

Lesson 4: Measurements of Association and Agreement

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Poll Everywhere Question 1

good / bad &

Learning Objectives

1. Identify cases when it is appropriate to use risk difference, relative risk, or odds ratios
2. Expand work on contingency tables to evaluate the agreement or reproducibility using Cohen's Kappa

Last class

- Used contingency tables to test and measure association between two variables
 - Categorical outcome variable (Y)
 - One categorical explanatory variable (X) → grp 1 & grp 2
- We looked at risk difference, risk ratio, and odds ratio to measure association

Measure	Estimate
Risk difference	$\widehat{RD} = \hat{p}_1 - \hat{p}_2 = \frac{n_{11}}{n_1} - \frac{n_{21}}{n_2}$
Relative risk / risk ratio	$\widehat{RR} = \frac{\hat{p}_1}{\hat{p}_2} = \frac{n_{11}/n_1}{n_{21}/n_2}$
Odds ratio	$\widehat{OR} = \frac{odds_1}{odds_2} = \frac{\hat{p}_1/(1 - \hat{p}_1)}{\hat{p}_2/(1 - \hat{p}_2)}$

A taste of regression for a binary outcome (we will come back to this!!)

```
1 logreg = glm(case ~ glucimp, data = SHS, family = binomial) ←
```

```
1 summary(logreg)
```

more exp vars can be added

Call:

```
glm(formula = case ~ glucimp, family = binomial, data = SHS)
```

Coefficients:

	Estimate	Std. Error	z value	Pr(> z)	
(Intercept)	-0.52287	0.08969	-5.83	5.55e-09	***
glucimpNormal	-1.53684	0.12982	-11.84	< 2e-16	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 1646.3 on 1663 degrees of freedom
Residual deviance: 1501.3 on 1662 degrees of freedom
AIC: 1505.3

Number of Fisher Scoring iterations: 4

```
1 library(epiDisplay)  
2 logistic.display(logreg)
```

Logistic regression predicting case

	OR (95%CI)
P(Wald's test)	P(LR-test)
glucimp (cont. var.)	0.22 (0.17,0.28)
< 0.001	< 0.001

Log-likelihood = -750.6533
No. of observations = 1664
AIC value = 1505.3066

OR
compar normal GT to impaired GT

Learning Objectives

1. Identify cases when it is appropriate to use risk difference, relative risk, or odds ratios
2. Expand work on contingency tables to evaluate the agreement or reproducibility using Cohen's Kappa

Relationship Between RR and OR (1/2)

- Notice that odds ratio is not equivalent to relative risk (or risk ratio)

$$\frac{\hat{p}_1}{\hat{p}_2}$$

- However, when the **probability of “success” is small** (e.g., rare disease), \widehat{OR} is a nice approximation of \widehat{RR}

\hat{p}_1 & \hat{p}_2
small

$$\widehat{OR} = \frac{\hat{p}_1 / (1 - \hat{p}_1)}{\hat{p}_2 / (1 - \hat{p}_2)} = \widehat{RR} \cdot \frac{1 - \hat{p}_2}{1 - \hat{p}_1} \approx 1$$

- The fraction in the last term of the above expression approximately equals to 1.0 if \hat{p}_1 and \hat{p}_2 BOTH quite small (< 0.1)

- The \widehat{OR} and \widehat{RR} are not very close to each other in SHS: diabetes not a rare disease

- $\widehat{OR} = 4.65$
- $\widehat{RR} = 3.29$

Relationship Between RR and OR (2/2)

- An example where a disease rare over the whole sample (~1%), but ...
 - \widehat{OR} is not a good estimate of \widehat{RR} in "rare" disease

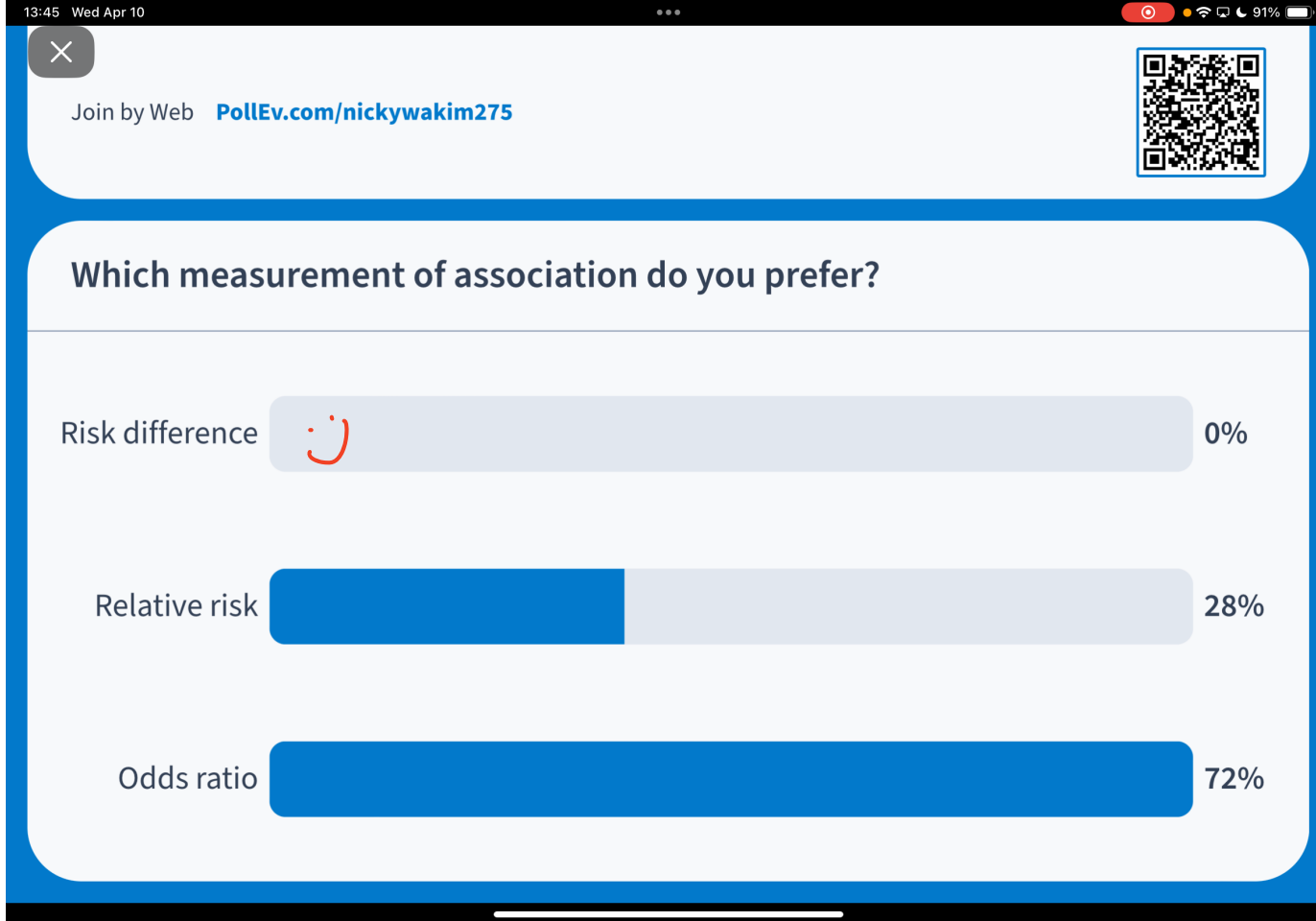
Risk factor status	Disease Status		Total	Risk
	<u>Disease</u>	No disease		
→ Exposed	<u>9</u>	<u>9</u>	18	<u>0.5</u> \hat{p}_1
Not exposed	1	981	982	0.00102 \hat{p}_2
<u>Total</u>	<u>10</u>	<u>990</u>	1000	0.01010 →

- \hat{p}_1 is 0.5: thus \widehat{OR} and \widehat{RR} are very different

$$\widehat{RR} = \frac{0.5}{0.00102} = 490 \text{ and } \widehat{OR} = \frac{0.5(1-0.5)}{0.00102(1-0.00102)} = 981$$

x close to 1
≈ 1

Poll Everywhere Question 2



link

$[0, 1]$

$\log()$ \uparrow
 \rightarrow $\log(p)$

$\left\{ \begin{array}{l} \text{logit}() \\ \log\left(\frac{p}{1-p}\right) \end{array} \right.$

$\log\left(\frac{p}{1-p}\right)$

$[0, \infty)$

①

RR in retrospective case-control study (1/3)

- In retrospective case-control studies: we **identify cases** (patients with the outcome), then select a number of controls (patients without the outcome)
 - Case-control study to require much smaller sample size than equivalent cohort studies
 - So we pick out the cases and controls first, then see if there is exposure
- However, the proportion of cases in the sample does not represent the proportion of cases in the population
 - RR compares probability of the outcome (case) for exposed and unexposed groups
 - Number of outcomes has been artificially inflated for case-control study

RR in retrospective case-control study (2/3)

- Assume a 1:2 case-control study summarized in below table:

Group	Outcome		Total
	<i>Case</i> Diseased	<i>Not Case</i> Not diseased	
Exposed	40 (n_{11})	40 (n_{12})	80 (n_{1+})
Not exposed	60 (n_{21})	160 (n_{22})	220 (n_{2+})
Total	100 (n_{+1})	200 (n_{+2})	300 (n)

↑

- Assume we compute the RR as if it is from a cohort study:

$$\widehat{RR} = \frac{\widehat{p}_1}{\widehat{p}_2} = \frac{n_{11}/n_{1+}}{n_{21}/n_{2+}} = \frac{40/80}{60/220} = 1.8333$$

RR in retrospective case-control study (3/3)

- In real world, the proportion of controls (not diseased) is typically much higher. Assume the table below shows the proportion in the population in a cohort study

Group	Outcome		Total
	Diseased <i>case</i>	Not diseased <i>ctrl</i>	
Exposed	400	4000	4400
Not exposed	600	16000	16600
Total	1000	20000	21000

- The estimated RR for the patient population is:

$$\widehat{RR} = \frac{\widehat{p}_1}{\widehat{p}_2} = \frac{400/4400}{600/16600} = \underline{2.5152}$$

Notes for Odds Ratios

- The OR is valid for
 - Case-control studies (where the RR is not appropriate)
 - Prospective cohort studies *RR*
 - Cross-sectional studies → *RR depends on pros/retro and inflation of cases*
- It can be interpreted either as...
 - Odds of event for exposed vs. unexposed individuals, or
 - Odds of exposure for individuals with vs. without the event of interest
- Pay attention to the numerator and denominator for the OR

OR in retrospective case-control study

- While we cannot estimate RR from a case-control study, we can still estimate OR for case-control study
 - OR does not require us to distinguish between the outcome variable and explanatory variable in the contingency table
 - AKA: Odds ratio of disease comparing exposed to not exposed is same as odds ratio of being exposed comparing diseased and not diseased

- For case-control study where the probability of having outcome is small, the \widehat{OR} is a nice approximation to \widehat{RR}

- For the 1:2 case-control table:

$$\widehat{OR} = \frac{40 \cdot 160}{40 \cdot 60} = 2.667$$

- Population cohort study: $\widehat{RR} = 2.5152$

Group	Outcome		Total
	Diseased	Not diseased	
Exposed	40 (n_{11})	40 (n_{12})	80 (n_{1+})
Not exposed	60 (n_{21})	160 (n_{22})	220 (n_{2+})
Total	100 (n_{+1})	200 (n_{+2})	300 (n)

$$\text{odds}_E = \frac{0.5}{1-0.5} \quad \widehat{OR} = \frac{\text{odds}_E}{\text{odds}_{NE}}$$

$$\text{odds}_{NE} = \frac{0.27}{1-0.27}$$

Which measurement should one use?

Measurement	Pros and Cons
Risk difference	<ul style="list-style-type: none">• Can provide additional information, but can be misleading on its own• Not the preferred measurement ✓
Risk ratio	<ul style="list-style-type: none">• Easy to interpret because is a ratio of probabilities• Cannot use in retrospective, case-control studies
Odds ratio	<ul style="list-style-type: none">• Adequate for all studies• Good estimate of RR for rare diseases• Not as easy to interpret or translate to clinical setting as RR• Most preferred by statisticians because integrated into logistic regression

Learning Objectives

1. Identify cases when it is appropriate to use risk difference, relative risk, or odds ratios

2. Expand work on contingency tables to evaluate the agreement or reproducibility using Cohen's Kappa

Measuring Agreement

- Still within the realm of contingency tables
- What if we are NOT looking at the association between two variables?

- What if we want to look at the agreement between two things?

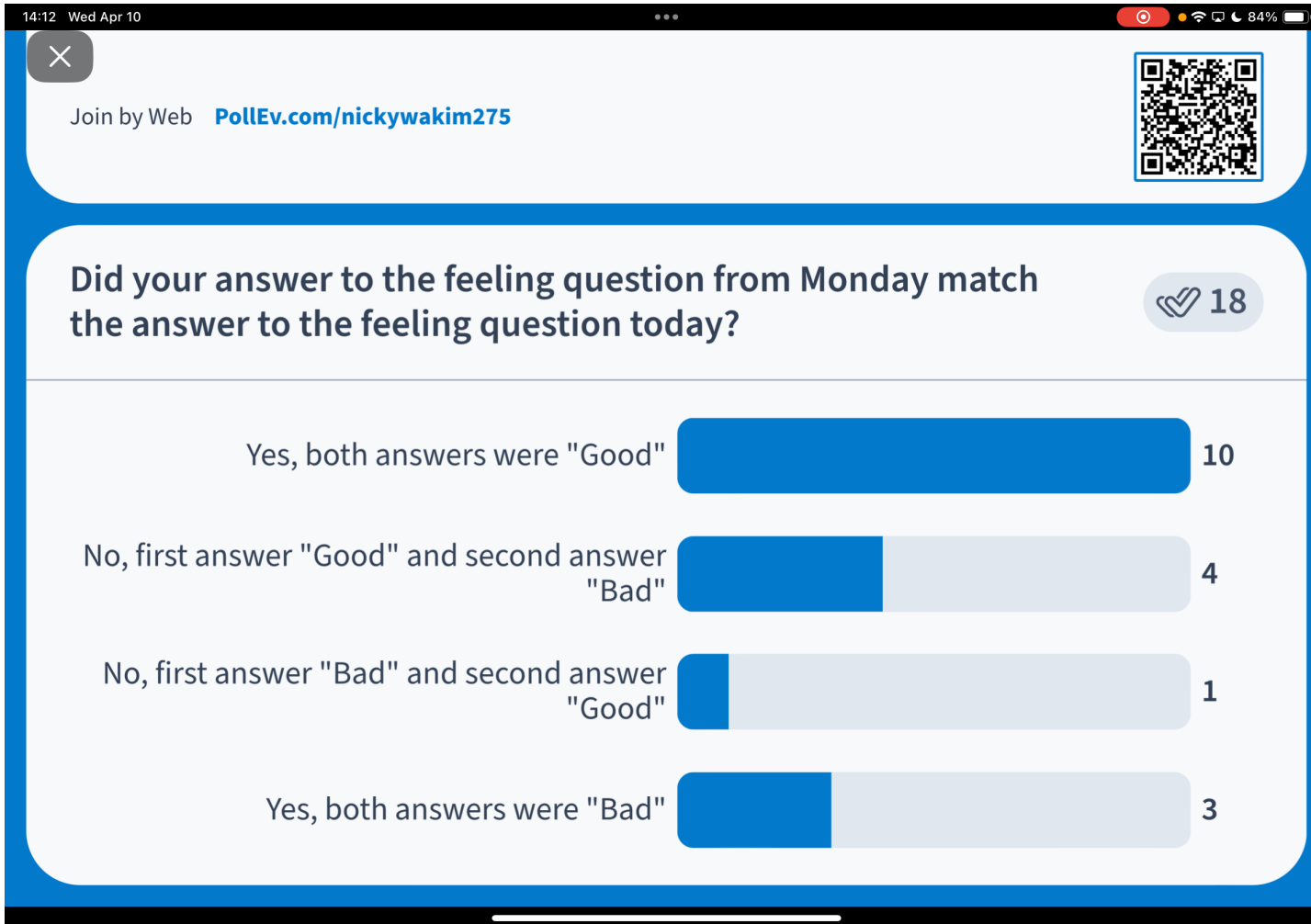
- Answers of same subjects for same survey taken at different times ✓
- Two different radiologists' assessment of the same X-ray

- Cohen's Kappa statistics: widely used as a measure of agreement

- Example: Reliability studies, interobserver agreement

↓
X-ray

Poll Everywhere Question 3



Let's get our mood data down!

Monday's response	Wednesday's response		Total
	Good	Bad	
Good	<u>100</u>	40	140
Bad	10	<u>30</u>	40
Total	110	70	180

if only diag counts: $\hat{K} = -1$

if only off diag $\hat{K} = 1$

Measuring Agreement

- If **perfect agreement** among the two raters/surveys:
 - We would expect nonzero entries only in the diagonal cells of the table
- p_o is the observed proportion of complete agreement (concordance)
- p_E is the expected proportion of complete agreement if the agreement is just due to chance
- If the p_o is much greater than p_E , then the agreement level is high.
 - Otherwise, the agreement level is low
- Cohen's Kappa is based on the difference between p_o and p_E :

$$\hat{\kappa} = \frac{p_o - p_E}{1 - p_E}$$

- $\hat{\kappa} = 0$: No agreement between surveys/raters other than what would be expected by chance
- $\hat{\kappa} = 1$: Complete agreement

Measuring Agreement: Cohen's Kappa

- Point estimate:

$$\hat{\kappa} = \frac{p_o - p_E}{1 - p_E}$$

- With $\underline{p_o} = \frac{\sum_i n_{ii}}{n}$ (sum of diagonals divided by total)
- With $\underline{p_E} = \sum_i a_i b_i$
- With range of point estimate from $\underline{[-1, 1]}$

- Approximate standard error:

$$\rightarrow SE_{\hat{\kappa}} = \sqrt{\frac{1}{n(1 - p_e)^2} \left\{ p_e^2 + p_e - \sum_i [a_i b_i (a_i + b_i)] \right\}}$$

- 95% Wald confidence interval for $\hat{\kappa}$:

→ What's $\sum_i a_i b_i$?

For i responses (row/columns), a_i is proportion of i response category in first survey and b_i is proportion of i response category in second survey (we'll show this in the example)

$$\hat{\kappa} \pm 1.96 \cdot SE_{\hat{\kappa}}$$

Example: Our moods (1/3)

Agreement of surveys

Compute the point estimate and 95% confidence interval for the agreement between our Monday and Wednesday moods.

Monday's response	Wednesday's response		Total
	Good	Bad	
Good	100	40	140
Bad	10	30	40
Total	110	70	180

Needed steps:

1. Compute the kappa statistic
2. Find confidence interval of kappa
3. Interpret the estimate

Example: Our moods (2/3)

Agreement of surveys

Compute the point estimate and 95% confidence interval for the agreement between our Monday and Wednesday moods.

Monday's response	Wednesday's response		Total
	Good	Bad	
Good	100	40	140
Bad	10	30	40
Total	110	70	180

Needed steps:

1/2. Compute the kappa statistic and find confidence interval of kappa

```
1 library(epiR)      100 40 10 30
2 moods = matrix(c(13, 9, 6, 24), nrow = 2, byrow = T)
3 epi.kappa(moods, method = "cohen")$kappa
```

```
      est      se      lower      upper
1 0.3981481 0.131082 0.1412321 0.6550642
   0.366      0.216      0.515
```

Example: Our moods (3/3)

Agreement of surveys

Compute the point estimate and 95% confidence interval for the agreement between our Monday and Wednesday moods.

Monday's response	Wednesday's response		Total
	Good	Bad	
Good			
Bad			
Total			

Needed steps:

3. Interpret the estimate

The kappa statistic is 0.366 (95% CI: 0.217, 0.515), indicating poor agreement.

Since the 95% confidence interval does not contain 0, we do not have sufficient evidence that there is poor agreement between our mood on Monday and our mood on Wednesday.

Measuring Agreement: Observed Kappas

- Guidelines for evaluating Kappa (Rosner TB)

- Excellent agreement if $\hat{\kappa} \geq 0.75$
- Fair to good agreement if $0.4 < \hat{\kappa} < 0.75$
- Poor agreement if $\hat{\kappa} \leq 0.4$

clinical meaningfulness

If $\hat{\kappa} < 0$, suggest agreement less than by chance

↳ discordance
disagreement

Learning Objectives

1. Identify cases when it is appropriate to use risk difference, relative risk, or odds ratios
2. Expand work on contingency tables to evaluate the agreement or reproducibility using Cohen's Kappa

Measurement of Association So Far

- Used contingency tables to test and measure association between two variables
 - Categorical outcome variable (Y)
 - One categorical explanatory variable (X)
- We looked at risk difference, risk ratio, and odds ratio to measure association
- Such an association is called crude association
 - No adjustment for possible confounding factors
 - Also called marginal association
- But we cannot expand analysis based on contingency tables past 3 variables
 - We can get into stratified contingency tables to bring in a 3rd variable
 - But I don't think it's worth it because regression can bring in (adjust for) many variables

**Extra example in case the mood example fails
beautifully**

Just in case our data doesn't work out: Beef Consumption in Survey

A diet questionnaire was mailed to 537 female American nurses on two separate occasions several months apart. The questions asked included the quantities eaten of more than 100 separate food items. The data from the two surveys for the amount of beef consumption are presented in the below table. How can reproducibility of response for the beef-consumption data be quantified?

Survey 1	Survey 2		Total
	≤ 1 serving/week	> 1 serving/week	
≤ 1 serving/week	136	92	228
> 1 serving/week	69	240	309
Total	205	332	537

Example: Beef Consumption in Survey (1/3)

Agreement of surveys

Compute the point estimate and 95% confidence interval for the agreement between beef consumption surveys. Similar to question: Are results reproducible for the beef-consumption in the survey?

Survey 1	Survey 2		Total
	≤ 1 serving/week	> 1 serving/week	
≤ 1 serving/week	136	92	228
> 1 serving/week	69	240	309
Total	205	332	537

Needed steps:

1. Compute the kappa statistic
2. Find confidence interval of kappa
3. Interpret the estimate

Example: Beef Consumption in Survey (2/3)

Agreement of surveys

Compute the point estimate and 95% confidence interval for the agreement between beef consumption surveys. Similar to question: Are results reproducible for the beef-consumption in the survey?

Survey 1	Survey 2		Total
	≤ 1 serving/week	> 1 serving/week	
≤ 1 serving/week	136	92	228
> 1 serving/week	69	240	309
Total	205	332	537

Needed steps:

1/2. Compute the kappa statistic and find confidence interval of kappa

```
1 library(epiR)
2 beef = matrix(c(136, 92, 69, 240), nrow = 2, byrow = T)
3 epi.kappa(beef, method = "cohen")$kappa
```

	est	se	lower	upper
1	0.3781906	0.04100635	0.2978196	0.4585616

Example: Beef Consumption in Survey (3/3)

Agreement of surveys

Compute the point estimate and 95% confidence interval for the agreement between beef consumption surveys. Similar to question: Are results reproducible for the beef-consumption in the survey?

Survey 1	Survey 2		Total
	≤ 1 serving/week	> 1 serving/week	
≤ 1 serving/week	136	92	228
> 1 serving/week	69	240	309
Total	205	332	537

Needed steps:

3. Interpret the estimate

The kappa statistic is 0.378 (95% CI: 0.298, 0.459), indicating fair agreement.

Since the 95% confidence interval does not contain 0, we have sufficient evidence that there is fair agreement between the surveys for beef consumption. The survey is not reliably reproducible since we did not achieve excellent agreement.

