National Cancer Institute

measurement ERROR webinar series

Assessing diet-health relationships: Focus on dietary components consumed daily by nearly all persons

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

measurement ERROR webinar series

This series is dedicated to the memory of

Dr. Arthur Schatzkin

In recognition of his internationally renowned contributions to the field of nutrition epidemiology and his commitment to understanding measurement error associated with dietary assessment.

Presenters and Collaborators

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Objectives

Learning objectives

- Understanding:
  - That measurement error leads to bias in estimated diet-health associations
  - Concepts involved in regression calibration, a method to correct for this bias
  - The role of calibration studies in regression calibration
- Learning how to apply regression calibration in diet and health studies

Introduction

Main results on impact of measurement error

From webinar 6,

- When there is a **single** dietary exposure measured with error in a diet-health model:
  1) Estimated diet-health relationship (risk) is **attenuated** (underestimated)
  2) Power to detect relationship is **decreased**
  3) Statistical tests are still **valid**
- Same conclusions seem to hold approximately when **several** dietary exposures are included in a model
- In this webinar we will (mostly) address problem 1)

Introduction

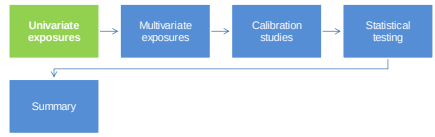
Why adjust the risk estimate?

- Unadjusted estimates will underestimate
  - True health risk due to unhealthy eating
  - True health benefit due to healthy eating
- As a result:
  - Public health impact of dietary change would be underestimated
  - Health officials could mistakenly ignore the potential impact

Introduction

Methods of adjusting the risk estimate

- **Regression calibration**
- SIMEX
- Maximum likelihood
- Multiple imputation
- Moment reconstruction
- … and more!

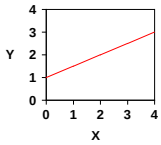


REGRESSION CALIBRATION FOR UNIVARIATE EXPOSURES

Regression calibration for univariate exposures

Linear equations and linear functions

- The equation for a **line** in **two** dimensions is
  - $Y = a_0 + a_1X$



- The equation for a **line** in **k** dimensions is
  - $Y = a_0 + a_1X_1 + a_2X_2 + \ldots + a_kX_k$
- This relationship can be expressed as a function
  - $f(Y) = a_0 + a_1X_1 + a_2X_2 + \ldots + a_kX_k$
- A function of this form is called a **linear function**

Regression calibration for univariate exposures

Risk model

- Risk model (logistic regression):

$$\log\{\mathrm{Odds}(Y=1)\} = \alpha_0 + \alpha_T T + \alpha_{Z1}Z_1 + \ldots + \alpha_{Zp}Z_p$$

  - Y = health outcome variable (0 or 1)
  - Odds(Y=1) = Prob(Y=1) / Prob(Y=0)
  - T = true dietary intake
  - $Z_1, \ldots, Z_p$ = other variables in disease model
  - $Z = \{Z_1, \ldots, Z_p\}$
  - $\alpha_T, \alpha_{Z1}, \ldots, \alpha_{Zp}$ = regression coefficients = log odds ratios

Regression calibration for univariate exposures

Risk model

- Risk model:

$$\log\{\mathrm{Odds}(Y=1)\} = \alpha_0 + \alpha_T \cancel{T}\,Q + \alpha_{Z1}Z_1 + \ldots + \alpha_{Zp}Z_p$$

- Problem:
  - We are unable to measure **true** intake T
  - Instead, we obtain **reported** intake Q which is subject to measurement error
  - If we use Q instead of T in the risk model, the estimate of α_T will be biased (attenuated)

Regression calibration for univariate exposures

Regression calibration

- Risk model:

$$\log\{\mathrm{Odds}(Y=1)\} = \alpha_0 + \alpha_T \cancel{T}\,E(T|Q,Z) + \alpha_{Z1}Z_1 + \ldots + \alpha_{Zp}Z_p$$

- Regression calibration method:
  - Step 1: Calculate E(T|Q, Z) = conditional expectation of T given Q and Z

    E(T|Q, Z) is the "**predicted value**" of T given Q and Z
  - Step 2: Replace T with E(T|Q, Z) in risk model

Regression calibration for univariate exposures

Regression calibration

- Risk model:

$$\log\{\text{Odds}(Y=1)\} = \alpha_0 + \alpha_T T + \alpha_{Z1} Z_1 + \ldots + \alpha_{Zp} Z_p$$

E(T|Q,Z)

- Regression calibration assumption:
  - Q has "nondifferential error" with respect to disease Y
  - Q has no information about Y beyond that provided by T and Z
- Under this assumption, regression calibration estimates are (approximately) unbiased

Regression calibration for univariate exposures

How do we calculate E(T|Q, Z)?

- In order to predict T, we need to develop a "**prediction equation**"
- Example: **linear** prediction equation

$$E(T|Q, Z) = \lambda_0 + \lambda_Q Q + \lambda_{Z1} Z_1 + \ldots + \lambda_{Zp} Z_p$$

- If T were observable in a sample of participants, could estimate the parameters in prediction equation by regressing T on Q and Z

Regression calibration for univariate exposures

How do we calculate E(T|Q, Z)?

- Instead of observing T, we observe a "**reference measure**" that we call R
- Assumption: R is **unbiased** for T
  - R = T + e
  - e is random error with mean zero
  - e is uncorrelated with T, Q and Z
- Under this assumption, E(R|Q, Z) = E(T|Q, Z)
- Estimate prediction equation by regressing R on Q and Z in a sample of participants

Regression calibration for univariate exposures

Calibration studies

- Prediction equation (calibration equation) is developed in a sample on which the reference instrument is measured
- A sample collected for this purpose is called a "**calibration study**"
- We will learn more about calibration studies later in this webinar

Regression calibration for univariate exposures

Summary of regression calibration

- Regression calibration involves 2 regressions:
  - Step 1: Regress R on Q and Z to get prediction equation E(T|Q, Z)
  - Step 2: Regress health outcome Y on E(T|Q, Z) and Z
- Regression calibration makes 2 assumptions:
  - Q has nondifferential error with respect to Y
  - R is unbiased for T

Regression calibration for univariate exposures

Linear regression calibration

- We will focus on **linear** regression calibration
- In linear regression calibration:
  - Predicted value of T is a **linear** function of Q and Z

$$E(T|Q, Z) = \lambda_0 + \lambda_Q Q + \lambda_{Z1} Z_1 + \ldots + \lambda_{Zp} Z_p$$

  - Parameters in prediction equation (λ_0, …, λ_{Zp}) are estimated by **linear** regression of R on Q and Z

Regression calibration for univariate exposures

Potential problem with linear regression calibration

- Sometimes we want to fit a risk model where T is on a **transformed** scale

  Risk model:

$$\log\{\text{Odds}(Y=1)\} = \alpha_0 + \alpha_T g(T) + \alpha_{Z1} Z_1 + \ldots + \alpha_{Zp} Z_p$$

- Examples of transformation g(T):
  - Log transformation: $g(T) = \log(T)$
  - Square root transformation: $g(T) = \sqrt{T}$

Regression calibration for univariate exposures

Potential problem with linear regression calibration

- Risk model:

$$\log\{\text{Odds}(Y=1)\} = \alpha_0 + \alpha_T g(T) + \alpha_{Z1} Z_1 + \ldots + \alpha_{Zp} Z_p$$

- Prediction equation is also on transformed scale

$$E\{g(T)|Q, Z\} = \lambda_0 + \lambda_Q g(Q) + \lambda_{Z1} Z_1 + \ldots + \lambda_{Zp} Z_p$$

- Estimate parameters in prediction equation by regressing g(R) on g(Q) and Z

Regression calibration for univariate exposures

Potential problem with linear regression calibration

- Assumption for reference instruments

$$E(R|Q, Z) = E(T|Q, Z)$$

- After transformation, this equality is only approximate

$$E\{g(R)|Q, Z\} \approx E\{g(T)|Q, Z\}$$

- In practice, approximation is usually assumed good enough for dietary components consumed (nearly) every day

Regression calibration for univariate exposures

Example: dietary fat and breast cancer

- NIH-AARP Diet and Health Study
- Observational cohort (1995-present)
  - 550,644 participants
  - Food frequency questionnaire (FFQ = Q)
- Calibration sub-study (1996)
  - 1942 participants
  - Two 24-hour dietary recalls (24HR = R)

Regression calibration for univariate exposures

Example: dietary fat and breast cancer

- Thiebaut et al. (J Nat Cancer Inst, 2007)
- Nested case-control analysis
- 3501 invasive breast cancer cases, with 4 matched controls per case:
  - Year of entry (1995, 1996, 1997)
  - Age at entry (+/- 1 year)
  - Person-years at risk (≥ years for case)
  - Hormone use (never/former, current)

Regression calibration for univariate exposures

Example: dietary fat and breast cancer

- Logistic regression of breast cancer status (Y) on log total fat intake (T)
- Other covariates (Z)
  - Body mass index (< 25, 25-30, ≥ 30)
  - Age at first birth / number of children (nulliparous, <30 / 1-2, <30 / 3+, ≥30 / 1+)
  - Hormone use (never/former, current)
  - Age at entry

Example: dietary fat and breast cancer

- Regression calibration:
- Step 1: Estimate prediction equation by linear regression of R on Q and Z in calibration study

$$E(T|Q,Z) = 4.5 + 0.28\times Q + 0.06\times BMI_2 + 0.04\times BMI_3 + 0.01\times AFB_1 - 0.03\times AFB_2 + 0.05\times AFB_3 + 0.01\times Hormone - 0.002\times Age$$

- Use prediction equation to predict intake for each subject in main study

Example: dietary fat and breast cancer

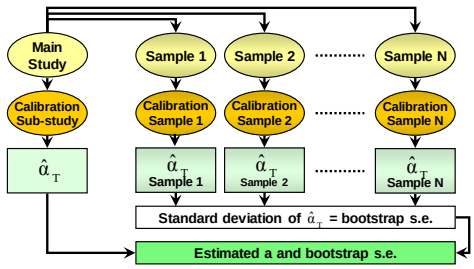
- Regression calibration:
- Step 2: Logistic regression of Y on E(T|Q,Z) and Z in main study

$$\log\{Odds(Y=1)\} = -2.4 + 0.11\times E(T|Q,Z) + 0.06\times BMI_2 + 0.17\times BMI_3 - 0.26\times AFB_1 - 0.36\times AFB_2 + 0.01\times AFB_3 + 0.03\times Hormone + 0.004\times Age$$

- Estimated log odds ratio: $\hat{\alpha}_T = 0.11$
- Estimated odds ratio: $\exp(\hat{\alpha}_T) = 1.12$

Bootstrap standard error for log odds ratio

- Bootstrap: sampling with replacement
- Both calibration data and disease model data



Thanks to Anne-Claire Vergnaud

Confidence intervals

- Estimated log odds ratio: $\hat{\alpha}_T = 0.11$
- Bootstrap s.e. log odds ratio: $\text{s.e. } \hat{\alpha}_T = 0.10$
- Estimated odds ratio: $\exp \hat{\alpha}_T = 1.12$
- 95% confidence interval for log odds ratio:

$$\hat{\alpha}_T \pm 1.96\times \text{s.e. } \hat{\alpha}_T = -0.09, 0.31$$

- 95% confidence interval for odds ratio:

$$\exp\{-0.09\}, \exp\{0.31\} = 0.91, 1.36$$

Rosner's method for linear regression calibration

Rosner et al. (Am J Epidemiol, 1990)

From previous lecture (lecture 6):

- Expected log odds ratio estimate is attenuated

$$E\ \hat{\alpha}_Q = \lambda_Q \alpha_T$$

- α_T = true log odds ratio
  λ_Q = attenuation factor (from prediction equation)
- Solution: divide attenuated log odds ratio by λ_Q

$$\hat{\alpha}_T = \hat{\alpha}_Q / \lambda_Q$$

Rosner's method for linear regression calibration

- Step 1: Same as step 1 for regular method
- Prediction equation:

$$E(T|Q,Z) = 4.5 + 0.28\times Q + 0.06\times BMI_2 + 0.04\times BMI_3 + 0.01\times AFB_1 - 0.03\times AFB_2 + 0.05\times AFB_3 + 0.01\times Hormone - 0.002\times Age$$

- Estimated attenuation factor: $\hat{\lambda}_Q = 0.28$
- Standard error: $\text{s.e.}(\hat{\lambda}_Q) = 0.03$

Regression calibration for univariate exposures

Rosner's method for linear regression calibration

- Step 2: Logistic regression of Y on Q and Z in the main study

$$\log\{\text{Odds}(Y=1)\} = -1.7 + 0.03\times Q + 0.08\times BMI_2 + 0.18\times BMI_3 - 0.26\times AFB_1 - 0.37\times AFB_2 + 0.02\times AFB_3 + 0.03\times \text{Hormone} + 0.003\times \text{Age}$$

- Attenuated log odds ratio: $\hat{\alpha}_Q = 0.03$
- Standard error: $\text{s.e.}(\hat{\alpha}_Q) = 0.03$

Regression calibration for univariate exposures

Rosner's method for linear regression calibration

- Step 3: Divide attenuated log odds ratio by attenuation coefficient

$$\hat{\alpha}_T = \hat{\alpha}_Q / \hat{\lambda}_Q = 0.03 / 0.28 = 0.11$$

- Rosner's method and regular linear regression calibration: estimates are the same

Regression calibration for univariate exposures

Rosner's method for linear regression calibration

- Step 4: Estimate standard error using delta method

$$\text{s.e.}(\hat{\alpha}_T) \approx \sqrt{\left(\frac{\text{s.e.}(\hat{\alpha}_Q)}{\hat{\lambda}_Q}\right)^2 + \left(\frac{\hat{\alpha}_Q \text{s.e.}(\hat{\lambda}_Q)}{\hat{\lambda}_Q^2}\right)^2} = 0.09$$

- Bootstrap and delta method standard errors are similar but not exactly the same

Regression calibration for univariate exposures

Example: dietary fat and breast cancer

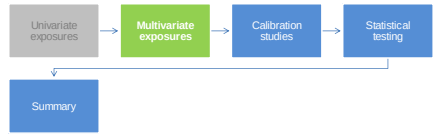
Dietary fat intake and breast cancer risk in NIH-AARP

Correction for Measurement Error	Log Odds Ratio (s.e.)	Odds Ratio (95% CI)
Uncorrected	0.03 (0.03)	1.03 (0.98, 1.09)
Regression calibration	0.11 (0.10)	1.12 (0.93, 1.35)
Rosner's method	0.11 (0.09)	1.12 (0.94, 1.33)

Regression calibration for univariate exposures

Summary of Rosner's method

- Advantage: standard errors can be computed quickly and easily
- Limitation: Only applies when the regression calibration model is **linear**
- Next webinar (webinar 8) will focus on situation where regression calibration model is **nonlinear**



REGRESSION CALIBRATION FOR MULTIVARIATE EXPOSURES

Motivation: energy-adjusted analysis

- Researchers often perform an "energy-adjusted" analysis by adding total energy intake to model
- Sometimes, the main exposure variable is also modified
  - Example: Percent energy from fat
- Reasons for energy adjustment:
  - Interest in association between dietary composition and health
  - Energy-adjustment often decreases measurement error in reported intake

Regression calibration with two dietary exposures

- Disease model:

$$\log\{\mathrm{Odds}(Y=1)\} = \alpha_0 + \alpha_{T1}T_1 + \alpha_{T2}T_2 + \alpha_{Z1}Z_1 + \ldots + \alpha_{Zp}Z_p$$

- Replace T_1 and T_2 with $E(T_1|Q_1,Q_2,\underline{Z})$ and $E(T_2|Q_1,Q_2,\underline{Z})$
- $E(T_1|Q_1,Q_2,\underline{Z})$ is the **predicted value** of T_1 given reported intakes Q_1 and Q_2 and explanatory variables $Z_1, \ldots, Z_p$
- Confidence intervals for odds ratios calculated using the bootstrap method, exactly as described for a single exposure

Linear regression calibration

- Prediction equations:

$$E(T_1|Q_1,Q_2,Z) = \lambda_{01} + \lambda_{Q11}Q_1 + \lambda_{Q21}Q_2 + \lambda_{Z11}Z_1 + \ldots + \lambda_{Zp1}Z_p$$

$$E(T_2|Q_1,Q_2,Z) = \lambda_{02} + \lambda_{Q12}Q_1 + \lambda_{Q22}Q_2 + \lambda_{Z12}Z_1 + \ldots + \lambda_{Zp2}Z_p$$

- Reference measures R_1 and R_2 for T_1 and T_2
- Linear regression of R_1 and R_2 on Q_1, Q_2 and Z in calibration study

Rosner's method for linear regression calibration

$$\log\{\mathrm{Odds}(Y=1)\} = \alpha_0 + \alpha_{T1}T_1 + \alpha_{T2}T_2 + \alpha_{Z1}Z_1 + \ldots + \alpha_{Zp}Z_p$$

$$E(T_1|Q_1,Q_2,\underline{Z}) = \lambda_{01} + \lambda_{Q11}Q_1 + \lambda_{Q21}Q_2 + \lambda_{Z11}Z_1 + \ldots + \lambda_{Zp1}Z_p$$

$$E(T_2|Q_1,Q_2,\underline{Z}) = \lambda_{02} + \lambda_{Q12}Q_1 + \lambda_{Q22}Q_2 + \lambda_{Z12}Z_1 + \ldots + \lambda_{Zp2}Z_p$$

- From lecture 6, log odds ratios estimated using Q_1 and Q_2 actually estimate:

$$\alpha_{Q1} = \lambda_{Q11}\times\alpha_{T1} + \lambda_{Q12}\times\alpha_{T2}$$
$$\alpha_{Q2} = \lambda_{Q22}\times\alpha_{T2} + \lambda_{Q21}\times\alpha_{T1}$$

contamination

attenuation

Rosner's method for linear regression calibration

$$\alpha_{Q1} = \lambda_{Q11}\times\alpha_{T1} + \lambda_{Q12}\times\alpha_{T2}$$
$$\alpha_{Q2} = \lambda_{Q22}\times\alpha_{T2} + \lambda_{Q21}\times\alpha_{T1}$$

- Equations can be written in matrix notation

$$\alpha_Q = \Lambda_Q\alpha_T$$

where:

$$\Lambda_Q = \begin{pmatrix}\lambda_{Q11} & \lambda_{Q12}\\ \lambda_{Q21} & \lambda_{Q22}\end{pmatrix},\quad \alpha_T = \begin{pmatrix}\alpha_{T1}\\ \alpha_{T2}\end{pmatrix},\quad \alpha_Q = \begin{pmatrix}\alpha_{Q1}\\ \alpha_{Q2}\end{pmatrix}$$

- Λ_Q is called the "attenuation-contamination" matrix

Rosner's method for linear regression calibration

Univariate case:

- Bias: $\alpha_Q = \lambda_Q\alpha_T$
- Estimate: $\alpha_T = \alpha_Q / \lambda_Q = \lambda_Q^{-1}\alpha_Q$

Bivariate case:

- Bias: $\alpha_Q = \Lambda_Q\alpha_T$
- Estimate: $\alpha_T = \Lambda_Q^{-1}\alpha_Q$
- Standard errors for α_{T1} and α_{T2} can be estimated by multivariate delta method

Example: energy-adjusted fat and breast cancer

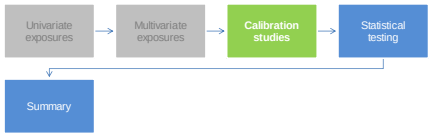
- NIH-AARP Diet and Health Study
- Logistic regression of breast cancer status (Y) on log total fat intake (T_1) and log non-alcohol energy intake (T_2)
- Substitution effect: adding fat intake while keeping non-alcohol energy constant
- Other covariates (Z) same as for univariate fat and breast cancer example

Example: energy-adjusted fat and breast cancer

Dietary fat intake and breast cancer risk in NIH-AARP

Correction for Measurement Error	Log Odds Ratio (s.e.)	Odds Ratio (95% CI)
Uncorrected	0.15 (0.05)	1.16 (1.05, 1.29)
Regression calibration	0.29 (0.11)	1.34 (1.09, 1.66)
Alternate method	0.29 (0.10)	1.34 (1.10, 1.64)

- Adjusted for non-alcohol energy intake



CALIBRATION STUDIES

Calibration studies

- Studies performed to “calibrate” the main study instrument (Q) to a reference instrument (R)
- To calibrate Q means to develop a prediction equation to predict R given Q
- The information from these studies can be used as the basis for regression calibration

Types of calibration studies

- Internal calibration study: random subsample of main study participants
- External calibration study: separate study of participants that are similar to those participating in the main study
- Participants must complete the same study instrument (Q) that is used in the main study
- Internal calibration is preferable

Reference instrument: ideal properties

- Unbiased measure of individual true usual intake
- Errors uncorrelated with true usual intake
- Errors uncorrelated with errors in study instrument

Calibration studies

Reference instrument: examples

- Doubly labeled water for energy intake
- 24-hour urinary nitrogen for protein intake
- 24-hour urinary potassium for potassium intake

Calibration studies

Reference instrument

- Instruments that are usually used as a reference
  - 24-hour recalls (one or more)
  - Multiple-day food records
- Problems
  - Biased for true intake
  - Errors correlated with true intake
  - Errors correlated with errors in FFQ

Calibration studies

Performance of 24HR as reference

OPEN Study: Attenuation factors estimated using recovery biomarker or 24HR as reference (Freedman et al., J Nat Cancer Inst, 2011)

Nutrient	Gender	Reference Biomarker	Reference 24HR
Energy	Men	0.08 (0.03)	0.21 (0.04)
	Women	0.03 (0.03)	0.09 (0.05)
Protein Density	Men	0.43 (0.07)	0.35 (0.07)
	Women	0.33 (0.08)	0.45 (0.06)
Potassium Density	Men	0.57 (0.08)	0.59 (0.05)
	Women	0.61 (0.08)	0.62 (0.07)

Calibration studies

Performance of 24HR as reference

- Attenuation factors appear to be similar for energy-adjusted nutrients
- Freedman et al. (2011) concluded that regression calibration with 24HR improves estimation (on average) compared to no adjustment
- Caveat: conclusion based on only three nutrients: protein, potassium and energy

Calibration studies

Design of calibration studies

- Two important factors:
  - Number of participants in calibration study
  - Number of reference measures per participant

Calibration studies

Size of calibration study

$$s.e.(\hat{\alpha}_T) \approx \frac{\alpha_Q}{\lambda_Q}\sqrt{\left(\frac{s.e.(\hat{\alpha}_Q)}{\alpha_Q}\right)^2 + \left(\frac{s.e.(\hat{\lambda}_Q)}{\lambda_Q}\right)^2}$$

- 1st term is uncertainty of estimating attenuated log odds ratio in main study of size N
- 2nd term is uncertainty of estimating attenuation factor in calibration study of size n

$$s.e.(\hat{\lambda}_Q) = \sqrt{\frac{\sigma_\varepsilon^2}{n\,\sigma_Q^2}}$$

- σ_ε^2 = residual variance in regression of R on Q

Calibration studies

Size of calibration study

$$s.e.(\hat{\alpha}_T) \approx \frac{\alpha_Q}{\lambda_Q}\sqrt{\left(\frac{s.e.(\hat{\alpha}_Q)}{\alpha_Q}\right)^2 + \left(\frac{\sigma^2_\varepsilon}{n\lambda_Q^2\sigma_Q^2}\right)}$$

- Choose n so that 2nd term is a small fraction of 1st term, say 1/10th

$$\frac{\sigma^2_\varepsilon}{n\lambda_Q^2\sigma_Q^2} = \frac{1}{10}\left(\frac{s.e.(\hat{\alpha}_Q)}{\alpha_Q}\right)^2$$

- Solve for n

$$n = 10\left(\frac{\sigma^2_\varepsilon}{\lambda_Q^2\sigma_Q^2}\right)\left(\frac{\alpha_Q}{s.e.(\hat{\alpha}_Q)}\right)^2$$

Calibration studies

Example: size of calibration study

$$n = 10\left(\frac{\sigma^2_\varepsilon}{\lambda_Q^2\sigma_Q^2}\right)\left(\frac{\alpha_Q}{s.e.(\hat{\alpha}_Q)}\right)^2$$

- 95% CI: $\hat{\alpha}_Q \pm 1.96 \times s.e.\ \hat{\alpha}_Q$
- Choose $s.e.(\hat{\alpha}_Q) = \alpha_Q / 2$

$$n = 40\left(\frac{\sigma^2_\varepsilon}{\lambda_Q^2\sigma_Q^2}\right)$$

For fat intake in AARP

$$\lambda_Q = 0.28,\ \sigma^2_Q = 0.25,\ \sigma^2_\varepsilon = 0.34$$

- n = 694

Calibration studies

Number of reference measurements

- Calibration study of sample size n, with k administrations of R per participant
- $\bar{R}_k$ = average of k repeats of R for participant
- Estimate λ_Q by regressing $\bar{R}_k$ on Q

$$s.e.(\hat{\lambda}_Q) = \sqrt{\frac{\sigma^2_{\varepsilon k}}{n\sigma_Q^2}}$$

- $\sigma^2_{\varepsilon k}$ = residual variance in regression of $\bar{R}_k$ on Q

Calibration studies

Number of reference measurements

$$\sigma^2_{\varepsilon k} = \sigma_{RR} + \left(\sigma^2_R - \sigma_{RR}\right)/k - \lambda_Q^2\sigma_Q^2$$

- σ^2_R is the variance of a single R and σ_{RR} is the covariance between repeat R's

$$s.e.(\hat{\lambda}_Q) = \sqrt{\frac{\sigma^2_{\varepsilon k}}{n\sigma_Q^2}} = \sqrt{\frac{\sigma_{RR} + \left(\sigma^2_R - \sigma_{RR}\right)/k - \lambda_Q^2\sigma_Q^2}{n\sigma_Q^2}}$$

- Gain in precision due to additional reference measurements depends on the size of $\sigma^2_M - \sigma_{MM}$

Calibration studies

Example: number of reference measurements

$$s.e.(\hat{\lambda}_Q) = \sqrt{\frac{\sigma^2_{\varepsilon k}}{n\sigma_Q^2}} = \sqrt{\frac{\sigma_{RR} + \left(\sigma^2_R - \sigma_{RR}\right)/k - \lambda_Q^2\sigma_Q^2}{n\sigma_Q^2}}$$

- For fat intake in AARP

$$\lambda_Q = 0.28,\ \sigma^2_Q = 0.25,\ \sigma^2_R = 0.350,\ \sigma_{RR} = 0.133$$

$$s.e.(\hat{\lambda}_Q) = \sqrt{\frac{0.454 + 0.868/k}{n}}$$

- s.e. is a function of n and k

Calibration studies

Example: number of reference measurements

- Relative sample size required in a calibration study with k repeats of M per participant

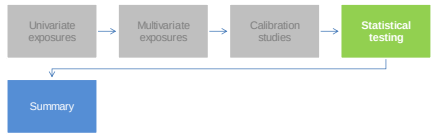
k	n
1	1000
2	672
3	563
4	508

(Based on fat intake in AARP)

Calibration studies

Minimum number of reference instruments

- Performing regression calibration when regression calibration model is linear
  - Minimum number = 1
- Performing regression calibration when regression calibration model is nonlinear
  - Minimum number = 2
- Estimating correlation of Q and T
  - Minimum number = 2
  - Estimating power
  - Assessing the quality of Q (validity)



STATISTICAL TESTING AND REGRESSION CALIBRATION

Statistical testing and regression calibration

Hypothesis testing

- Null hypothesis: no association between dietary intake and the health outcome ($\alpha_T = 0$)
- Wald test statistic: estimated log odds ratio divided by its standard error

$$W = \hat{\alpha}_T / s.e.(\hat{\alpha}_T)$$

- W is approximately normal with
  - mean = $E(\hat{\alpha}_T) / s.e.(\hat{\alpha}_T)$
  - standard deviation = 1

Statistical testing and regression calibration

Hypothesis testing

- Assumption: under null hypothesis, W has mean = 0
- Wald test: reject null hypothesis if W is too large

$$|W| \geq c$$

- Type I error = reject null when null is true
  Type II error = not reject null when null is false
- Significance level: probability of Type I error
  Power: 1 – probability of Type II error
- Controlling Type I error: choose c so that probability of Type 1 error is small, typically 5%

Statistical testing and regression calibration

Validity of statistical tests

- A statistical test is valid if probability of a type I error really is at the chosen significance level
- For Wald test, condition holds only if the mean of W = 0 under the null hypothesis
- Since mean of W = $E(\hat{\alpha}_T) / s.e.(\hat{\alpha}_T)$, Wald test is valid only if

$$E(\hat{\alpha}_T) = 0 \text{ whenever } \alpha_T = 0$$

- If estimator is unbiased (i.e., if $E(\hat{\alpha}_T) = \alpha_T$), then Wald test is valid

Statistical testing and regression calibration

Is the uncorrected test valid?

- Wald test performed on the uncorrected log odds ratio will be called the "uncorrected test"
- For univariate exposures, the uncorrected log odds ratio is biased

$$E(\hat{\alpha}_Q) = \lambda_Q \alpha_T$$

- Nevertheless, if $\alpha_T = 0$, then $E(\hat{\alpha}_Q) = 0$
- Uncorrected Wald test for univariate exposure is valid

Is the uncorrected test valid?

- For bivariate exposures, the uncorrected log odds ratio has mean

$$E(\hat{\alpha}_{Q1}) = \lambda_{Q11}\alpha_{T1} + \lambda_{Q12}\alpha_{T2}$$

- When $\alpha_{T1} = 0$,

$$E(\hat{\alpha}_{Q1}) = \lambda_{Q12}\alpha_{T2}$$

- Uncorrected Wald test for bivariate exposures is not valid
- If contamination factor λ_{Q12} is sufficiently small, then uncorrected test is approximately valid

Is the uncorrected test valid?

OPEN – Estimated Contamination Factors (Freedman et al., J Nat Cancer Inst, 2011)

Nutrient	Gender	Energy	Protein Density	Potassium Density
Energy	Men	-	-0.01 (0.03)	0.13 (0.05)
	Women	-	0.03 (0.05)	0.10 (0.06)
Protein Density	Men	0.08 (0.05)	-	-0.01 (0.09)
	Women	0.06 (0.05)	-	0.00 (0.10)
Potassium Density	Men	0.04 (0.04)	-0.05 (0.06)	-
	Women	-0.04 (0.05)	0.00 (0.07)	-
Total Fat Density	Men	0.05 (0.05)	-0.03 (0.07)	0.00 (0.08)
	Women	-0.07 (0.05)	-0.02 (0.08)	-0.08 (0.10)
Saturated Fat Density	Men	0.10 (0.04)	-0.03 (0.05)	-0.04 (0.07)
	Women	-0.02 (0.04)	-0.01 (0.06)	0.07 (0.08)

Is the uncorrected test valid?

- Contamination factors are generally small and not statistically significant
- Freedman et al. (2011) concluded that statistical tests for uncorrected test with multiple dietary exposures will be approximately valid
- Caveat: conclusion based on only three nutrients: protein, potassium and energy

Statistical power

- Statistical power is the probability of rejecting the null hypothesis when the null hypothesis is false
- Equivalently, the probability of detecting an association as statistically significant
- Power depends on the size of true log odds ratio:
  - For α_T close to 0, power is small
  - As $|\alpha_T|$ increases, power increases

Statistical power for uncorrected test

- Power of Wald test depends on |E(W)| = absolute value of the expected value of Wald statistic W
- For univariate exposures, expected value of W for the uncorrected test is

$$E\ W = Corr(Q,T) \times E\ W_T$$

  $E(W_T)$ = expected value of W if T could be measured without error
- Since |Corr(Q,T)| ≤ 1, measurement error always leads to loss of power (unless |Corr(Q,T)| = 1)

Example: loss of power for uncorrected test

- NIH-AARP Diet and Health Study
- For fat intake, estimated $\rho_{QT} = 0.40$
- In a study with N subjects:
  - If power = 90% using true intake T, then power = 25% using Q instead of T
  - To get 90% power using Q, would need a sample size of $N / \rho_{QT}^2 = 6.25 \times N$
- Similar loss of power for multivariate exposures measured with error

Statistical power for regression calibration

- Regression calibration adjusts the estimated log odds ratio by dividing by the attenuation coefficient

$$\hat{\alpha}_T = \hat{\alpha}_Q / \hat{\lambda}_Q$$

- However, this adjustment changes the standard error of the estimate

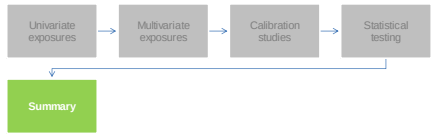
$$se(\hat{\alpha}_T) \approx \sqrt{\left(\frac{se(\hat{\alpha}_Q)}{\hat{\lambda}_Q}\right)^2 + \left(\frac{\hat{\alpha}_Q se(\hat{\lambda}_Q)}{\hat{\lambda}_Q^2}\right)^2} > \frac{se(\hat{\alpha}_Q)}{\hat{\lambda}_Q}$$

Statistical power for regression calibration

- As a result:
  - Expected value of test statistic W does not increase (it decreases slightly)
  - Wald test based on regression calibration has slightly less power than the unadjusted test
- Regression calibration in its usual form corrects for bias, but does recover power lost due to measurement error

Can regression calibration be made more powerful?

- An enhanced version of regression calibration can sometimes be used to recover (some of) the power lost due to measurement error
- Idea: predict T using E(T|Q, Z, C) instead of E(T|Q, Z), where C is a variable that:
  i. Helps to predict true intake, but
  ii. Is not related to disease outcome conditional on true intake and covariates Z
- See lecture 10 in the series for fuller discussion



SUMMARY

Summary

1. Measurement error causes attenuation of estimated risk parameters and loss of power to detect diet-health associations.
2. Regression calibration is an accessible method for adjusting these attenuated estimates to remove bias.
3. Calibration studies are needed to provide the information necessary to apply regression calibration.
4. In its usual form, regression calibration does not recover power lost due to measurement error.
5. Statistical tests of uncorrected risk estimates are, on current evidence, approximately valid.

QUESTIONS & ANSWERS

Moderator: Amy Subar

Please submit questions using the *Chat* function


National Cancer Institute
measurement ERROR webinar series
Next Session
Tuesday, November 8, 2011
10:00-11:30 EST
Assessing diet-health relationships with FFQ:
Focus on episodically-consumed dietary components
Victor Kipnis
National Cancer Institute
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health