

Full Covariate Models as an Alternative to Methods Relying on Statistical Significance for Inferences about Covariate Effects: A Review of Methodology and 42 Case Studies

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Marc R. Gastonguay, Ph.D.

Appropriate Inference?

Table III (continued)

Model	Question	Equation	Objective Function	Conclusion (Significance = Yes)
Model 15	Does condition (Healthy/asthmatic) affect the volume of distribution (V2) (LINEAR MODEL)?	$TVKA = \theta (1)$ $TVCL = \theta (2)$ $TVV2 = \theta (3)*COND + \theta (4)*(1 - COND)$ $\theta (1) = 4.42 \text{ h}^{-1}$ $\theta (2) = 392 \text{ L/h}$ $\theta (3) = 1170 \text{ L}$ $\theta (4) = 1510 \text{ L}$	-9603	No
Model 16	Does condition (Healthy/asthmatic) affect the clearance (POWER MODEL)?	$TVKA = \theta (1)$ $TVCL = \theta (2)*\theta (3)**COND$ $TVV2 = \theta (4)$ $\theta (1) = 4.42 \text{ h}^{-1}$ $\theta (2) = 363 \text{ L/h}$ $\theta (3) = 468$ $\theta (4) = 1720 \text{ L}$	-240	No
Model 17	Does condition (Healthy/asthmatic) affect the clearance (LINEAR MODEL)?	$TVKA = \theta (1)$ $TVCL = \theta (2)*COND + \theta (3)*(1 - COND)$ $(TVV2 = \theta (4))$ $\theta (1) = 4.42 \text{ h}^{-1}$ $\theta (2) = 384 \text{ L/h}$ $\theta (3) = 438 \text{ L/h}$ $\theta (4) = 1180 \text{ L}$	-9598	No
Model 18	Does weight affect clearance and volume of distribution (POWER MODEL)?	$TVCL = \theta (2)*(WT/75)**\theta (3)$ $TVV2 = \theta (4)*(WT/75)**\theta (5)$ $\theta (2) = 393 \text{ L/h}$ $\theta (3) = 0.56$ $\theta (4) = 1220 \text{ L}$ $\theta (5) = 1.28$	-9738	Yes

Appropriate Inference?

Covariate Effects:

Creatinine clearance was the most significant covariate on [REDACTED] clearance. The clinical importance of this finding is unknown, since less than 2% of [REDACTED] dose is excreted in the urine. This may be an artifact of the data as the current analysis data set did not include patients with moderate or severe renal impairment. Weight, age and sex were not significant covariates and, therefore, require no dose adjustment.

An Alternative...

Full Models

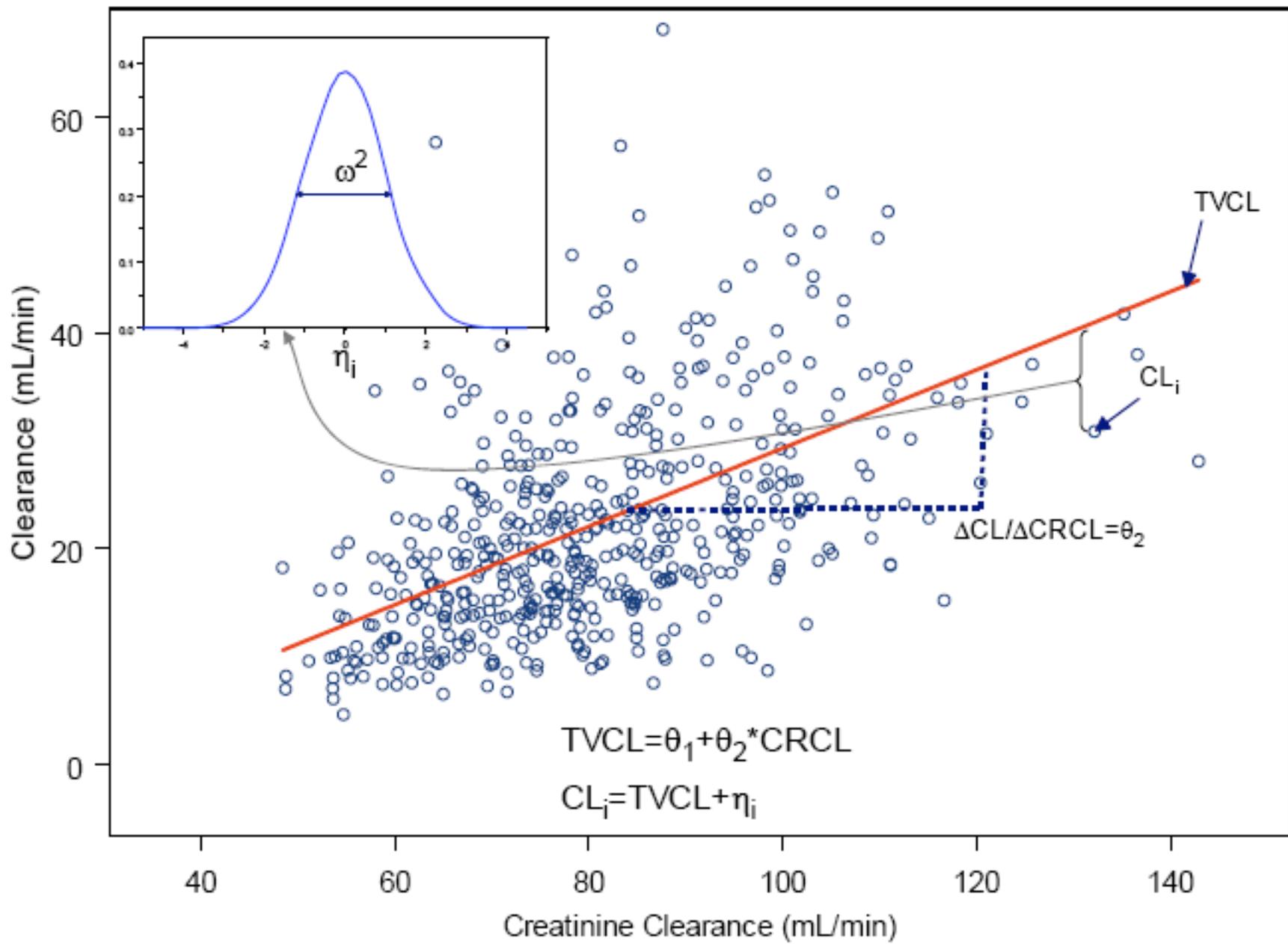
- Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med*. 1996;15(4):361-387.
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- Gastonguay, MR. A Full Model Estimation Approach for Covariate Effects: Inference Based on Clinical Importance and Estimation Precision. *The AAPS Journal*; 6(S1), Abstract W4354, 2004.

Overview

- Objectives of Covariate Model Building
- Problems with Traditional Stepwise Methods
- Full Covariate Models
 - Data Reduction
 - Model Development
 - Inferences about Covariate Effects
- Review of Case Studies
- Aligning Covariate Modeling Methods with Objectives
- Summary

Objectives of Covariate Model Development

- Explain “random” variability in parameters and response
- Understand causes of variability and apply the knowledge
 - For better clinical therapeutic use (dosing, adjustment, labeling)
 - To allow for better control in clinical trials
 - In other words, make inferences about covariate effects from modeling results
- Improve predictive performance of the model
 - For subjects in the current data set
 - For trial simulation of future studies
 - For future patient populations



Traditional Covariate Screening Methods in Pop PKPD

Outside of population model context:

- Exploratory Graphics of Individual Random Effects (η) vs. Covariates
- Generalized Additive Modeling

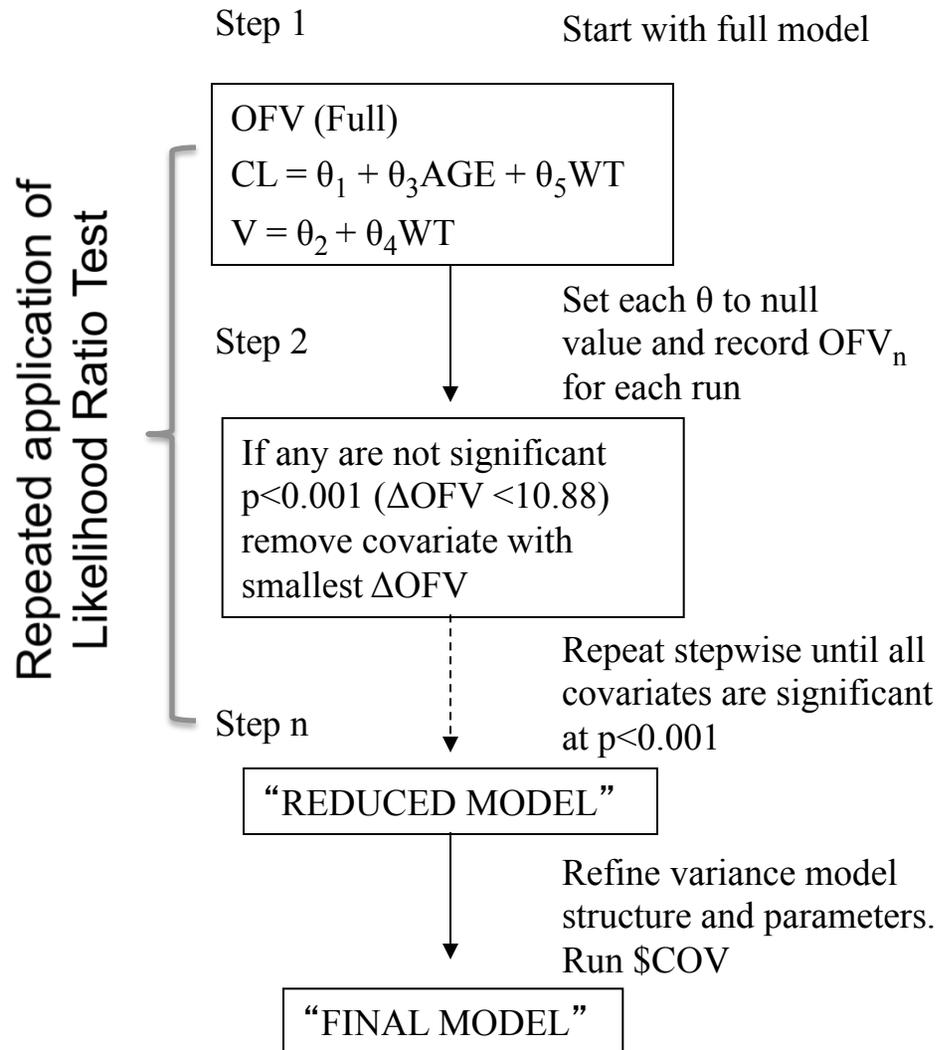
These are problematic in presence of:
 η -shrinkage, imbalanced designs, time-dependent covariates, plus other problems...

Within population model context:

- Stepwise Forward Addition
- Stepwise Backward Elimination
- Stepwise Forward/Backward

Other problems with these methods... more later.

Stepwise Backward Elimination



What happens when a covariate effect is statistically “significant”, but not clinically important?

If a covariate effect is not statistically “significant”, does this mean that there is no effect of that covariate?

Some Problems with Stepwise Regression

- Based on methods (e.g. F tests for nested models) that were intended to be used to test pre-specified hypotheses
- p-values are difficult to interpret and difficult to adjust appropriately for multiple comparisons
- Regression coefficients are typically over-estimated (e.g. selection bias, false-positive findings, or biased inference).
- Confidence intervals are falsely narrow.
- Severe problems in the presence of correlated or collinear predictors (estimation bias, interpretation difficulties).
- Resulting models may be predictive of the current data set, but often are difficult to interpret or generalize.

More Problems with Stepwise Regression

- NONMEM likelihood approximations can result in incorrect p-values, even when model is known.
- Reconciling statistically significant effects with clinically important effects is challenging.
- Lack of statistical significance does not necessarily indicate lack of effect.
- Even with very large data sets, and rigorous model building, testing and cross-validation (conditions not typically seen in population PKPD), stepwise selection often fails.

A Purpose-Driven Parsimony Principle

*“When competing hypotheses are **equal in other respects**, select the hypothesis that introduces the fewest assumptions and postulates the fewest entities while still **sufficiently answering the question**.” -Occam's razor*

- Stepwise p-value reduced models do not allow for inferences about “non-significant” covariate effects and result in biased standard errors and point estimates. They do not **sufficiently answer the question** about clinical importance of covariate effects.
- For the purpose of making inferences about covariate effects, the full covariate model is the most parsimonious model.

Parsimony Principle Restated

*“All things **being equal**, choose the simpler model.”*

- Unknown

*“We are to admit no more causes of natural things than such as are both **true and sufficient** to explain their appearances.”*

- Isaac Newton

*“Make everything as simple as possible, **but not simpler.**”*

- Albert Einstein

*“The simplest explanation that **covers all the facts** is usually the best.”*

- Unknown

Full Covariate Model Approach

- Define stable base model structure based on GOF criteria.
- Data Reduction:
 - Avoid searching across all possible covariates
 - Avoid correlated predictors
 - Rational selection of potential covariates for full model
- Re-parameterize as necessary to develop a stable full model.
- Estimate all parameters of full model and construct intervals or posterior distributions (bootstrap, Bayesian, cov-matrix of est.).
- Make inferences based on posterior predictive intervals of estimated covariate effects
- Explore remaining trends as secondary hypothesis-generating step

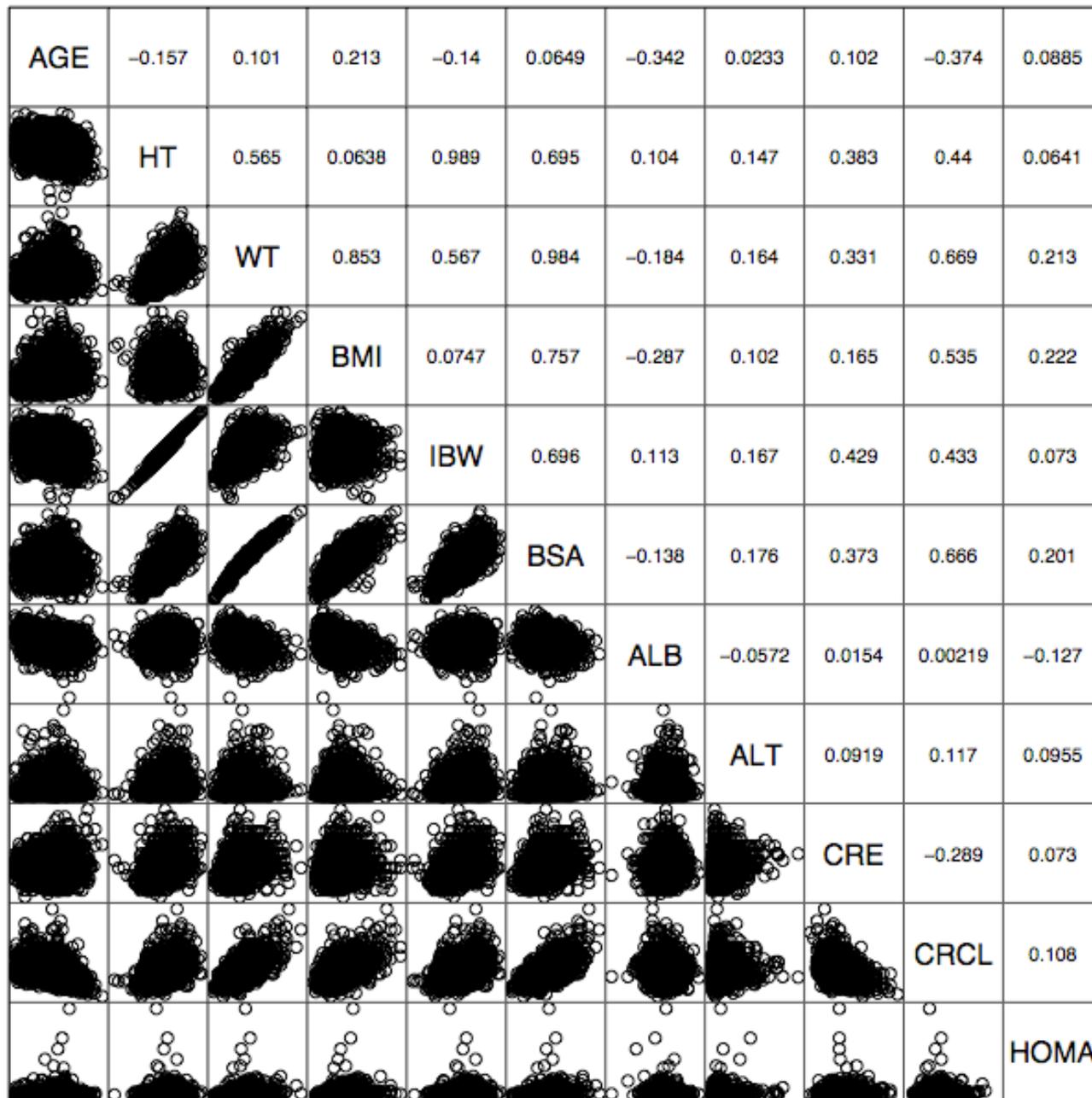
Before Covariate Model Building: Data Reduction

- Examine covariate data
 - Identify range & distribution of continuous covariates
 - Count number in each category for categorical covariates
 - Identify strong correlations or collinearity between covariates
 - ▶ Select covariates with unique information
 - ▶ May require composite/interaction to convert to single variable
- Was the study designed to estimate covariate effects?
- How do inclusion criteria impact choice of covariates to include in modeling?
- Does covariate make sense given prior knowledge?
- Which covariates are of interest from clinical perspective?

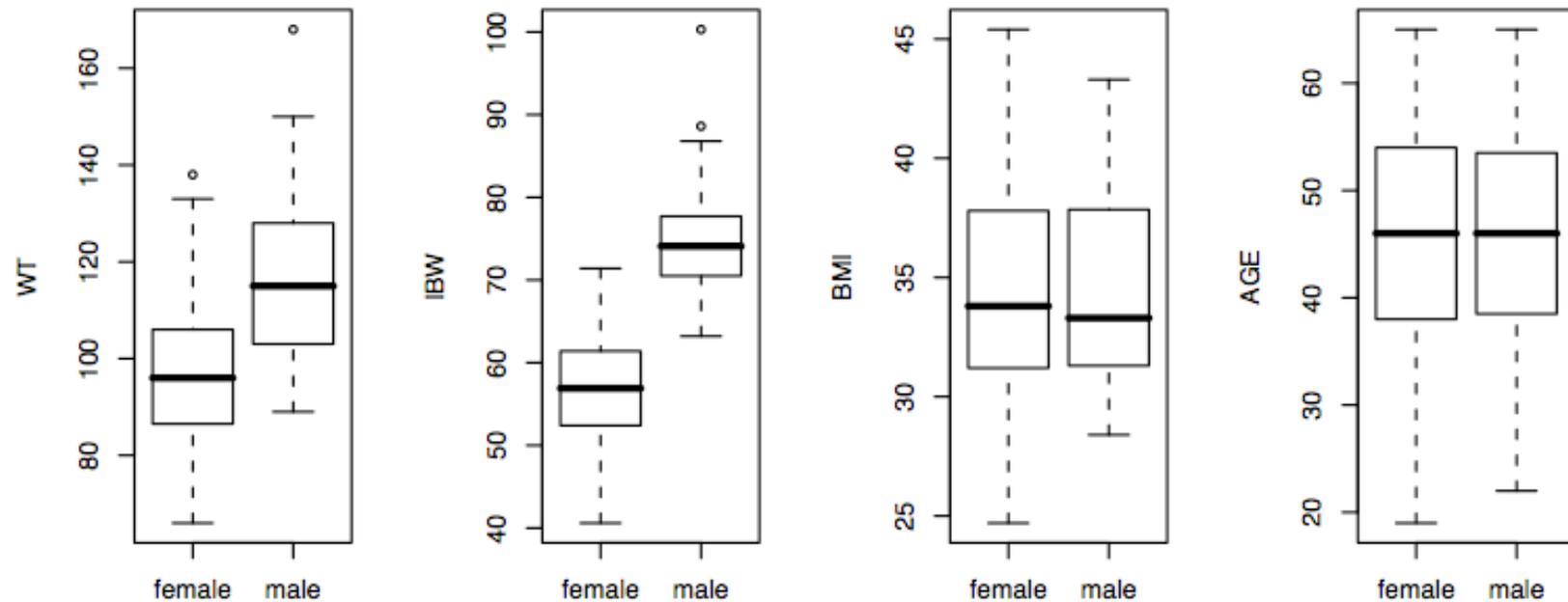
Correlation/ Collinearity

Covariate effects to be included in model should be independent, e.g. they carry unique information.

Rule of thumb:
Be cautious when
 $|\text{corr. coef.}| > 0.3$



Check for Independence of Covariates



- Relationships between continuous/categorical covariates
 - Explore graphically
 - Apply ANOVA and/or Kruskal-Wallis test

Solutions to Correlation / Collinearity

- Avoid simultaneous inclusion of suspect covariates
- Remove correlation
 - For example: MDRD calculation for renal function is normalized by BSA, and can be included simultaneously with measures of body size
- Seek additional data where the same variables are independent
 - Include data from renal impairment study where CRCL~WT are not likely to be correlated
- Create a single summary variable to represent correlated predictors
 - BMI reflects both weight and height
- Fix one of the covariate-parameter relationships
 - Age and weight are highly correlated in pediatrics, but fixing weight relationship to an allometric expression allows estimation of age effects
- Reserve correlated covariates for 2⁰ exploratory modeling

Guiding Factors for Selection of Covariates for FCM

- Perform data reduction step
- Create focused questions about specific covariate effects in the current data set, based on:
 - Scientific or clinical interest
 - Mechanistic plausibility
 - Prior knowledge about covariate effects(These should be defined *a priori* in the analysis plan).
- Pre-specified covariate selection is not subject to problems of eta-shrinkage or data-driven selection bias

Pre-Specified Covariate Plan

Covariate	Model Parameters	Rationale
Weight	CL, V1, Q, V2	Clinical interest
Age	CL	Clinical interest
Race	CL, V1	Clinical interest. Bridging goal.
Disease State Type	CL	Clinical interest
Child-Pugh Score	CL	Clinical interest. Prior knowledge of hepatic elimination mechanism; CYP3A4
Drug X Interaction	CL	Clinical interest. Known CYP3A4 inhibitor and common con-med
etc...		

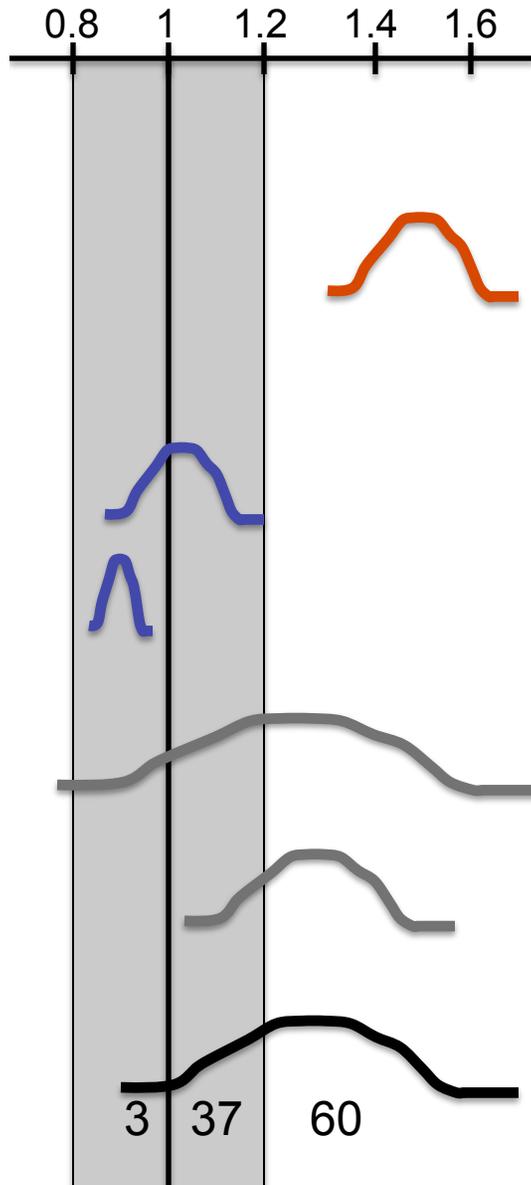
Stable Parameterization of Full Model

an example:

$$TVP = \theta_n \cdot \prod_1^m \left(\frac{cov_{mi}}{ref_m} \right)^{\theta_{(m+n)}} \cdot \prod_1^p \theta_{(p+m+n)}^{cov_{pi}}$$

where: the typical value of a model parameter (TVP) is described as a function of m individual continuous covariates (cov_{mi}) and p individual categorical (0-1) covariates (cov_{pi}) such that θ_n is an estimated parameter describing the TVP for an individual with covariates equal to the reference covariate values ($cov_{mi} = ref_m, cov_{pi} = 0$); $\theta_{(m+n)}$ and $\theta_{(p+m+n)}$ are estimated parameters describing the magnitude of the covariate-parameter relationships

Inferences Based on Posterior Distribution of Effect



First, define effect magnitude likely to be clinically important (e.g. greater than +/- 20% of null value)

Clinically Important: Entire 95% interval of posterior distribution for covariate effect lies within clinically important region (always SS)

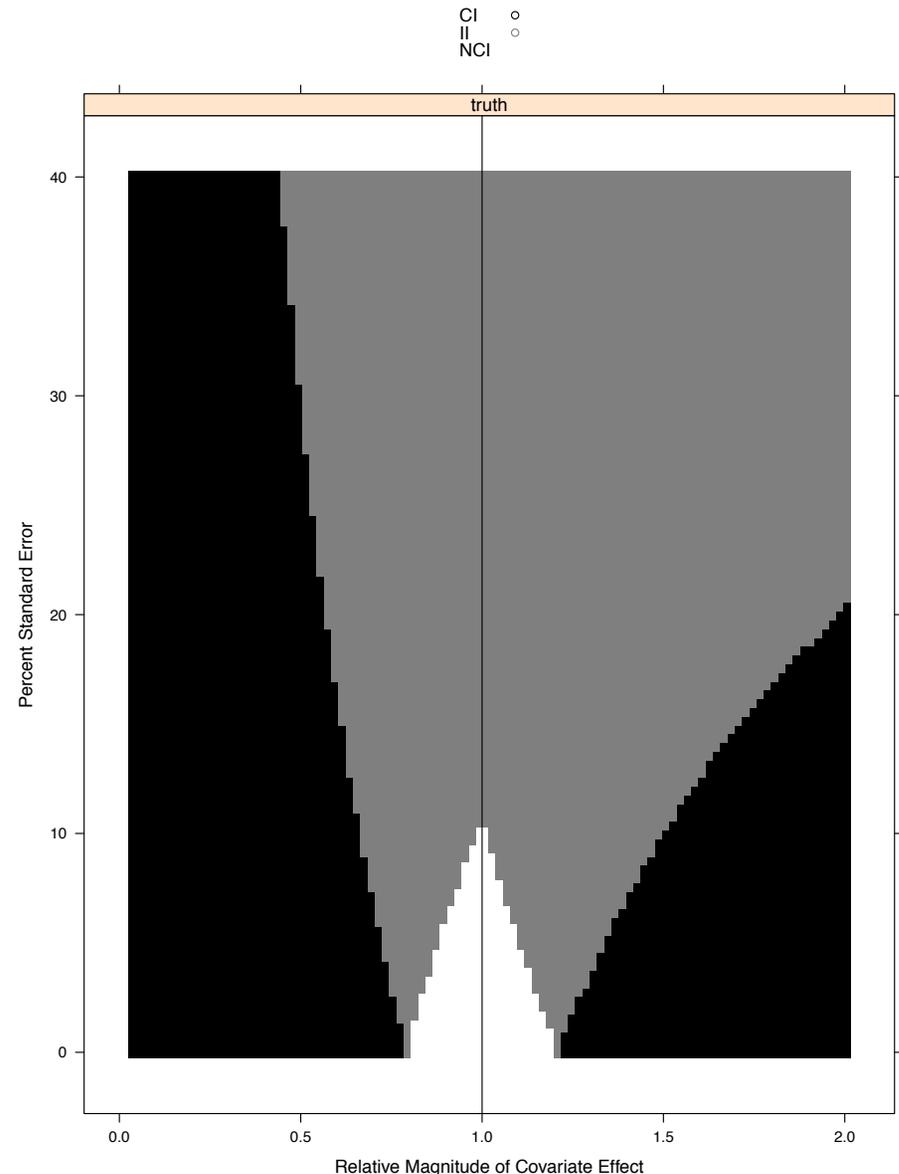
Not Clinically Important: Entire 95% interval of posterior distribution for covariate effect lies within clinically unimportant region. May be important in combination with other effects. (NSS or SS)

Insufficient Information: 95% interval of posterior distribution for covariate effect spans across values of covariate effect that are both clinically important and unimportant. (NSS or SS)

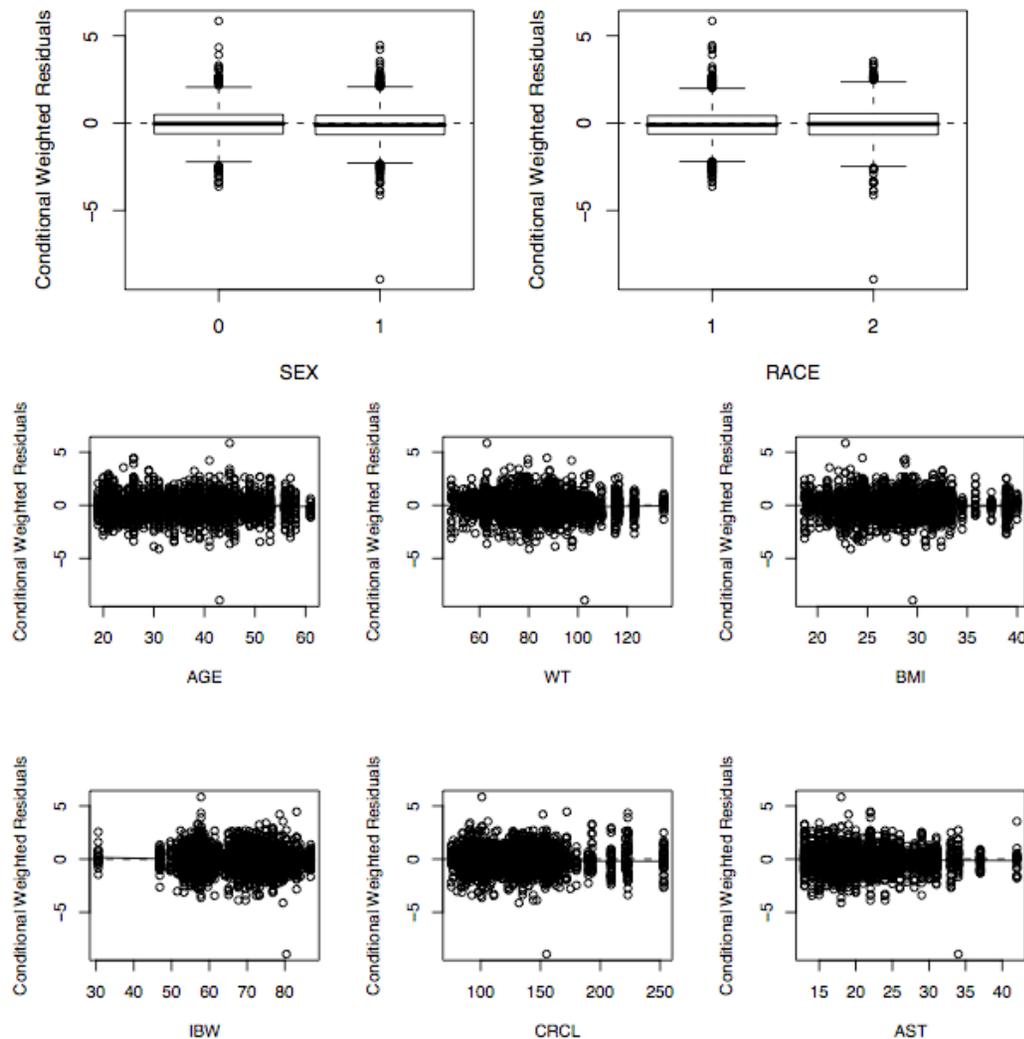
Or... Probabilistic Approach: Quantitatively describe probability of being clinically important using posterior distribution and reference range.

Covariate Effect Inferences: Magnitude and Precision

- Requires some measure of covariate effect parameter precision.
- Magnitude of covariate effect and precision of the estimate are key drivers of inferences, relative to clinically important effect size.
- Example: multiplicative binary categorical covariate effect ($TVP = \theta_1 * \theta_2^{\text{cat}}$)



Check Full Covariate Model for Remaining Trends



- Plot CWRES or η from Full Model vs. any covariates in database.

- and/or -

- Proceed with exploratory stepwise regression, starting at the full model. (For hypothesis-generating purposes).

Reduction of Full Model for Predictive Purposes

- Drop covariate effects that meet **both** of these criteria:
 - Not statistically significant (e.g. C.I. includes null value)
 - Not clinically important (e.g. entire C.I. is contained within no effect range)
- Retain all other effects (any one or more of these criteria):
 - Clinically important
 - Statistically significant (e.g. C.I. excludes null value)
 - Not statistically significant, but may be clinically important (e.g. characterized by insufficient information with C.I. extending into ranges of potential clinical importance)

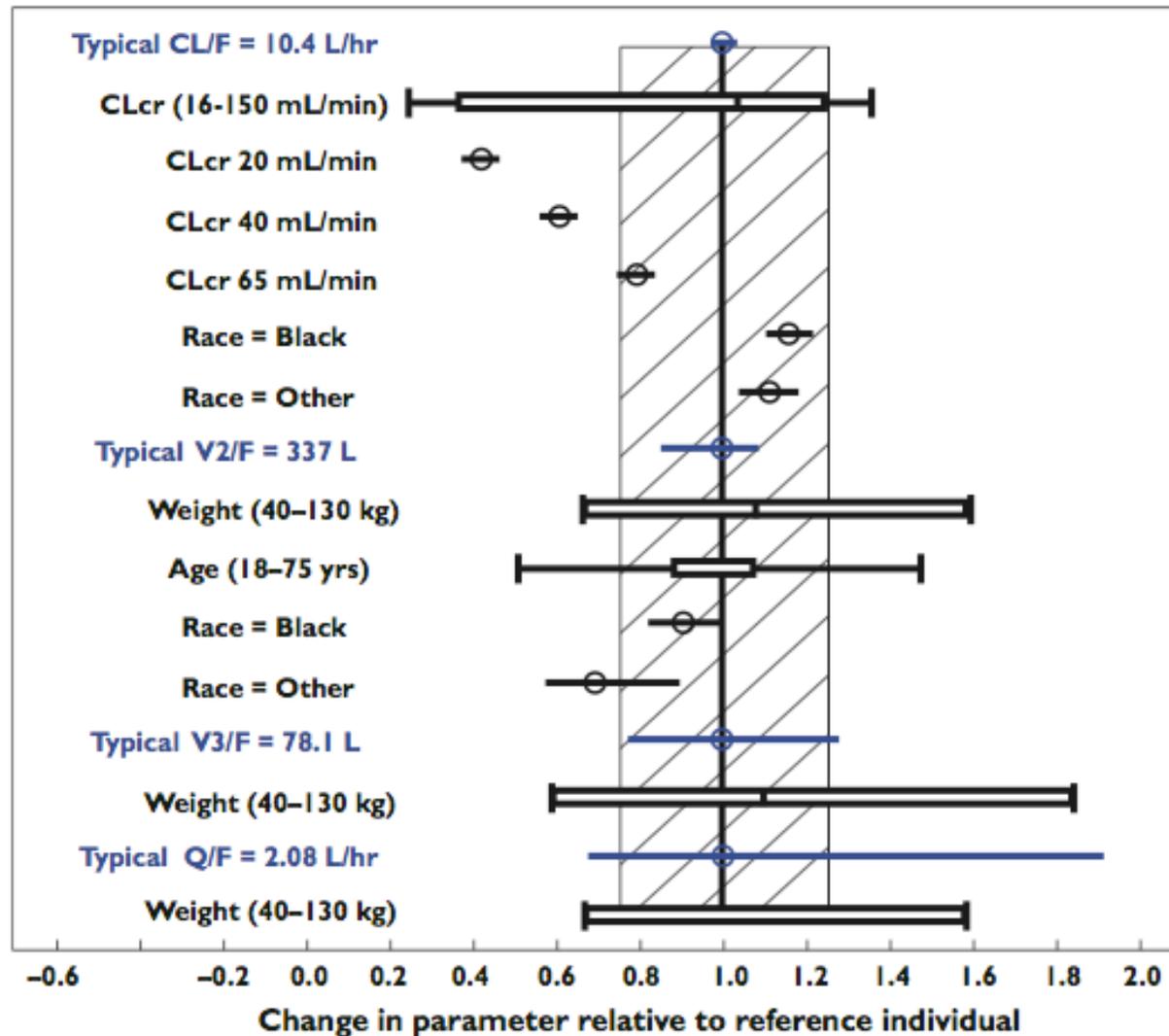
Removal of covariate effects should not impact coefficients for other remaining effects

Some Examples

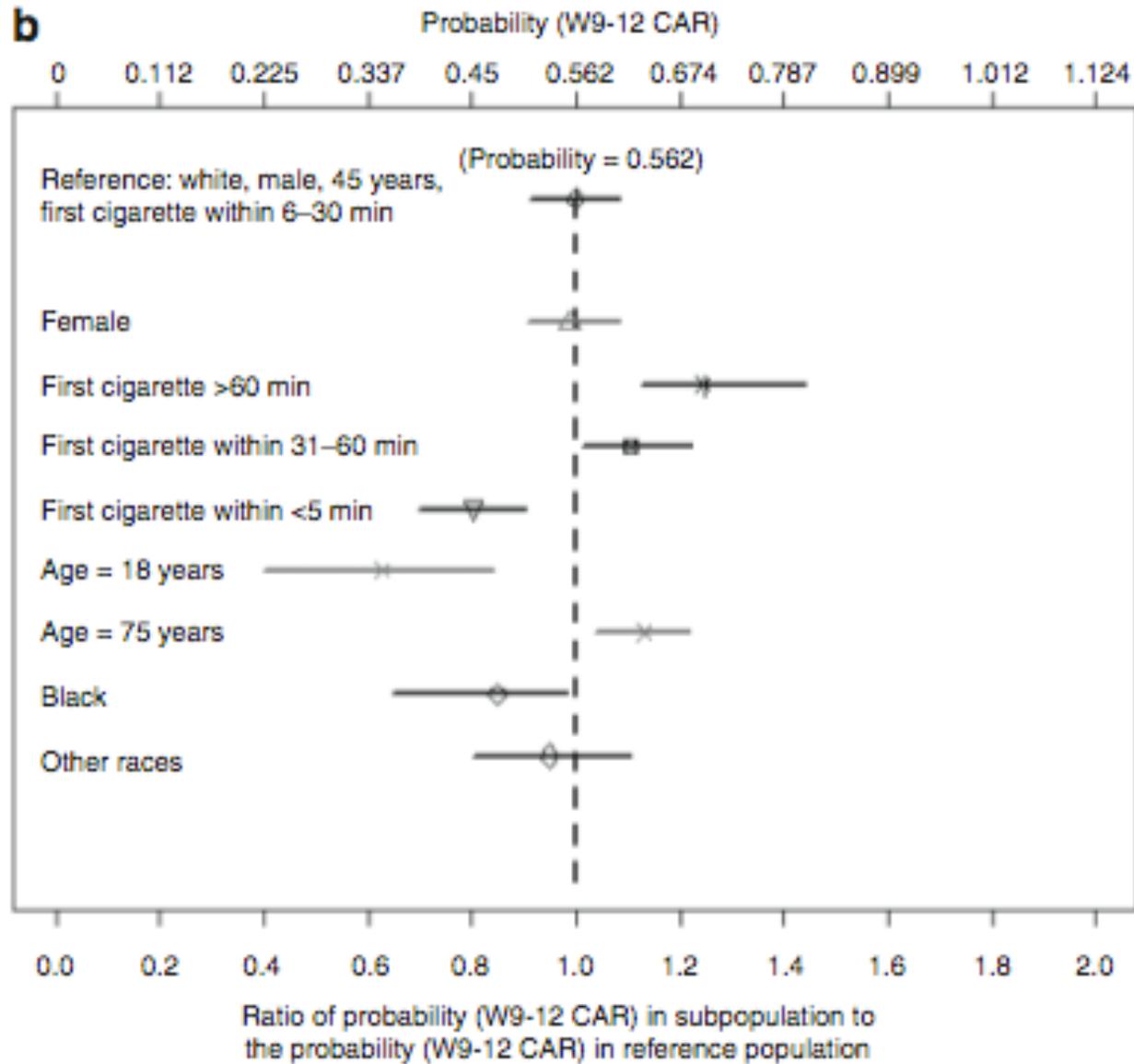
Population PK Model

Covariate effects on varenicline PK parameters

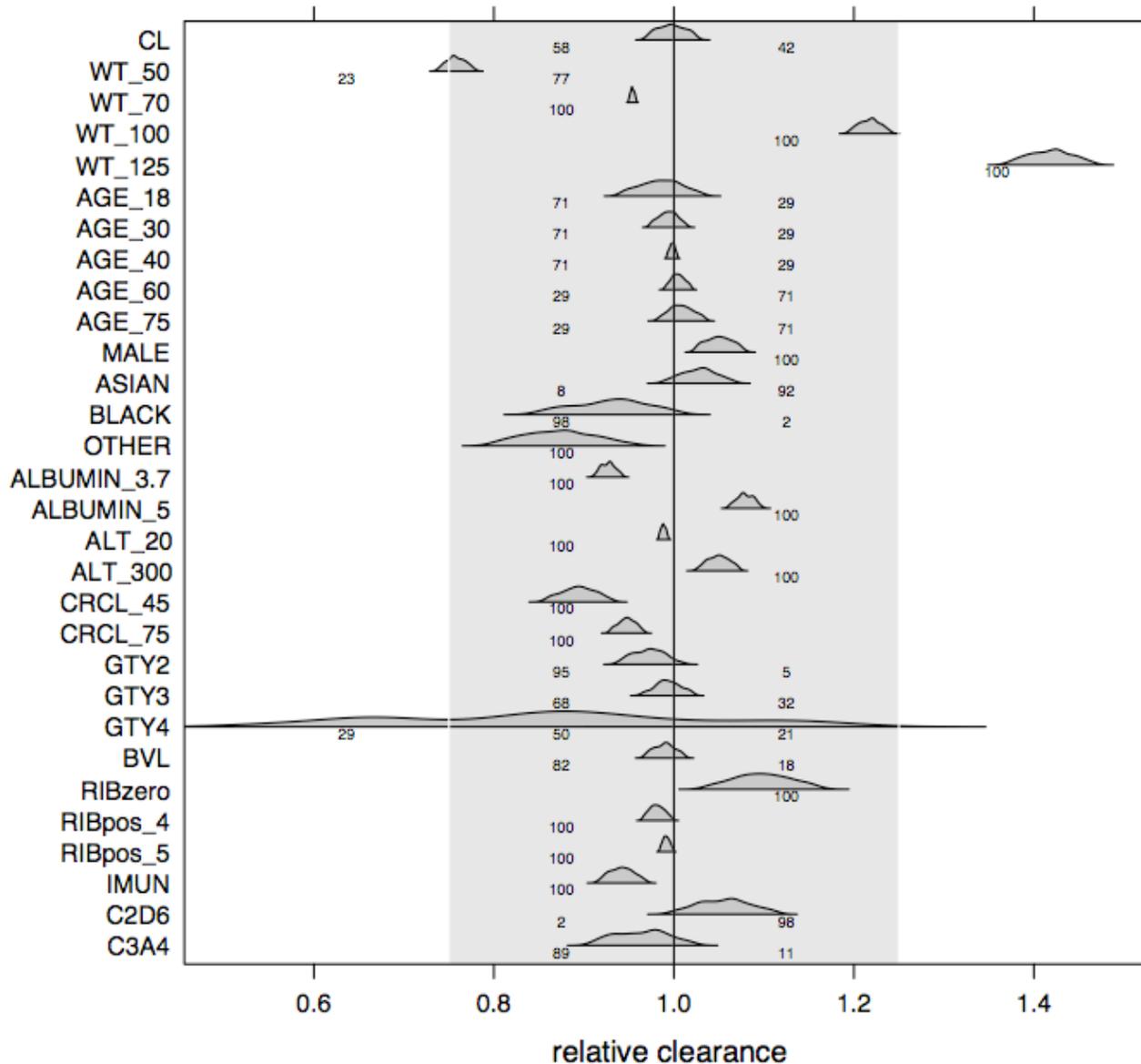
Typical individual: white, male, 45 years, CLcr = 100 mL/min, WT = 70 kg



Population PD Model



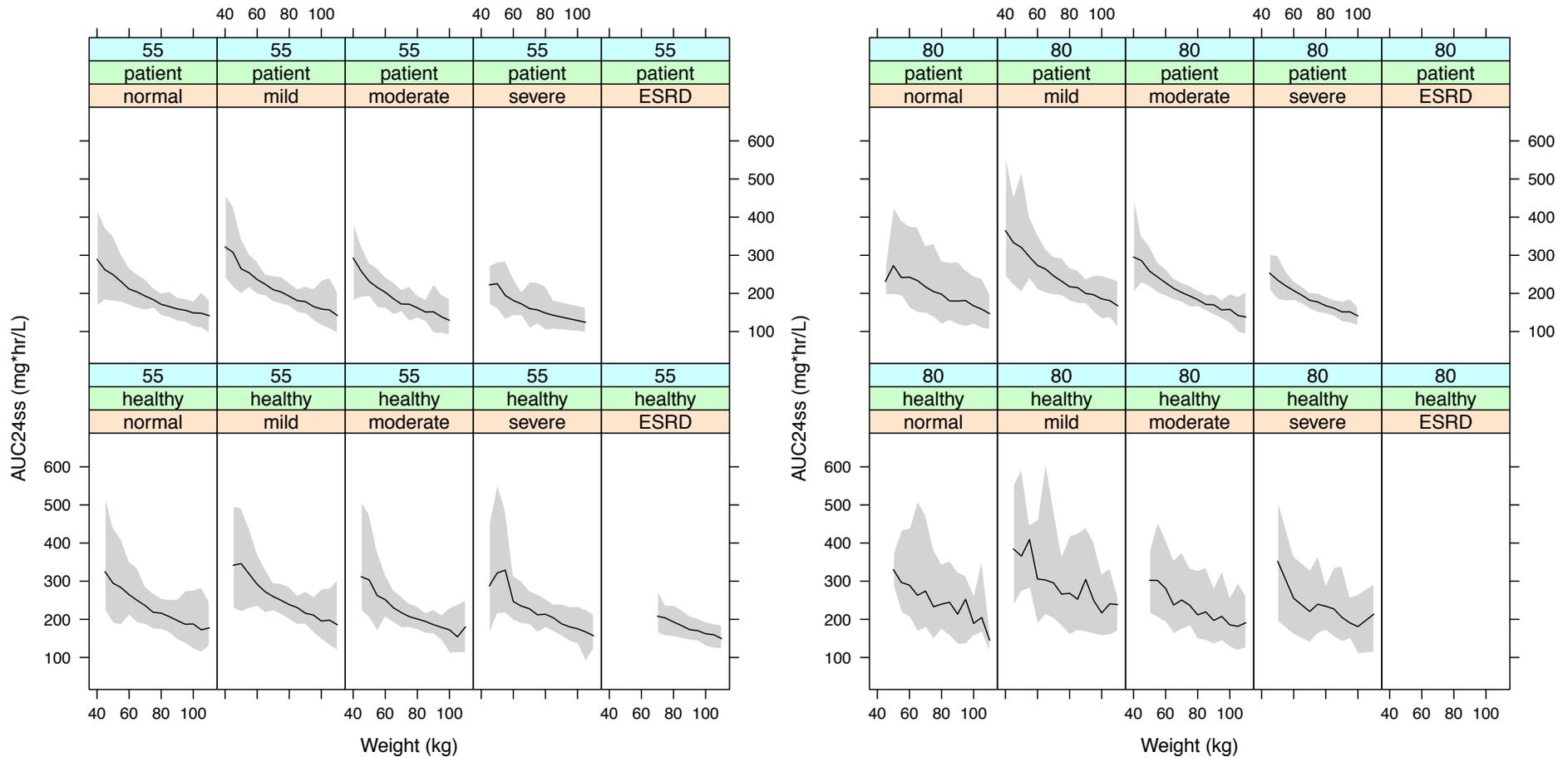
Probability-Based Assessment



Quantify probability of covariate effect being clinically important.

Numbers indicate percent of posterior probability distribution relative to reference region.

Expected Covariate Impact Across Multiple Effects



Posterior simulation (e.g. simulation with parameter uncertainty) of quantity of interest: posterior probability distribution of AUC_{24ss} vs. weight, conditioned by age (55 or 80 years), patient type, and degree of renal impairment.

Review of FCM Case Studies

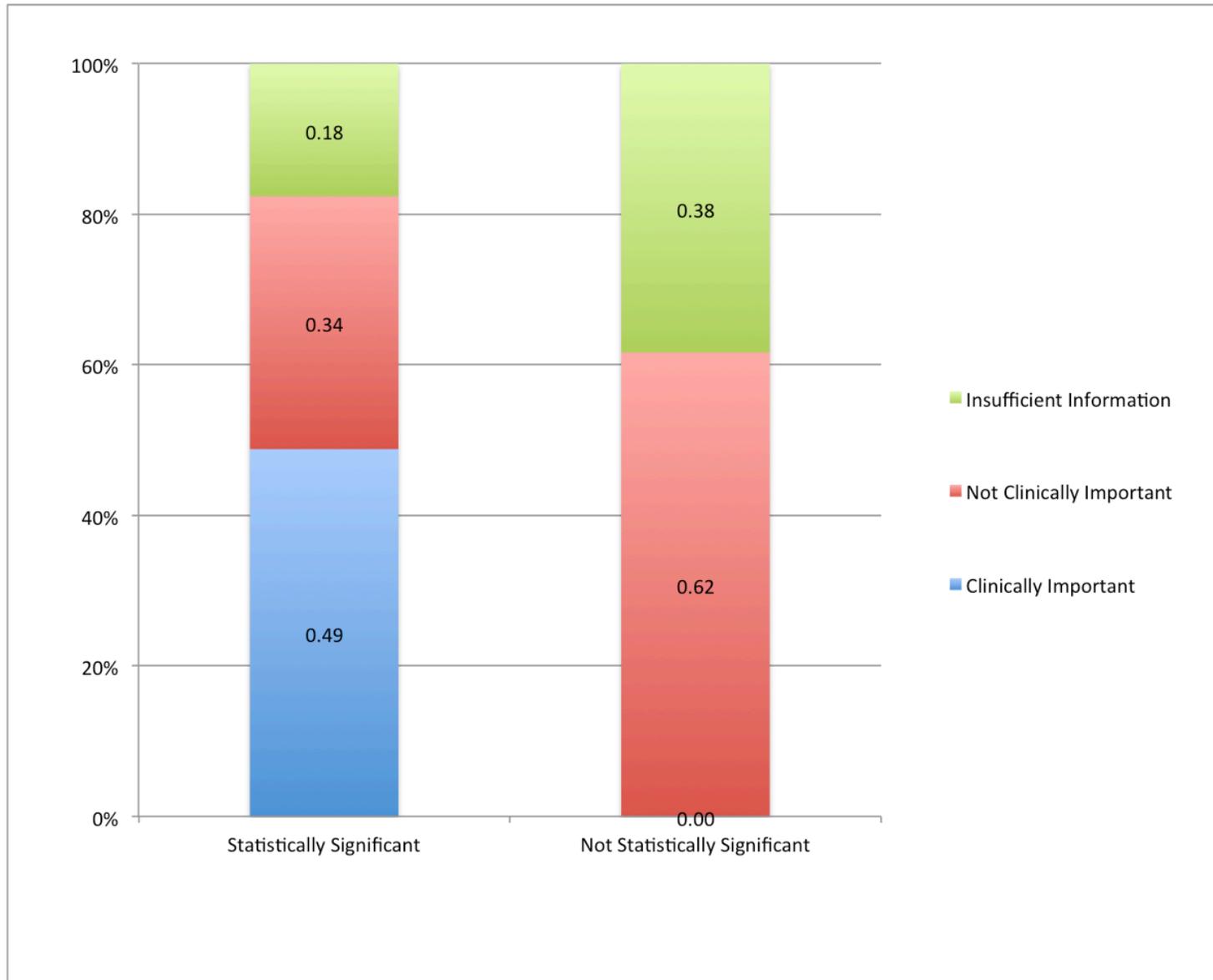
- 42 population analyses (32 PK, 10 PD) using NONMEM[®] v. 5, 6.x or 7.x
- All late stage development (end of Phase 2b, or Phase 3)
- 95% CI of parameter estimates obtained from stratified non-parametric bootstrap (95% of cases) or NONMEM[®] asymptotic standard errors (5% of cases)
- Statistical significance was defined as exclusion of null value in 95% CI
- Clinical importance was defined based on 95% CI relative to clinical no-effect range (e.g. null value +/- 20%) for AUC (PK) or a PD response parameter.

Results of FCM Case Studies

- Models converged successfully: 100%
- Successful \$COV step: 98%
- Number of covariates in source data: 14 (median), 4-60 (range)
- Number of covariates in FCM: 6 (median), 1-16 (range)
- Total number of covariate effects estimated: 258
 - Statistically significant covariates: 48%
 - Not statistically significant covariates: 52%

 - Clinically important covariate effects: 24%
 - Not clinically important effect: 48%
 - Insufficiently informed effect estimate: 28%

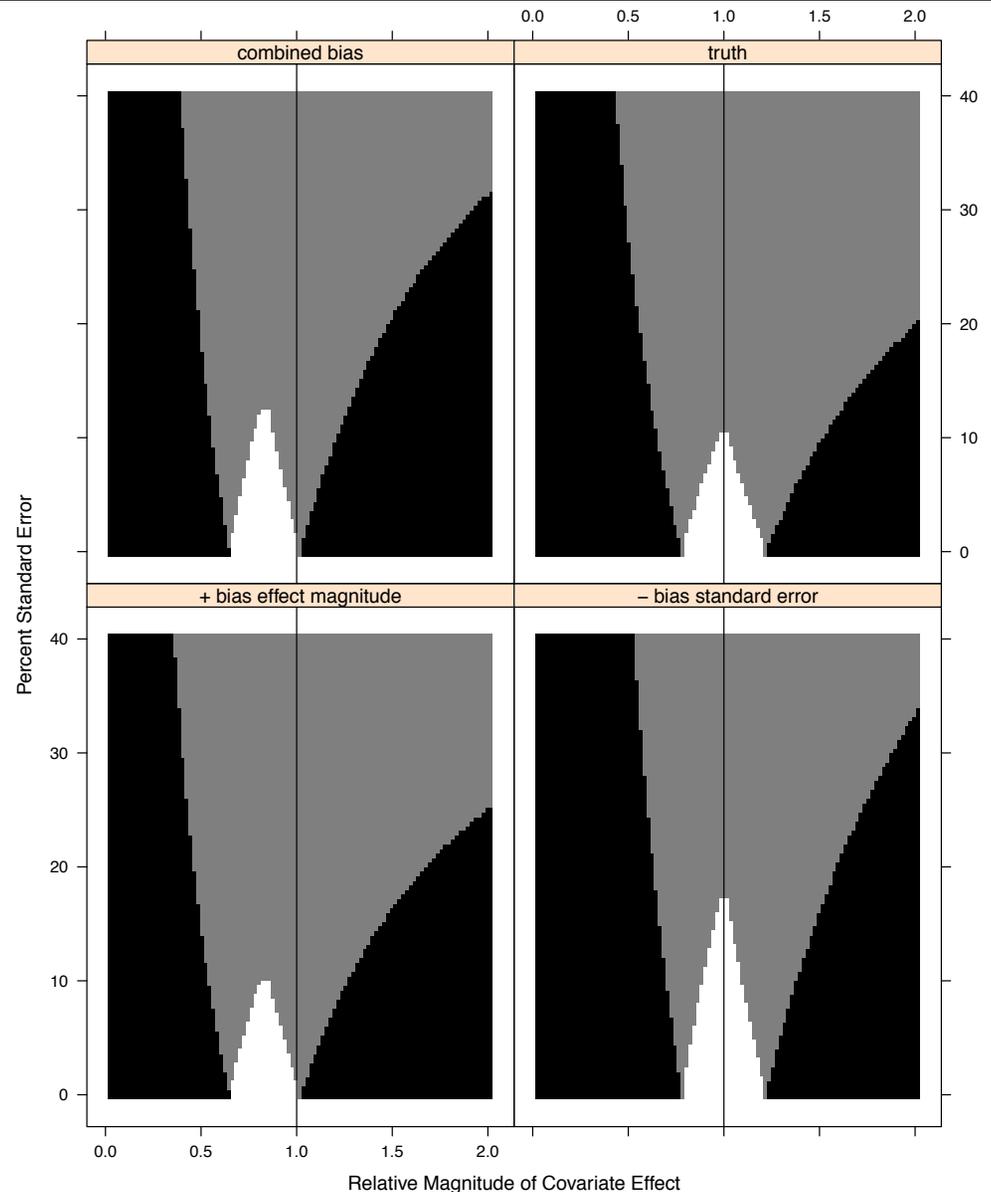
Results of Covariate Effect Inferences for Case Studies



Why Not Stepwise for Covariate Effect Inferences?

CI
II
NCI

- Covariate must be in model to make inference
- Inferences are sensitive to biases typically associated with stepwise methods:
 - effect magnitude (falsely increased)
 - precision (falsely narrow confidence intervals)
- Other issues mentioned earlier...



Align Methods with Modeling Purpose

- Hypothesis Generation / Data Mining
 - Stepwise methods are useful for exploratory goals
- Inferences Based on Estimation of Covariates Effects
 - Use full covariate model
- Prediction
 - Stepwise models are useful, with large enough data set, and adequate test data sets, when selection bias is likely to be low; still be careful to include data reduction step
 - Full covariate models result in more appropriate (larger) parameter uncertainty, but can lead to larger prediction error of response. Empirical Bayes estimates of individual model parameters are unaffected.
- Hypothesis Testing
 - Requires *a priori* adequately powered design and model specification
 - Stepwise methods are not always appropriate
 - Limit model to specific hypothesis to be tested (e.g. pre-defined)

Summary

- Statistical significance does not predict clinical importance and should not be used for covariate effect inferences.
- Inferences about clinical importance are driven by estimated magnitude of effect and associated precision, and are sensitive to biases in these metrics.
- Stepwise p-value driven approaches and FCM approaches both have utility in modeling and simulation:
 - Earlier stage exploratory data mining (stepwise p-value)
 - Later stage clinical inferences (FCM)

“The data analyst knows more than the computer... failure to use that knowledge produces inadequate data analysis”.

- Henderson and Velleman. Building multiple regression models interactively. 1981, *Biometrics* 37: 391–411.

Acknowledgements

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- Patanjali Ravva
- Industry/Academic Collaborators
- NMUSERS participants

Related Abstracts at PAGE 2011

I-11 A novel covariate search method intended for PKPD models with nonparametric parameter distributions. Paul G. Baverel (1), Radojka M. Savic (1), Scott F. Marshall (2), Mats O. Karlsson (1)

II-47 Selection Bias in Pre-Specified Covariate Models. Vijay D Ivaturi , Andrew C Hooker, Mats O Karlsson

II-53 Comparison of methods for handling missing covariate data. Åsa M. Johansson, Mats O. Karlsson

II-57 Evaluation of Stepwise Covariate Model Building Combined with Cross-Validation. Takayuki Katsube (1, 2), Akash Khandelwal (1), Kajsa Harling (1), Andrew C Hooker (1), Mats O Karlsson (1)

II-58 The bootstrap of Stepwise Covariate Modeling using linear approximations. Ron J Keizer, Akash Khandelwal, Andrew C Hooker, Mats O Karlsson

II-62 Influence of Correlated Covariates on Predictive Performance for Different Models. Akash Khandelwal, Andrew C Hooker, and Mats O Karlsson

III-62 Covariate Modelling in Aggregate Data Meta Analysis: A Simulation Study Evaluating Performance of Model Linearization. Patanjali Ravva (1), Mats O. Karlsson (2), Jonathan L. French (1)

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