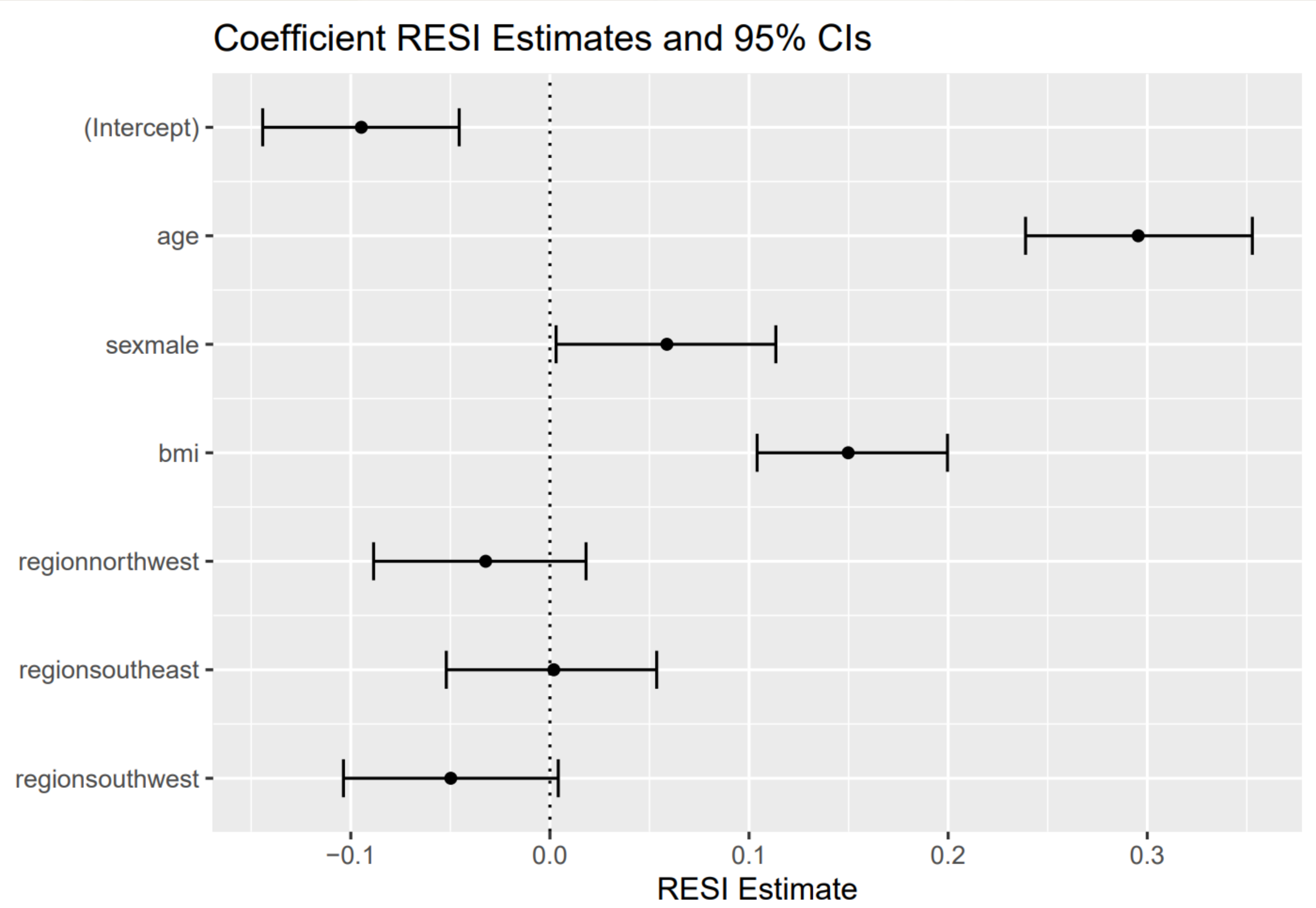
```r
resi_obj <- resi(fit)

summary(resi_obj)
```

```
Analysis of effect sizes based on RESI:
Confidence level =  0.05
Call:  lm(formula = charges ~ age + sex + bmi + region, data = RESI::insurance)

Coefficient Table
                     Estimate Std. Error t value Pr(>|t|)    RESI    2.5%   97.5%
(Intercept)        -6076.0047  1752.8118 -3.4664   0.0005 -0.0947 -0.1443 -0.0456
age                  244.2113    22.5846 10.8132   0.0000  0.2954  0.2389  0.3528
sexmale             1335.7007   621.2058  2.1502   0.0317  0.0587  0.0031  0.1134
bmi                  316.0607    57.6456  5.4828   0.0000  0.1498  0.1041  0.1997
regionnorthwest     -969.3440   820.8705 -1.1809   0.2379 -0.0323 -0.0886  0.0181
regionsoutheast       65.8786   923.1691  0.0714   0.9431  0.0019 -0.0520  0.0536
regionsouthwest    -1552.8043   852.0304 -1.8225   0.0686 -0.0498 -0.1037  0.0042
```

```
ggplot(resi_obj)
```

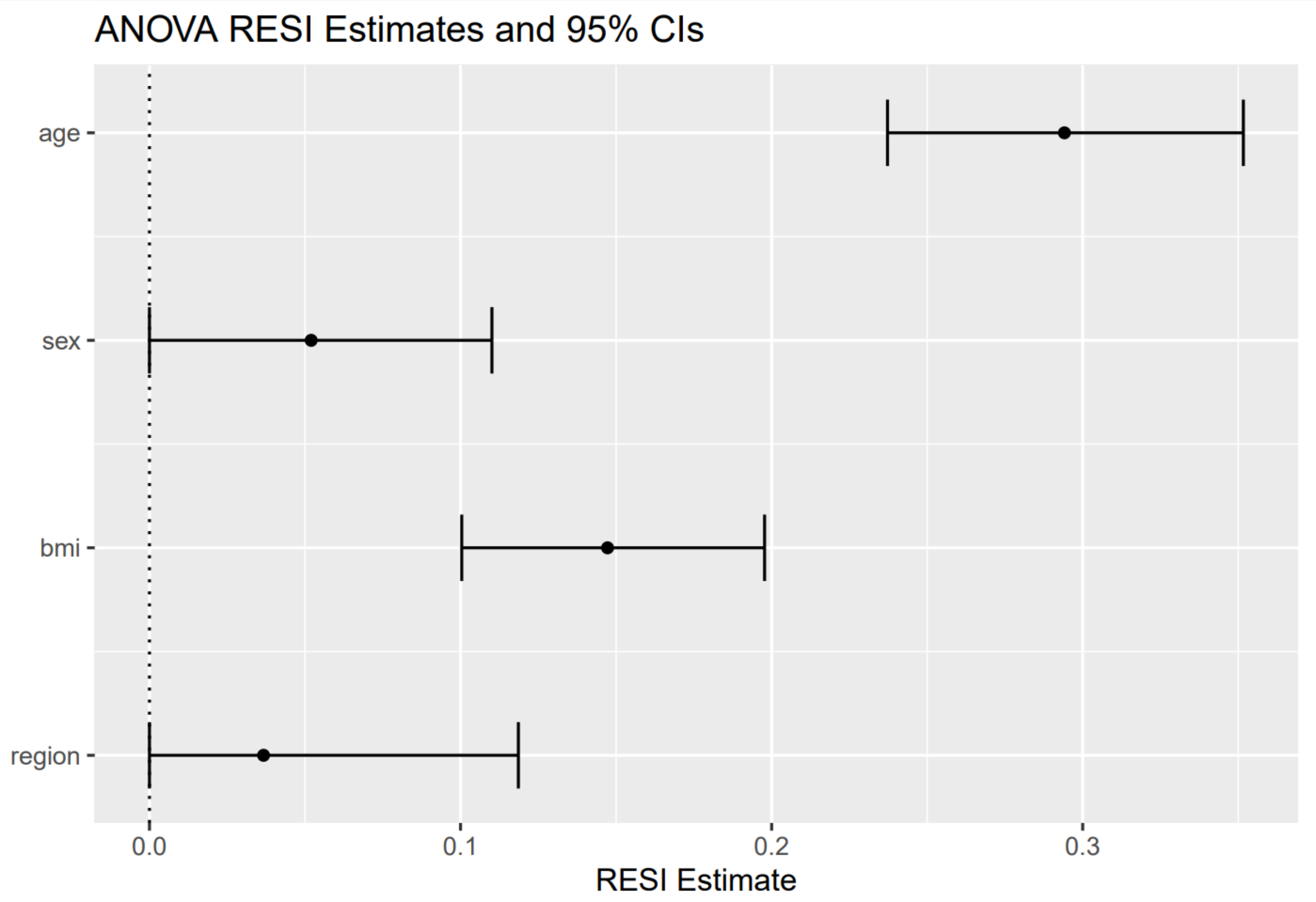


```r
anova(resi_obj)
```

```
Analysis of Deviance Table (Type II tests)

Response: charges
       Df        F   Pr(>F)     RESI    2.5%   97.5%
age     1 116.9252 0.000000 0.294125 0.23726 0.35165
sex     1   4.6232 0.031721 0.051988 0.00000 0.11008
bmi     1  30.0614 0.000000 0.147263 0.10039 0.19774
region  3   1.6026 0.186973 0.036683 0.00000 0.11859
```

```
ggplot(anova(resi_obj))
```



Overall Wald Test

```
omnibus(resi_obj)
```

```
Analysis of effect sizes based on RESI:
Confidence level =  0.05
Wald test

Model 1: charges ~ 1
Model 2: charges ~ age + sex + bmi + region
  Res.Df Df      F Pr(>F)   RESI   2.5%  97.5%
1   1337
2   1331  6 29.975      0 0.3602 0.3193 0.4123
```

RESI Summary

- The RESI R package makes it easy to obtain a useful standardized effect size
- Several arguments available to tailor the bootstrapping process, covariance estimation, etc.
- Can be easily implemented in the univariate neuroimaging setting

Multivariate Neuroimaging

Multivariate Neuroimaging

- **Goal**: Build reliable models using fMRI data that can generate predictions for external, unseen data
- Trend towards more personalized medicine (Johnson et al., 2021)
- Neuroimaging data is very high dimensional
  - Feature reduction techniques (e.g., independent component analysis, fewer regions of interest)
  - Flexible machine learning models (e.g., support vector machines, random forests)

Multivariate Modeling Steps (Bzdok and Ioannidis, 2019)

Model Building

- Decide which features to include
- Decide on model

→

Internal Validity

- Assess predictive accuracy within original data
- Sample splitting, *K*-fold cross validation

→

External Validity

- Assess predictive accuracy in independent dataset

→

Generalizability and Transposability

- Assess predictive accuracy in independent datasets less similar to original population

Recent Systematic Review Findings

- 108 neuroimaging studies of individual trait prediction from 2007-2021 (Yeung et al., 2022)
- Sharp increase in number of studies being published since 2017
- All studies reported internal validation metrics, but only 26 (24%) reported a measure of external validity
- Pearson correlation was most common predictive accuracy metric (75% of internal validity measures, 61.5% of external validity)

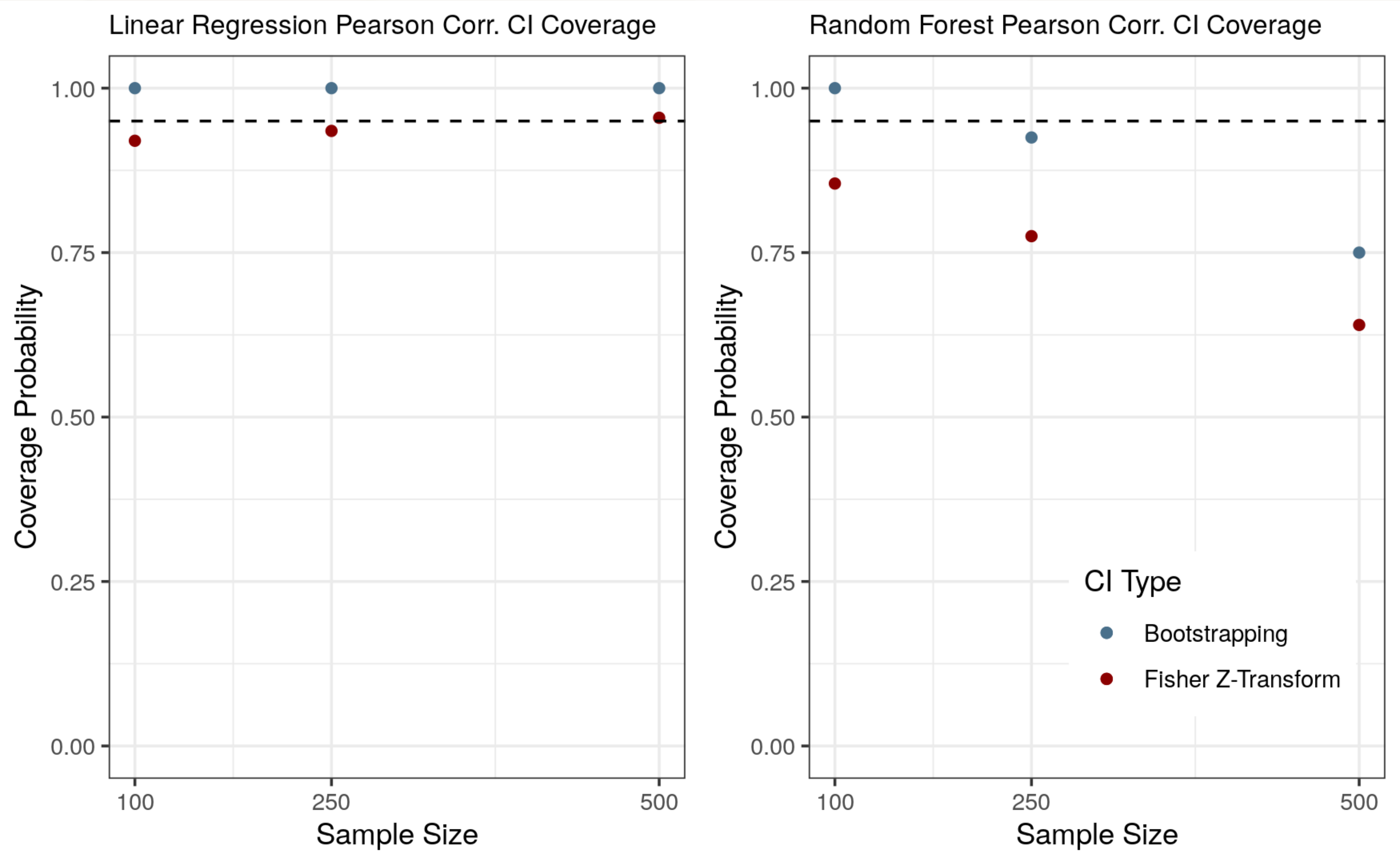
Pearson Correlation

- Common measure to compare the similarity between actual target features and the predicted feature
- Standardized effect size
  - Ranges from -1 to 1 (though often expected to be between 0 and 1 in this setting)
  - Magnitude is comparable across studies
- CI procedure for Pearson correlation exists in general (commonly Fisher Z-transformed interval), but typically not used in predictive neuroimaging (Yeung et al., 2022)
- *P* values reported via permutation test

Correlation from ML Models

- Consider predicting Y (e.g., age, intelligence) from $\boldsymbol{X}$ (imaging data)
- Model $\mu(\boldsymbol{X}) = \mathrm{E}[Y|\boldsymbol{X}]$
- Pearson correlation: $\frac{Cov(\mu(\boldsymbol{X}), Y)}{\sqrt{Var(\mu(\boldsymbol{X}))Var(Y)}}$
  - commonly estimated using the sample correlation
- Flexible machine learning models may not provide fast enough convergence
- Fisher Z transformed interval and bootstrapped interval will not have nominal coverage rates

Comparison of Coverage



Example dataset: ABIDE Preprocessed[29]

Applicable Semiparametric Theory

- Need tools that can help us construct consistent and asymptotically normal estimators even when using flexible machine learning techniques to build models
- We will use the theory of efficient influence functions and debiased one-step estimators
- Great introductions found in:
  - "Semiparametric Doubly Robust Targeted Double Machine Learning: A Review" by Edward Kennedy (2023)
  - "Visually Communicating and Teaching Intuition for Influence Functions" by Aaron Fisher and Edward Kennedy (2019)

Setup

- Consider a dataset of n independent and identically distributed observations
- $\boldsymbol{Z}_i = (Y_i, X_{i1}, \dots, X_{im})$
- $\boldsymbol{Z}_i \sim \mathbb{P}$
- Let $\mathbb{P}$ lie in the model $\mathcal{P}$ and have probability density function p
- We are interested in estimating a mapping of the true distribution to a real value, called the “functional” or “target parameter” and denoted $\psi(\mathbb{P})$

Parametric Submodels

- Consider a smooth parametric submodel $\mathcal{P}_\epsilon \subseteq \mathcal{P}$
  - $\mathcal{P}_\epsilon = \{P_\epsilon : \epsilon \in \mathbb{R}\}$
  - $P_0 = \mathbb{P}$, denote arbitrary parametric distribution $P_1 = \tilde{P}$ with pdf $\tilde{p}$
- Probability density functions for distributions P_ϵ:
  - $p_\epsilon(z) = (1-\epsilon)p(z) + \epsilon\tilde{p}(z)\ ; \epsilon \in [0,1]$
- Creates a "path" from the parametric distribution $\tilde{P}$ to the true distribution $\mathbb{P}$
- $\psi(P_\epsilon)$ exists for each ϵ along the path, though we only want to compute an estimate using $\tilde{P}$

Von Mises Expansion

- Under certain smoothness conditions, we can deconstruct the functional:

$$\psi(\mathbb{P}) = \psi(P_{\epsilon=1}) + \frac{d}{d\epsilon}\psi(P_\epsilon)\Big|_{\epsilon=1}(0-1) - R_2(P_{\epsilon=1}, \mathbb{P})$$

which is equivalent to

$$\psi(\mathbb{P}) = \psi(P_{\epsilon=1}) + \int \varphi(z; P_{\epsilon=1})d\mathbb{P}(z) - R_2(P_{\epsilon=1}, \mathbb{P})$$

- $\varphi(z; P)$ is the *influence function* for the functional on distribution P
  - Mean-zero, finite variance function
  - Represents how much an estimator changes in response to a slight perturbation of the sample distribution

One-Step Estimator

- Expansion suggests a method for a debiased estimator by adding the empirical mean ($\mathbb{P}_n$) of the influence function

$$\hat{\psi} = \psi\left(\hat{P}_{\epsilon=1}\right) + \mathbb{P}_n\{\varphi(Z;\hat{P}_{\epsilon=1})\}$$

- Decomposition of the difference between estimator and functional:

$$\hat{\psi} - \psi = \psi\left(\hat{P}_{\epsilon=1}\right) + \mathbb{P}_n\left\{\varphi\left(Z;\hat{P}_{\epsilon=1}\right)\right\} - \psi(\mathbb{P})$$

$$= (\mathbb{P}_n - \mathbb{P})\{\varphi(Z;\mathbb{P})\} + (\mathbb{P}_n - \mathbb{P})\left\{\varphi\left(Z;\hat{P}_{\epsilon=1}\right) - \varphi(Z;\mathbb{P})\right\}$$
$$+ R_2(P_{\epsilon=1},\mathbb{P})$$

$$\equiv S^* + T_1 + T_2$$

Asymptotic Normality

- S^* is asymptotically normally distributed by Central Limit Theorem with variance $\frac{var(\varphi)}{n}$
- T_1 can converge at $\frac{1}{\sqrt{n}}$ rate under complexity conditions or by using cross-fitting
  - Split data into K folds, estimate the distribution using all but k^{th} fold and compute functional estimate using observations in the k^{th} fold
  - Average estimates of functional and variance
- T_2 will often be negligible or depend on products or squares of differences between estimated and true distribution, so each term only needs to converge at $\frac{1}{n^{1/4}}$ rate

Confidence Intervals

- Can construct 95% confidence intervals as

$$\hat{\psi} \pm 1.96 \sqrt{\frac{\widehat{var}(\varphi(Z; \hat{P}_{\epsilon=1}))}{n}}$$

Current and Future Directions

Deriving Influence Function – Correlation

- Most general approach is to apply formal definition of pathwise derivative and explicitly solve for the influence function
- Luckily, we can apply derivative rules to influence functions and plug in known influence functions for simpler functionals
  - Can formally check after deriving
- Note influence function for $\mathrm{E}[X]$ is $X - \mathrm{E}[X]$ and influence function for $\mathrm{Var}[X]$ is $(X - \mathrm{E}[X])^2 - \mathrm{Var}[X]$ (Tsiatis, 2007)

Deriving Better Estimator

$$
\begin{aligned}
\psi &= \frac{\text{cov}(\mu(\mathbf{X}), Y)}{\sqrt{\text{var}(\mu(\mathbf{X}))\text{var}(Y)}} \\
&= \frac{\mathsf{E}[\mu(\mathbf{X})Y] - \mathsf{E}[\mu(\mathbf{X})]\mathsf{E}[Y]}{\sqrt{\text{var}(\mu(\mathbf{X}))\text{var}(Y)}} \\
&= \frac{\mathsf{E}\{\mathsf{E}[\mu(\mathbf{X})Y|\mathbf{X}]\} - \mathsf{E}\{\mathsf{E}[Y|\mathbf{X}]\}\mathsf{E}[\mu(\mathbf{X})]}{\sqrt{\text{var}(\mu(\mathbf{X}))\text{var}(Y)}} \\
&= \frac{\mathsf{E}[\mu(\mathbf{X})^2] - \mathsf{E}[\mu(\mathbf{X})]^2}{\sqrt{\text{var}(\mu(\mathbf{X}))\text{var}(Y)}} \\
&= \frac{\sqrt{\text{var}(\mu(\mathbf{X}))}}{\sqrt{\text{var}(Y)}}
\end{aligned}
$$

$$
\hat{\psi}_{pi} = \frac{\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))}}{\sqrt{\widehat{\text{var}}(Y)}}
$$

Deriving Influence Function

$$
\begin{aligned}
\mathbb{IF}(\psi) &= \mathbb{IF}\Big(\Big(\frac{\mathrm{var}(\mu(\mathbf{X}))}{\mathrm{var}(Y)}\Big)^{\frac{1}{2}}\Big) \\
&= \frac{1}{2}\Big(\frac{\mathrm{var}(\mu(\mathbf{X}))}{\mathrm{var}(Y)}\Big)^{-\frac{1}{2}}\mathbb{IF}\Big(\frac{\mathrm{var}(\mu(\mathbf{X}))}{\mathrm{var}(Y)}\Big) \\
&= \frac{1}{2}\Big(\frac{\mathrm{var}(\mu(\mathbf{X}))}{\mathrm{var}(Y)}\Big)^{-\frac{1}{2}}\frac{\mathbb{IF}(\mathrm{var}(\mu(\mathbf{X})))\mathrm{var}(Y) - \mathbb{IF}(\mathrm{var}(Y))\mathrm{var}(\mu(\mathbf{X}))}{\mathrm{var}(Y)^2} \\
&= \frac{1}{2}\Big(\frac{\mathrm{var}(\mu(\mathbf{X}))}{\mathrm{var}(Y)}\Big)^{-\frac{1}{2}}\frac{((\mu(\mathbf{X}) - \mathsf{E}[\mu(\mathbf{X})])^2 - \mathrm{var}(\mu(\mathbf{X})))\mathrm{var}(Y) - ((Y - \mathsf{E}[Y])^2 - \mathrm{var}(Y))\mathrm{var}(\mu(\mathbf{X}))}{\mathrm{var}(Y)^2} \\
&= \frac{1}{2\sqrt{\mathrm{var}(\mu(\mathbf{X}))}\mathrm{var}(Y)^{\frac{3}{2}}}((\mu(\mathbf{X}) - \mathsf{E}[\mu(\mathbf{X})])^2\mathrm{var}(Y) - \mathrm{var}(\mu(\mathbf{X}))\mathrm{var}(Y) \\
&\quad - (Y - \mathsf{E}[Y])^2\mathrm{var}(\mu(\mathbf{X})) + \mathrm{var}(Y)\mathrm{var}(\mu(\mathbf{X})) \\
&= \frac{1}{2\sqrt{\mathrm{var}(\mu(\mathbf{X}))}\mathrm{var}(Y)^{\frac{3}{2}}}((\mu(\mathbf{X}) - \mathsf{E}[Y])^2\mathrm{var}(Y) - (Y - \mathsf{E}[Y])^2\mathrm{var}(\mu(\mathbf{X}))) \\
&= \frac{(\mu(\mathbf{X}) - \mathsf{E}[Y])^2}{2\sqrt{\mathrm{var}(\mu(\mathbf{X}))\mathrm{var}(Y)}} - \frac{(Y - \mathsf{E}[Y])^2\sqrt{\mathrm{var}(\mu(\mathbf{X}))}}{2\mathrm{var}(Y)^{\frac{3}{2}}}
\end{aligned}
$$

One-Step Estimator

$$\hat{\psi} = \frac{\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))}}{\sqrt{\widehat{\text{var}}(Y)}} + \frac{1}{2n}\sum_{i=1}^{n}\left\{\frac{(\hat{\mu}(\mathbf{X}_i) - \hat{\mathsf{E}}[Y])^2}{\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))\widehat{\text{var}}(Y)}} - \frac{(Y_i - \hat{\mathsf{E}}[Y])^2\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))}}{\widehat{\text{var}}(Y)^{\frac{3}{2}}}\right\}$$

$$= \frac{\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))}}{\sqrt{\widehat{\text{var}}(Y)}} + \frac{\frac{1}{2n}\sum_{i=1}^{n}(\hat{\mu}(\mathbf{X}_i) - \hat{\mathsf{E}}[Y])^2}{\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))\widehat{\text{var}}(Y)}} - \frac{\frac{1}{2n}\sum_{i=1}^{n}(Y_i - \hat{\mathsf{E}}[Y])^2\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))}}{\widehat{\text{var}}(Y)^{\frac{3}{2}}}$$

$$= \frac{\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))}}{\sqrt{\widehat{\text{var}}(Y)}} + \frac{\frac{1}{2n}\sum_{i=1}^{n}(\hat{\mu}(\mathbf{X}_i) - \hat{\mathsf{E}}[Y])^2}{\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))\widehat{\text{var}}(Y)}} - \frac{\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))}}{2\sqrt{\widehat{\text{var}}(Y)}}$$

$$= \frac{\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))}}{2\sqrt{\widehat{\text{var}}(Y)}} + \frac{\frac{1}{2n}\sum_{i=1}^{n}(\hat{\mu}(\mathbf{X}_i) - \hat{\mathsf{E}}[Y])^2}{\sqrt{\widehat{\text{var}}(\hat{\mu}(\mathbf{X}))\widehat{\text{var}}(Y)}}$$

Current and Future Work

- Evaluate the one-step estimator performance in simulations using the ABIDE data
- Explore transformations similar to Fisher *Z* transform
- Explore targeted maximum likelihood estimation (TMLE) as an alternative to one-step estimation
- Connect estimators to RESI
- Apply similar theory for other problems, such as missing data, helping to increase the precision of effect size estimates

Thank you!

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