

National Cancer Institute

measurementERRORwebinar series

The problem of measurement error when examining diet-health relationships

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

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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

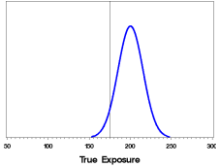
	Sharon Kirkpatrick <i>Series Organizer</i>	
Regan Bailey	Laurence Freedman	Douglas Midthune
Dennis Buckman	Patricia Guenther	Amy Subar
Raymond Carroll	Victor Kipnis	Fran Thompson
Kevin Dodd	Susan Krebs-Smith	Janet Tooze



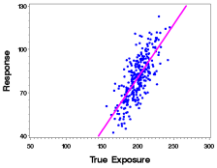
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Two main areas of interest

- Describing usual intake distributions: mean, percentiles, proportion above or below a threshold



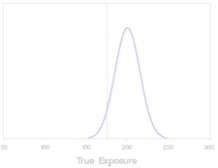
- Estimating diet-health relationships: regression coefficients



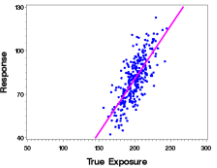
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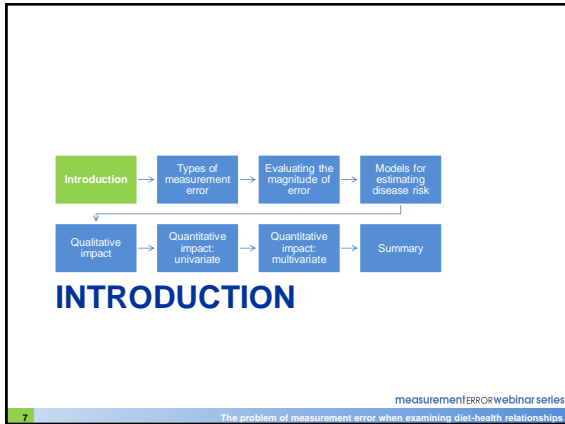


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Learning objectives

- Knowing the types and magnitudes of measurement error that occur in dietary data
- Reviewing statistical models for evaluating diet-health relationships
- Understanding the qualitative and quantitative impact of measurement error on studies of diet-health relationships

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Introduction

Types of “analytic” studies

- Animal experiments
- Ecological studies
- Cross-sectional studies**
- Case-control studies**
- Cohort studies**
- Randomized disease prevention trials

Red → Estimated diet-health relationship impacted by dietary measurement error

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Introduction

The exposure (1)

- In these studies we wish to relate:

Dietary Intake

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Health Outcome

- The measure of intake thought to be most relevant is:
 - usual intake, i.e., long-term average daily intake

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Introduction

The exposure (2)

- In surveillance studies, “long-term” is often taken to be 1 or 2 years
- In cohort and case-control studies, it is less-well defined but often may be thought of as covering several years

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Introduction

The exposure (3)

- Clearly, to measure an individual's average intake over a long period is a challenging task
- Fortunately, one does not need to measure usual intake exactly in order to make progress

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Introduction

Instruments (1)

- Food Frequency Questionnaires
 - Main instrument for large cohort and case-control studies
 - Inexpensive to administer
 - Aims to measure long-term average intake
- BUT**
 - Inaccurate long-term recall
 - Cognitively difficult
 - Conversion to nutrient and food group intakes is difficult

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Instruments (2)

HARVARD MEDICAL SCHOOL ■ Page 4 ■ NURSES' HEALTH STUDY

23. (continued) For each food listed, fill in the circle indicating how often on average you have used the amount specified during the past year.

Please try to average your seasonal use of foods over the entire year. For example, if a food such as cantaloupe is eaten 4 times a week during the approximate 3 months that it is in season, then the average use would be once per week.	FRUITS		None, or less than once per month	1-3 per month	1-3 per week	2-4 per 5-6 per week	1 per day per day	2-3 per day per day	4-5 per day per day	6+ per day per day
	Raisins (1 oz. or small pack) or grapes (1/2 cup)	Prunes or dried plums (6 prunes or 1/4 cup)								
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Types of measurement error

Types of measurement error (4)

Multiplicative/Additive Systematic Bias: T=true, R=reported

Usual Intake

Participant Number

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Types of measurement error

Types of measurement error (5)

- Person-specific (random) bias
 - Bias that occurs at the individual level - it is specific to an individual but can differ among individuals

$$R_i = \beta_0 + \beta_1 \times T_i + u_i$$

(In addition to additive and multiplicative systematic bias, there is a bias u_i that varies for each individual i)

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Types of measurement error

Types of measurement error (6)

- Person-specific (random) bias
 - The subject-specific bias u_i is a random term
 - Its magnitude is quantified by $SD(u_i)$, its standard deviation

$$R_i = \beta_0 + \beta_1 \times T_i + u_i$$

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Types of measurement error

Types of measurement error (7)

Multiplicative/Additive Group Bias Plus Person-Specific Bias

Usual Intake

Participant Number

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Types of measurement error

Types of measurement error (8)

- Within-person random error
 - Variation in reporting by an individual over a series of repeat reports

$$R_{ij} = \beta_0 + \beta_1 \times T_i + u_i + \epsilon_{ij}$$

- The extra subscript j denotes the sequence number in a series of reports
- The extra term ϵ_{ij} is the within-person error that is on average zero
- Its magnitude is quantified by $SD(\epsilon_{ij})$

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Types of measurement error

Types of measurement error (9)

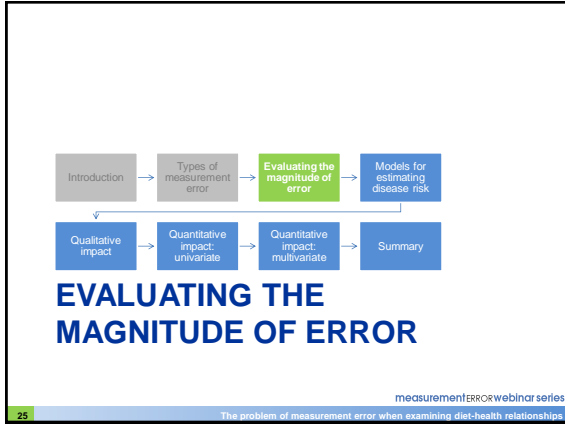
General Situation: systematic bias, person-specific bias, random error

Usual Intake

Participant Number

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Evaluating the magnitude of error

Evaluating the error (1)

- How can we study the errors made in dietary reporting?
 - Validation studies comparing reports with “reference” measures of dietary intake
- Ideal properties of a reference instrument
 - Unbiased
 - Errors uncorrelated to true intake
 - Errors uncorrelated with self-report errors

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Evaluating the magnitude of error

Evaluating the error (2)

- Do we have any ideal “reference” measures?
 - Direct observation (feeding studies)
 - “Recovery” biomarkers: based on recovery of specific biologic products that are directly related to intake and are not subject to substantial inter-individual differences in metabolism
 - Doubly labeled water for energy intake
 - 24-hour urinary nitrogen for protein intake
 - 24-hour urinary potassium for potassium intake
 - “Concentration” biomarkers (e.g., serum lipids) do not share these properties

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Evaluating the magnitude of error

Evaluating the error (3)

- OPEN (Observing Protein and Energy Study)
 - 261 men; 223 women
 - Adult volunteers residing in Maryland, USA
- Completed:
 - 24-hour recall x 2
 - Food frequency questionnaire x 2
 - 24-hour urinary nitrogen x 2
 - 24-hour urinary potassium x 2
 - Doubly-labeled water x 1 (in 25 persons x 2)

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Evaluating the magnitude of error

Evaluating the error (4)

Results from OPEN – Means

Sex	Method	Energy (kcal/d)	Protein (g/d)
Men	Marker	2842	105.5
	FFQ	1961	74.7
	24HR	2522	92.2
Women	Marker	2273	77.5
	FFQ	1524	57.2
	24HR	1919	70.9

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Evaluating the magnitude of error

Evaluating the error? (5)

Results from OPEN – Protein Intake (after log transformation)

Sex	Method	Scaling Factor, β_1	Person-Specific Bias (SD)	Within-Person Error (SD)
Men	FFQ	0.67	0.36	0.19
	24HR	0.70	0.20	0.30
Women	FFQ	0.65	0.33	0.22
	24HR	0.60	0.16	0.35

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Evaluating the magnitude of error

Evaluating the error? (6)

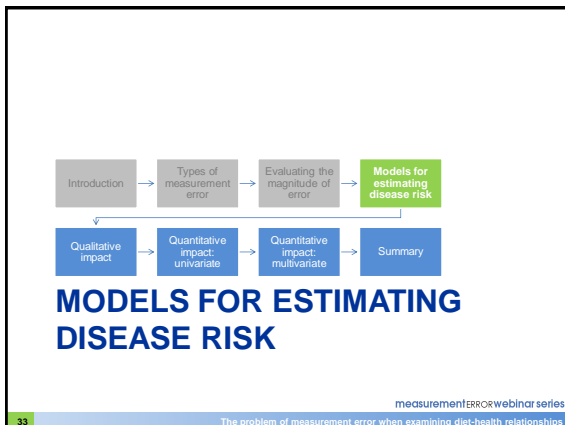
Results from OPEN – Protein Density (after log transformation)

Sex	Method	Scaling Factor, β_1	Person-Specific Bias (SD)	Within-Person Error (SD)
Men	FFQ	0.46	0.13	0.11
	24HR	0.61	0.11	0.24
Women	FFQ	0.37	0.15	0.12
	24HR	0.39	0.11	0.26

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- Evaluating the magnitude of error
- ### Evaluating the error? (7)
- Summary of results of OPEN and other large validation studies (AMPM, NBS)
- Serious under-reporting**
 Energy: FFQ by 30% and 24HR by 10%
 - Food frequency questionnaire (FFQ)**
 Large systematic error, large person-specific bias, small within-person random error
 - The biases and random error can be reduced by energy adjustment
 - 24-hour recall (24HR)**
 Smaller systematic error, large within-person random error, smaller person-specific bias
 - The within-person random error of the 24HR is largely day-to-day variation and can be reduced by using several repeats
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- Models for estimating disease risk
- ### Estimating disease risk (1)
- Before we study the impact of measurement error on studying diet-health relationships, we need to review measures and statistical models for disease risk
 - The two main measures of disease risk are:
 - Relative risk
 - Odds ratio
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Models for estimating disease risk

Estimating disease risk (2)

- When comparing two groups, exposed and unexposed:

$$\text{Relative risk} = \frac{\text{Prob (disease in exposed)}}{\text{Prob (disease in unexposed)}}$$

$$\text{Odds (disease)} = \frac{\text{Prob (disease)}}{1 - \text{Prob(disease)}}$$

$$\text{Odds ratio} = \frac{\text{Odds (disease in exposed)}}{\text{Odds (disease in unexposed)}}$$

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- Models for estimating disease risk
- ### Estimating disease risk (3)
- Elements of a nutrition regression model
 - A health outcome variable (Y)
 - A set of explanatory variables, $(T_1, T_2, Z_1, \dots, Z_p)$
 The T-variables are dietary exposures, and the Z-variables are other exposures, confounders, effect modifiers or intermediate variables
 - An equation linking the outcome to the explanatory variables
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Models for estimating disease risk

Estimating disease risk (4)

For example, logistic regression:

$$\log\{\text{Odds}(Y = 1)\} = \alpha_0 + \alpha_{T_1} T_1 + \alpha_{T_2} T_2 + \alpha_{Z_1} Z_1 + \dots + \alpha_{Z_p} Z_p$$

- Where:
 - Y is a binary variable;
 - Y=1 denotes disease ("case")
 - Y=0 denotes no disease ("healthy")
- α 's are the regression parameters and represent log odds ratios
- Each α represents the increase in the log odds of disease associated with increasing the corresponding variable by 1 unit while keeping the other variables fixed.

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Models for estimating disease risk

Estimating disease risk (5)

Estimating an odds ratio: binary exposure
Israeli National Ovarian Cancer Case-Control Study

- Oral Contraceptive use (0=<6m use, 1=6m+ use)
889 cases; 1747 controls

$$\log\{\text{Odds}(Y = 1)\} = \alpha_0 + \alpha_1 \text{OC}$$

- Output from logistic regression program

Coefficients:

	Value	Std. Error	p value
(Intercept)	-0.65	0.046	<0.0001
ocon1	-0.13	0.10	0.19

- Odds ratio estimate for OC = $\exp(\alpha_1) = \exp(-0.13) = 0.87$

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Models for estimating disease risk

Estimating disease risk (6)

Estimating an odds ratio: continuous exposure
Animal Fat intake (kcal/d) from a FFQ

$$\log\{\text{Odds}(Y = 1)\} = \alpha_0 + \alpha_1 \text{afatcal}$$

Output from logistic regression program

	Value	Std. Error	p value
(Intercept)	-1.18	0.10	<0.0001
afatcal	0.0017	0.00030	<0.0001

- Odds ratio estimate for increase in animal fat intake of 1kcal/d = $\exp(\alpha_1) = \exp(0.0017) = 1.0017$
- Odds ratio estimate for increase in animal fat of 100kcal/d = $\exp(100 \times \alpha_1) = \exp(100 \times 0.0017) = 1.18$

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Models for estimating disease risk

Estimating disease risk (7)

Energy adjustment

- Practical question:
 - A study has been conducted with a FFQ as the main dietary instrument
- When evaluating an association between a FFQ-reported nutrient intake and the health outcome should one adjust for FFQ-reported total energy?

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Models for estimating disease risk

Estimating disease risk (8)

Possible reasons for energy adjustment

(see Willett, Howe and Kushi, 1997)

- Energy is a confounder
- The energy-adjusted relative risk is more relevant to public health interests
- The adjustment increases the precision of the relative risk estimate**

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Models for estimating disease risk

Estimating disease risk (9)

Energy adjustment models

- There are several different methods for energy adjustment – we will look at two:
 - Standard model
 - Density model

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Models for estimating disease risk

Estimating disease risk (10)

Energy adjustment models

- Standard model:**
Add total energy intake as a second explanatory variable, for example:
$$\log\{\text{Odds}(Y = 1)\} = \alpha_0 + \alpha_1 \text{afatcal} + \alpha_2 \text{energy}$$
- Meaning of the coefficient α_1 changes:
The log odds ratio associated with increasing animal fat intake by 1 kcal while keeping total energy intake fixed
- which means:**
The log odds ratio associated with **substituting** 1 kcal of animal fat for 1 kcal of other nutrients

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Models for estimating disease risk

Estimating disease risk (11)

Energy adjustment: Standard model

$$\log\{\text{Odds}(Y = 1)\} = \alpha_0 + \alpha_1 \text{afatcal} + \alpha_2 \text{energy}$$

	Value	Std. Error	p value
(Intercept)	-1.39	0.13	<0.0001
afatcal	0.00093	0.00042	0.027
energy	0.00025	0.000098	0.009

- Odds ratio for 100kcal increase = $\exp(0.00093 \times 100) = 1.10$
- Remember that this association is with **substituting** 100kcal of animal fat for 100kcal of other food sources

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Models for estimating disease risk

Estimating disease risk (12)

Energy adjustment models

- Density model:**
Nutrient density = 100 x (nutrient intake in kcal / total energy intake in kcal)%
- Express the nutrient as a **nutrient density** and add total energy intake as a second explanatory variable.

For example:

$$\log\{\text{Odds}(Y = 1)\} = \alpha_0 + \alpha_1 \text{afatdens} + \alpha_2 \text{energy}$$

- Meaning of the coefficient α_1 :
The log odds ratio associated with increasing animal fat density by 1% while keeping total energy intake fixed

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Models for estimating disease risk

Estimating disease risk (13)

Energy adjustment: Density model

$$\log\{\text{Odds}(Y = 1)\} = \alpha_0 + \alpha_1 \text{afatdens} + \alpha_2 \text{energy}$$

	Value	Std. Error	p value
(Intercept)	-1.66	0.20	<0.0001
afatdens	0.01560	0.00760	0.041
energy	0.00041	0.00007	<0.0001

- Odds ratio for 5% increase = $\exp(0.0156 \times 5) = 1.08$
- Remember that this association is with increasing animal fat density by 5% while keeping energy intake fixed

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QUALITATIVE IMPACT OF MEASUREMENT ERROR

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Qualitative impact

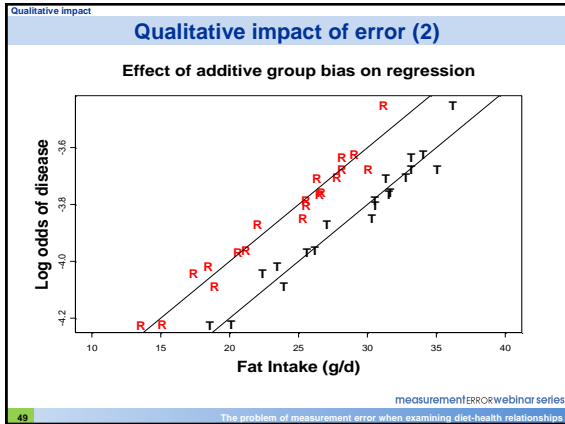
Qualitative impact of error (1)

Additive systematic bias

- Suppose we have an instrument with additive systematic bias but no subject-specific bias and no random error.
$$R_i = \beta_0 + T_i$$
- Then:
 - Log odds ratio estimates are unchanged
 - Scatter about the regression line is unchanged
 - Significance tests are unaffected
 - Study power is unaffected
- Additive systematic bias is not a problem for detecting a relationship!
But translation to public health message is affected

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Qualitative impact

Qualitative impact of error (3)

Additive and multiplicative systematic bias

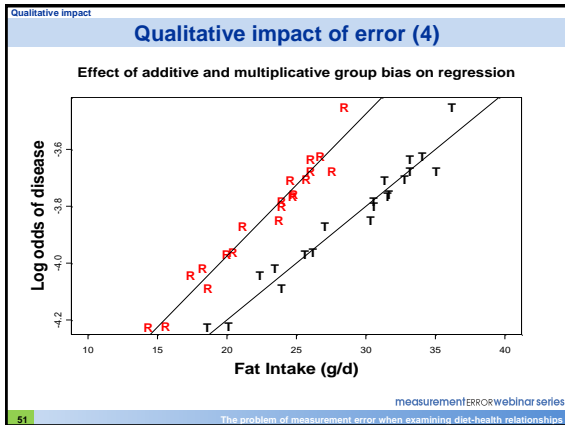
- Suppose we have an instrument with additive and multiplicative systematic bias but no person-specific bias and no random error

$$R_i = \beta_0 + \beta_1 \times T_i$$

- Then:
 - Log odds ratio estimates are scaled by $1/\beta_1$
 - Scatter about the regression line is unchanged
 - Significance tests are unaffected
 - Study power is unaffected
- Systematic bias is not the major problem for detecting a relationship!

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Qualitative impact

Qualitative impact of error (5)

Person-specific bias and within-person random error

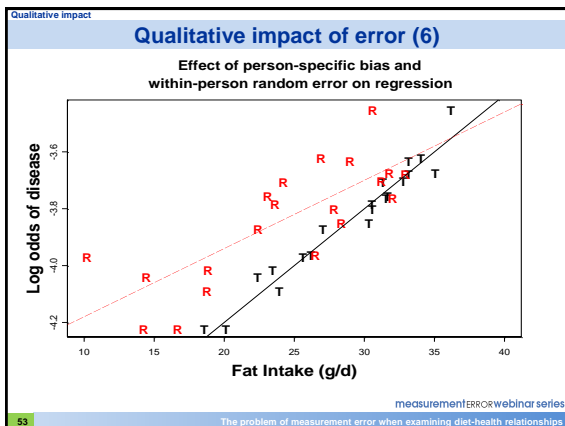
- Suppose we have an instrument with systematic bias and also person-specific bias and within-person random error

$$R_{ij} = \beta_0 + \beta_1 \times T_i + u_i + \epsilon_{ij}$$

- Then:
 - Log odds ratio estimates are factored down (attenuated)
 - Scatter about the regression line is increased
 - Significance tests are less powerful but still valid
 - Study power is decreased
- Person-specific bias and within-person random error are a major problem for detecting a relationship!

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Qualitative impact

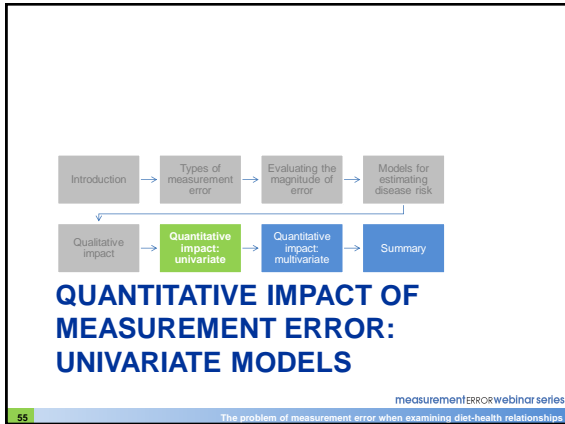
Qualitative impact of error (7)

Summary

- When a **single** dietary exposure measured with error is included in a disease outcome regression model:
 - Then:
 - Log odds ratio estimates are factored down (attenuated)
 - Study power is decreased
 - Significance tests are less powerful but still valid
- These conclusions seems to hold also for **several** dietary exposures entered together in the same model (e.g., energy-adjustment models) – see later details
- We now quantify the seriousness of these problems

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Quantitative impact: univariate models

Quantitative impact of error (1)

- We will now quantify the extent of the two main problems:
 - Log odds ratio estimates are attenuated
 - Study power is decreased

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Quantitative impact: univariate models

Quantitative impact of error (2)

Log odds ratio attenuation for a single continuous dietary intake variable

- Assume we have systematic error, subject-specific bias and random error.
- Expected log odds ratio estimate = $\lambda \times$ true value,**
- where
 - λ = attenuation factor = slope of regression of T (truth) on R (report)
 - λ is nearly always < 1 and usually a lot less!
- When the log odds ratio is attenuated, the odds ratio moves towards 1.0

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Quantitative impact: univariate models

Quantitative impact of error (3)

Log odds ratio attenuation for a single continuous dietary intake

- OPEN: Attenuation Factors for FFQ and 24HR (Men)
 - (Obtained by regressing recovery biomarker on self-report)

	FFQ	24HR
Energy	0.08	0.18
Protein	0.16	0.20
Protein Density	0.40	0.23

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Quantitative impact: univariate models

Quantitative impact of error (4)

Implications of these results

- Suppose the attenuation factor λ is **0.16** (as for protein)
- Suppose the true odds ratio between the 90th and 10th percentiles of true intake is **2.5** (i.e., substantial)
 - $\log \text{OR} = \log(2.5) = 0.92$
 - Expected estimated log OR = $0.92 \times 0.16 = 0.147$
 - Expected estimated OR = $\exp(0.147) = \mathbf{1.16}$

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Quantitative impact: univariate models

Quantitative impact of error (5)

Implications of these results (cont'd)

- Almost impossible to detect an OR of 1.16 in a case-control or cohort study**
- Reasons:
 - Enormous sample sizes required to obtain statistical significance (see later)
 - Cannot eliminate **all** confounding
- The limit of detection for an OR is probably around 1.25

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Quantitative impact: univariate models

Quantitative impact of error (6)

Implications of these results (cont'd)

- Fortunately, after energy adjustment, attenuation factors with an FFQ are larger (e.g., **0.40** for protein density)
- Suppose the true odds ratio between the 90th and 10th percentiles is **2.5** (i.e., substantial)
 - $\log OR = \log(2.5) = 0.92$
 - Expected estimated $\log OR = 0.92 \times 0.40 = 0.368$
 - Expected estimated $OR = \exp(0.368) = \mathbf{1.44}$
- Such an odds ratio is more possible to detect, although still difficult!

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Quantitative impact: univariate models

Quantitative impact of error (7)

Log odds ratio attenuation for a single categorized dietary intake

- Assume we categorize our intake into quantiles (e.g., tertiles, quartiles or quintiles)
- The log odds ratio is still attenuated but by a different amount:
- Expected log odds ratio estimate = $\rho \times \text{true value}$** , where ρ = correlation between R (report) and T (truth)
- In other words, for analysis by quantiles, log odds ratios are attenuated by ρ , instead of λ

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Quantitative impact: univariate models

Quantitative impact of error (8)

Log odds ratio attenuation for a single categorized dietary intake

OPEN: Correlations with True Usual Intake for FFQ and 24HR (Men)

	FFQ	24HR
Energy	0.20	0.34
Protein	0.32	0.38
Protein Density	0.43	0.38

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Quantitative impact: univariate models

Quantitative impact of error (9)

Log odds ratio attenuation for categorized variables

- Implications of these results are similar to those stated earlier
- After energy adjustment, the estimated log odds ratios will be greatly attenuated by a factor of about 0.4 for protein density

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Quantitative impact: univariate models

Quantitative impact of error (10)

Decrease in study power

- Assume we have systematic bias, subject-specific bias and within-person random error

Effective sample size = Actual sample size $\times \rho^2$

- Where: ρ = correlation of R (report) with T (truth)

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Quantitative impact: univariate models

Quantitative impact of error (11)

Decrease in study power

OPEN: Correlations with 'truth' for FFQ and 24HR (Men)

	FFQ	24HR
Energy	0.20	0.34
Protein	0.32	0.38
Protein Density	0.43	0.38

- Example: Protein Density**
FFQ: Effective sample size = $0.43^2 \times \text{actual sample size}$
= $0.18 \times \text{actual sample size}$
- We effectively lose 82% of our sample size!

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Quantitative impact: univariate models

Quantitative impact of error (12)

Decrease in study power

- Suppose that we had calculated a sample size of **50,000** for a cohort study that would give **90%** power for detecting an association the 5% significance level, assuming that we could measure dietary intake exactly
- Then, because of the measurement error we would need $50,000/\rho^2 = 50,000/0.432^2 =$ **270,000** to preserve the power of 90%

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Quantitative impact: univariate models

Quantitative impact of error (13)

Decrease in study power

- If we proceeded with the study with sample size 50,000 then the statistical power would be decreased by measurement error from 90% to 28%
 - The formula is given by:

$$\text{Power} = \Phi^{-1}(3.24\rho - 1.96)$$
 - Where the symbol Φ^{-1} denotes the inverse of the standard normal cumulative distribution function

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QUANTITATIVE IMPACT OF MEASUREMENT ERROR: MODELS WITH MULTIVARIATE EXPOSURE

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Quantitative impact: multivariate models

Quantitative impact: multivariate exposures (1)

Two or more dietary variables in the disease regression model

- Typical example: Standard energy-adjustment model

$$\log\{\text{Odds}(Y=1)\} = \alpha_0 + \alpha_1 \text{fatcal} + \alpha_2 \text{energy}$$
- The effects of measurement error in these models is in theory less straightforward:
 - Estimated log odds may be biased but not attenuated (i.e., inflated)
 - Statistical tests may not be valid

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Quantitative impact: multivariate models

Quantitative impact: multivariate exposures (2)

- These problems arise from **residual confounding**:
 - One error-prone exposure and one exactly measured exposure in the same model
 - If the two (true) exposures are correlated, then the exactly measured one will adopt part of the effect of the error-prone exposure
 - When both are measured with error, they will each adopt different fractions of the other's effect!

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Quantitative impact: multivariate models

Quantitative impact: multivariate exposures (3)

- Suppose we have two nutrient intakes. There exists an "attenuation-contamination" matrix, as follows:

λ_{11}	λ_{12}
λ_{21}	λ_{22}
- If the true log odds ratios for the two nutrients are α_1 and α_2 , then the estimated ones are expected to be: $\lambda_{11} \times \alpha_1 + \lambda_{12} \times \alpha_2$ and $\lambda_{22} \times \alpha_2 + \lambda_{21} \times \alpha_1$
- The magnitudes of λ_{12} and λ_{21} tell us how serious is the residual confounding. We call them **contamination factors**

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Quantitative impact: multivariate models

Quantitative impact: multivariate exposures (4)

- If λ_{12} and λ_{21} are small, then the only bias in the estimated log odds ratios comes essentially from attenuation, then:
 - The estimated log odds ratio is attenuated
 - The significance test is valid
- So we need to know for dietary data, how large are the contamination factors
- We can estimate them from the OPEN study

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Quantitative impact: multivariate models

Quantitative impact: multivariate exposures (5)

OPEN – Estimated Contamination Factors
(Freedman, Schatzkin, Midthune, Kipnis, J Nat Cancer Inst 2011)

Dietary Component	Gender	Protein Density	Potassium Density	Energy
Energy	Men	-0.01 (0.03)	0.13 (0.05)	-
	Women	0.03 (0.05)	0.10 (0.06)	-
Protein Density	Men	-	-0.01 (0.09)	0.08 (0.05)
	Women	-	0.00 (0.10)	0.06 (0.05)
Potass. Density	Men	-0.05 (0.06)	-	0.04 (0.04)
	Women	0.00 (0.07)	-	-0.04 (0.05)
Total Fat Density	Men	-0.03 (0.07)	0.00 (0.08)	0.05 (0.05)
	Women	-0.02 (0.08)	-0.08 (0.10)	-0.07 (0.05)
Sat. Fat Density	Men	-0.03 (0.05)	-0.04 (0.07)	0.10 (0.04)
	Women	-0.01 (0.06)	-0.07 (0.08)	-0.02 (0.04)

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Quantitative impact: multivariate models

Quantitative impact: multivariate exposures (6)

OPEN: Contamination factors

- Contamination factors generally appear small, meaning that residual confounding does not appear to be a serious problem
 - However, note that OPEN and other recovery biomarker validation studies examine only energy, protein and potassium
 - Similar findings for other nutrients cannot be guaranteed

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SUMMARY

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Summary

Summary

- Errors in self-reported dietary intake have a complex structure including systematic biases, person-specific biases and within-person random error
- The person-specific biases and within-person random error have a profound impact on the estimation of disease risk parameters such as the log odds ratio. Estimates of these are severely attenuated
- For a FFQ, these effects can be partially mitigated by energy-adjustment
- The same biases and random errors also cause loss of statistical power for detecting diet-health relationships

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Summary

What's coming next?

- In the next lecture, we will study how we can correct the attenuation in the estimated disease risk parameter
- This will require us to learn about calibration studies and also a neat statistical method known as regression calibration

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QUESTIONS & ANSWERS
 Moderator: Sharon Kirkpatrick

Please submit questions using the *Chat* function

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Next Session Tuesday, November 1, 2011
 10:00-11:30 EDT

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

Douglas Midthune
 National Cancer Institute

National Cancer Institute

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