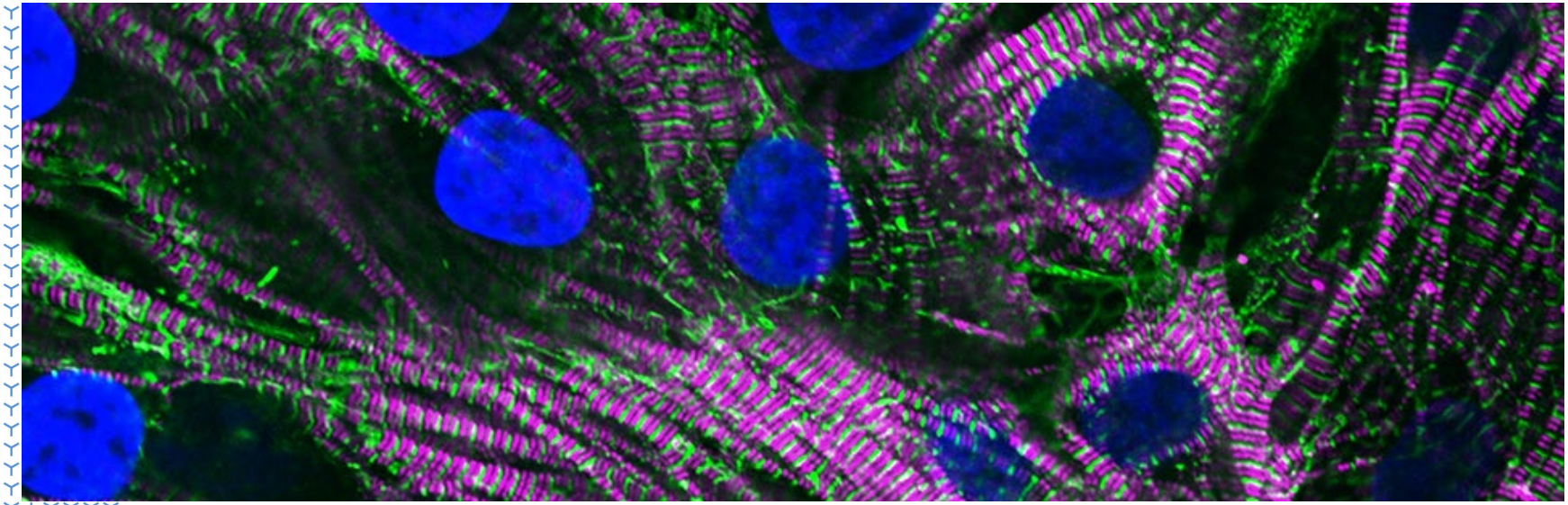

Update from task force on conditional vs marginal effects

Björn Bornkamp on behalf of conditional vs marginal task force

PSI Conference Göteborg

June 14, 2022

NOVARTIS | Reimagining Medicine

Conditional versus marginal task force

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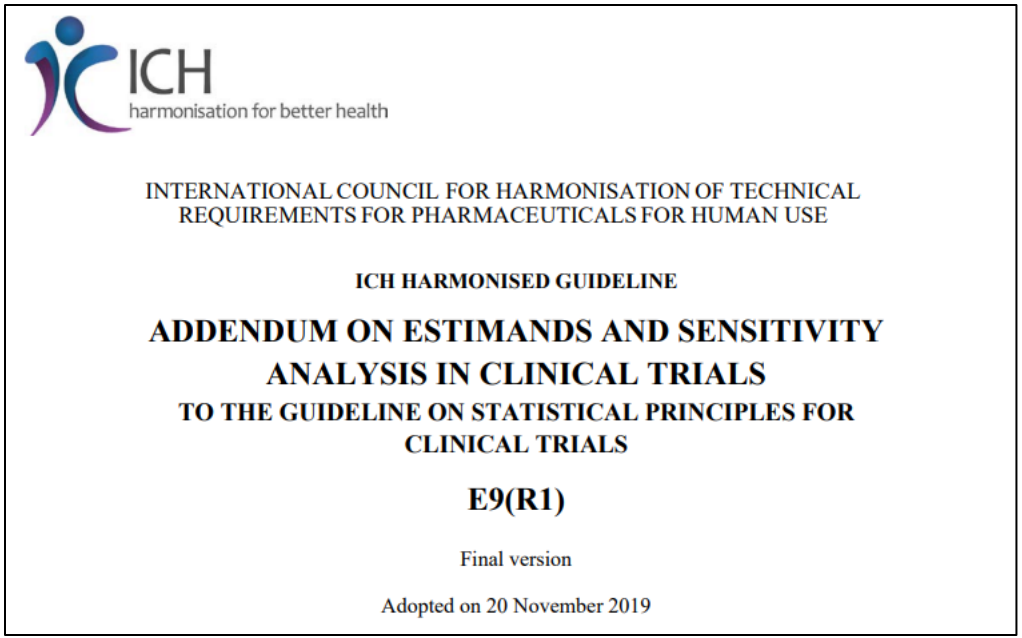
Objective

We would like to bring the complex concept and methods about conditional and marginal treatment effect into a simplified and interpretable way. Potential topics including adjusted or unadjusted analysis; stratified vs unstratified hazard ratio; collapsibility and subgroup; p-values; etc. We will give clinically relevant opinions and recommendations based on our interpretation, and illustrate the idea using some case studies.

Agenda

- Definition & illustrations
- Covariate adjustment for binary data
- Current work and next steps

Why of interest?



ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

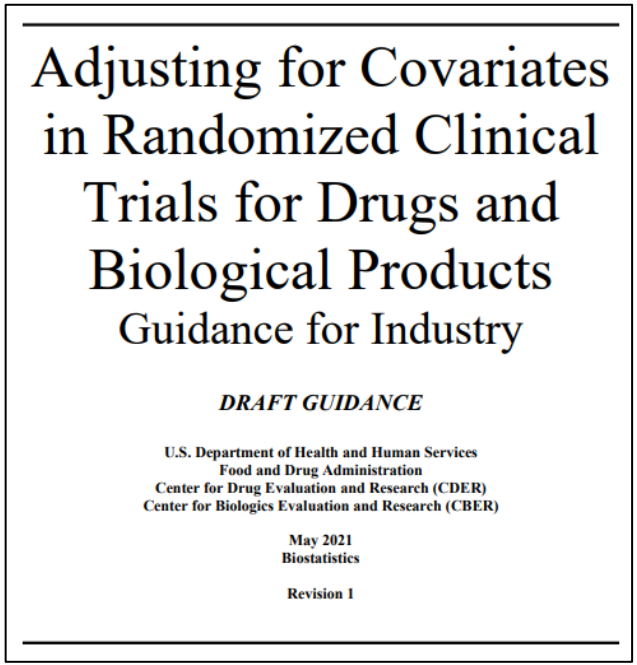
ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

Adopted on 20 November 2019



Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products
Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
Biostatistics

Revision 1

Marginal versus conditional

- Marginal (unconditional) treatment effect
  - $Y(0)$ vs. $Y(1)$
  - Treatment effect had all patients in the trial population taken treatment vs. had all patients taken control
- Conditional treatment effect
  - $Y(0)|\boldsymbol{X} = \boldsymbol{x}$ vs. $Y(1)|\boldsymbol{X} = \boldsymbol{x}$
  - Treatment effect had all patients in subgroup $\boldsymbol{x}$ taken treatment vs. had they all taken control

Estimation by regression models

- Traditionally treatment by covariate interactions not included
- In a linear regression model the treatment coefficient then targets
  - the unconditional treatment effect
  - ... but also the conditional treatment effect (treatment effect in all subgroups)! Note that this is assumed constant across subgroups in the model.
  - $E\big(Y(1)\big) - E\big(Y(0)\big) = \frac{1}{n}\sum_{i=1}^{n} E[Y(1)|X = x_i] - \frac{1}{n}\sum_{i=1}^{n} E[Y(0)|X = x_i]$

    $= \frac{1}{n}\sum_{i=1}^{n} \beta_0 + \beta_1 + \beta_2 x_i - (\frac{1}{n}\sum_{i=1}^{n} \beta_0 + \beta_2 x_i) = \boldsymbol{\beta_1}$

Logistic regression

- Logistic regression: $\text{logit}(\Pr(Y = 1|Z, X)) = \beta_0 + \beta_1 Z + \beta_2 X$
- Conditional odds ratio is defined as $\frac{E[Y(1)|X=x]}{1-E[Y(1)|X=x]} \Big/ \frac{E[Y(0)|X=x]}{1-E[Y(0)|X=x]}$
- $\frac{E[Y(1)|X=x]}{1-E[Y(1)|X=x]} \Big/ \frac{E[Y(0)|X=x]}{1-E[Y(0)|X=x]} = \frac{\text{expit}(\beta_0+\beta_1+\beta_2 x)}{1-\text{expit}(\beta_0+\beta_1+\beta_2 x)} \Big/ \frac{\text{expit}(\beta_0+\beta_2 x)}{1-\text{expit}(\beta_0+\beta_2 x)} = \mathbf{exp}\,\boldsymbol{\beta_1}$
- Conditional odds ratio equal to $\mathbf{exp}\,\boldsymbol{\beta_1}$ and equal across all subgroups (does not depend on x)

Logistic regression

- Logistic regression: $\text{logit}(\Pr(Y = 1|Z, X)) = \beta_0 + \beta_1 Z + \beta_2 X$
- Unconditional odds ratio is defined as $\frac{E[Y(1)]}{1-E[Y(1)]} \Big/ \frac{E[Y(0)]}{1-E[Y(0)]}$
- $$\frac{E[Y(1)]}{1-E[Y(1)]} \Big/ \frac{E[Y(0)]}{1-E[Y(0)]} = \frac{\frac{1}{n}\sum_{i=1}^{n} E[Y(1)|X=x_i]}{1-\frac{1}{n}\sum_{i=1}^{n} E[Y(1)|X=x_i]} \Big/ \frac{\frac{1}{n}\sum_{i=1}^{n} E[Y(0)|X=x_i]}{1-\frac{1}{n}\sum_{i=1}^{n} E[Y(0)|X=x_i]}$$

$$= \frac{\frac{1}{n}\sum_{i=1}^{n} \text{expit}(\beta_0+\beta_1+\beta_2 x_i)}{1-\frac{1}{n}\sum_{i=1}^{n} \text{expit}(\beta_0+\beta_1+\beta_2 x_i)} \Big/ \frac{\frac{1}{n}\sum_{i=1}^{n} \text{expit}(\beta_0+\beta_2 x_i)}{1-\frac{1}{n}\sum_{i=1}^{n} \text{expit}(\beta_0+\beta_2 x_i)}$$

$\neq \exp \beta_1$ if $\beta_1 \neq 0$ or $\beta_2 \neq 0$

Hypothetical example

	Percentage of target population	Success rate		Odds ratio
		New drug	Placebo	
Males	50%	80.0%	33.3%	8.0
Females	50%	25.0%	4.0%	8.0
Combined	100%	52.5%	18.7%	4.8

Source: FDA draft guidance on Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products

- Conditional odds-ratios in subgroups
  - Males: (0.80/0.20)/(0.333/0.667) = 8.0
  - Females: (0.25/0.75)/(0.04/0.96) = 8.0
- Unconditional odds-ratio
  - (0.525/0.475)/(0.187/0.813) = 4.8

Odds ratio as effect measure is *non-collapsible.*

More on non-collapsibility: Daniel et al (2021) and Morris et al (2022)

Logistic regression: Treatment effects not constant across subgroups

- If treatment effects are not constant across all subgroups
  - Interpretation of results challenging: FDA draft guideline

  "... When estimating a conditional treatment effect through nonlinear regression [...] results can be difficult to interpret if the model is misspecified and treatment effects substantially differ across subgroups. ..."

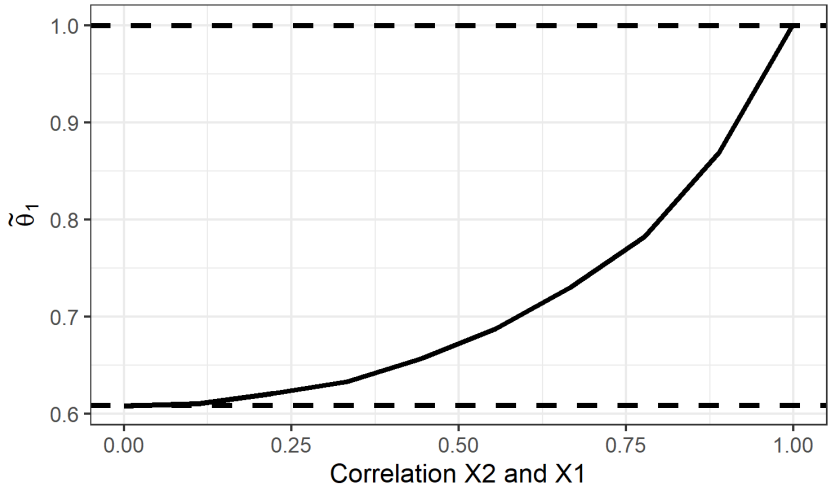
Model mis-specification

- Generally strong focus on model mis-specification in draft FDA guideline
  - ***Target of estimation (estimand)*** changes, based on which logistic regression model is fitted (e.g. which covariates are adjusted for)
  - (Even if subgroup treatment effects are constant on logit scale)

Model mis-specification

- Assume that
  - the data are truly generated by a model
$$\text{logit}(\Pr(Y = 1|Z, X)) = \beta_0 + \beta_1 Z + \beta_2 X_1$$
  - ... but we have not measured X_1, only X_2 (correlated with X_1),
  - What happens if we fit the incorrect model
$$\text{logit}(\Pr(Y = 1|Z, X)) = \theta_0 + \theta_1 Z + \theta_2 X_2$$
- Maximum likelihood estimator of mis-specified model targets value $\tilde{\theta}_1$ with minimum Kullback-Leibler distance to the true model (Huber, 1967)
  - In general $\tilde{\theta}_1 \neq \beta_1$ → Target of estimation (estimand) depends on the fitted model

Plot of $\widetilde{\theta}_1$ for $\beta_1 = 1$ and $\beta_2 = 2$



- Targeted "true" estimand $\widetilde{\boldsymbol{\theta}}_{\mathbf{1}}$ changes depending on "how mis-specified" the model is
  - Ranges between the unconditional log odds-ratio and the conditional log odds-ratio from the data generating model
- Unconditional odds-ratio is unchanged

Model mis-specification and unconditional odds ratio

- Unconditional odds ratio defined “nonparametrically”
  - Defined in terms of response probabilities per treatment arm
  - Defined without reference to a specific model
- How to perform covariate adjustment to estimate unconditional treatment effect?

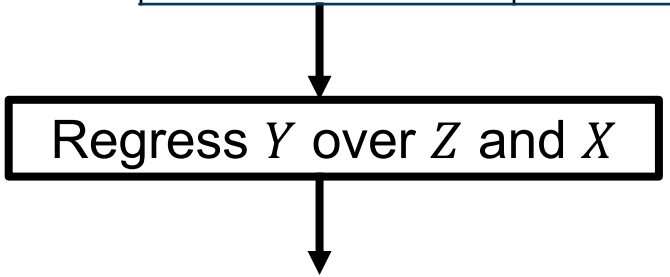
Estimating unconditional treatment effects from logistic regression

- Procedure for this is referenced in FDA draft guidance
- Applies beyond odds-ratio (also risk difference and risk ratio) and beyond binary data
- **Standardization** (standardized estimator, g-computation)
  1. Model fitting
  2. Predicting
  3. Averaging

Step 1 in standardization:

Fit a logistic regression model

Treatment (Z)	Covariates (X)	Response (Y)
1	x_1	y_1
0	x_2	y_2
⋮	⋮	⋮



- $g\{\cdot\}$: logit link $g\{\cdot\} = \log(\frac{\cdot}{1-\cdot})$

Model fit: $\hat{E}[Y|Z,X] = g^{-1}\{\hat{\beta}_0 + \hat{\beta}_1 Z + \hat{\beta}_2 X\}$

Step 2 in standardization:

Predict potential outcomes

All patients under $z = 0$

Treatment $z = 0$	Covariate (X)
0	x_1
0	x_2
⋮	⋮

Model fit: $\hat{E}[Y|Z,X] = g^{-1}\{\hat{\beta}_0 + \hat{\beta}_1 Z + \hat{\beta}_2 X\}$

Predict

All patient under $z = 1$

Treatment $z = 1$	Covariate (X)
1	x_1
1	x_2
⋮	⋮

Potential response under $z = 0$
$\hat{E}[Y(0)\|X = x_1] = g^{-1}\{\hat{\beta}_0 + \hat{\beta}_2 x_1\}$
$\hat{E}[Y(0)\|X = x_2]$
⋮

Potential response under $z = 1$
$\hat{E}[Y(1)\|X = x_1] = g^{-1}\{\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 x_1\}$
$\hat{E}[Y(1)\|X = x_2]$
⋮

Step 3 in standardization:

Average over individual predictions

Potential response under $z = 0$
$\hat{E}[Y(0)\|X = x_1] = g^{-1}\{\hat{\beta}_0 + \hat{\beta}_2 x_1\}$
$\hat{E}[Y(0)\|X = x_2]$
$\vdots$

Potential response under $z = 1$
$\hat{E}[Y(1)\|X = x_1] = g^{-1}\{\hat{\beta}_0 + \hat{\beta}_1 + \hat{\beta}_2 x_1\}$
$\hat{E}[Y(1)\|X = x_2]$
$\vdots$

Averaging (marginalizing over covariates)

$$\hat{E}[Y(0)] = \frac{1}{n}\sum_{i=1}^{n} \hat{E}[Y(0)|X = x_i]$$

Averaging (marginalizing over covariates)

$$\hat{E}[Y(1)] = \frac{1}{n}\sum_{i=1}^{n} \hat{E}[Y(1)|X = x_i]$$

Estimated population average causal treatment effect, unconditional odds-ratio $\frac{\hat{E}[Y(1)]}{1-\hat{E}[Y(1)]} \Big/ \frac{\hat{E}[Y(0)]}{1-\hat{E}[Y(0)]}$

Properties

- Even if the used logistic regression model is mis-specified, procedure leads to
  - an asymptotically unbiased estimator of the unconditional odds-ratio
  - confidence intervals with asymptotically correct coverage
  - The same result holds for this procedure under a wide range of generalized linear models with canonical link functions (see Rosenblum & van der Laan (2010))
- Standard error for marginal odds-ratio usually smaller with covariate adjustment

Survival data

- Proportional hazard assumption can only hold unconditionally or conditionally on covariates, and censoring distribution adds further complexity
- Application of standardization method to estimate the marginal hazard ratio is not straightforward (Daniel et al. 2021 propose simulation-based standardization)
- Semiparametric estimators (Lu and Tsiatis 2008) are quite complex and its properties need further exploration, application in real trials is limited
- One could consider alternative summary measures such as restricted mean survival time (RMST) or survival probability difference, however such experience in clinical trials is still limited
  - Statistical analysis methods then include G computation (Karrison et al. 2018), inverse probability weighted estimator (IPW) and double robust estimators (e.g. TMLE, see Diaz et al (2016))

Conclusion

- It is important to determine the target treatment effect (estimand), whether it is unconditional or conditional
- Statistical analysis shall align with the estimand, and it is important to understand properties of estimators for a better alignment with estimands
- For unconditional treatment effect, standardization is a robust and efficient approach under randomization
- The application of standardization cannot easily be extended to TTE endpoints for marginal hazard ratio, alternative summary measures might be considered

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Thank you

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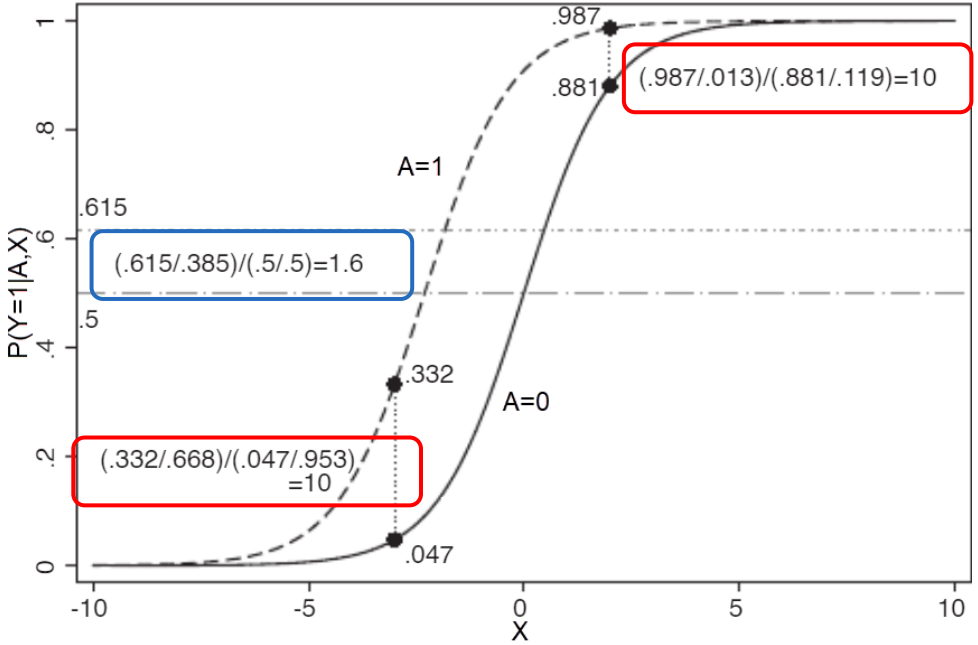
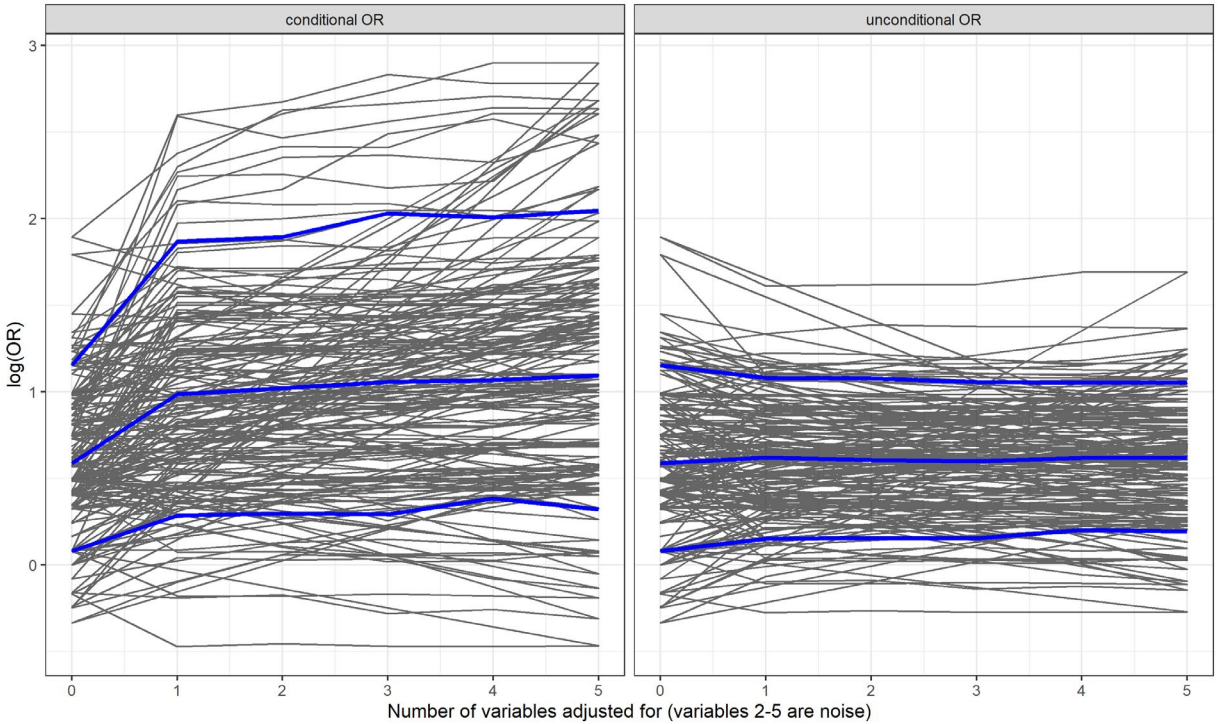
Illustration: Marginal versus conditional odds-ratio



Source: Daniel et al. (2021), Biometrical Journal

- Assume true model
  - logit(P(Y=1 | Z , X) = log(10)Z + X
  - X uniformly distributed on [-10,10]
  - For every X: true conditional OR=10
- Averaging response probabilities over X → unconditional OR = 1.6
  - Difference due to averaging on probability scale → No major difference between trt and control on probability scale for X in [-10,-6] and [6,10] → ~40% of patients

Simulation



- Simulate 100 clinical trials
- n=100 (1-1 randomization)
- $\text{logit}(\Pr(Y = 1|Z, X)) = \beta_0 + \beta_1 Z + \beta_2 X_1$
- $\beta_1 = 1$ and $\beta_1 = 2$
- $X_1, \ldots, X_5 \sim N(0,1)$
- Conditional treatment effect estimates increase (on average) with each variable included (also the noise variables) (corresponding standard deviation also increases)
- Unconditional treatment effect estimates stay constant (standard deviation slightly decreases)