Meta Analyses: Benefits & Pitfalls

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Meta Analyses: Benefits and Pitfalls

Introduction

- In the last 10 years we have seen many papers using meta analysis in the dairy area
- Looking at various nutritional subjects
- Determining the value of different products
- This is a tool that has been used in the human medical & social sciences for many years
- Many recommendations have been made in human health based on these analyses (see Cochrane Collaboration @ cochrane.org)

Meta Analyses: Benefits and Pitfalls
Introduction

- We often have conflicting and confusing nutritional results when looking at several individual papers
- Meta analysis is a statistical tool that allows us to achieve an empirical and maybe more mechanistic understanding of the effects of a practice or product
- In an unbiased manner using a scientifically valid approach
- Our focus today is to show some positive results and outline some of the principles of valid meta analyses

Meta Analyses: Benefits and Pitfalls

Why Do a Meta-Analysis?

- We often have a substantial body of literature using a particular intervention
  - Changing a nutritional parameter
  - Inclusion of a feed component
- Doing a quantitative analysis we can obtain an estimate of
  - The average effect
  - The distribution around the effect
- Evaluate the variability or consistency in responses to the intervention
- Identify if evidence is probably missing

Meta Analyses: Benefits and Pitfalls

Why Do a Meta-Analysis?

- In practical terms
- We can provide a much better estimate of the likely overall effect of the intervention
  - With a confidence interval around the intervention
  - Also an assessment can be provided on the likelihood of seeing a response
  - This can also allow us to estimate the return on the investment

Meta Analyses: Benefits and Pitfalls

Why Do a Meta-Analysis?

- We will be able to better identify the factors affecting the response
- We can provide better guidelines as to which groups the intervention will provide an economic response
  - For example, close-up, fresh, high, late lactation
- We can provide the producer a better estimate of the effect of the intervention
- Give them confidence around the estimate
  - Where or when to apply the intervention for best effects

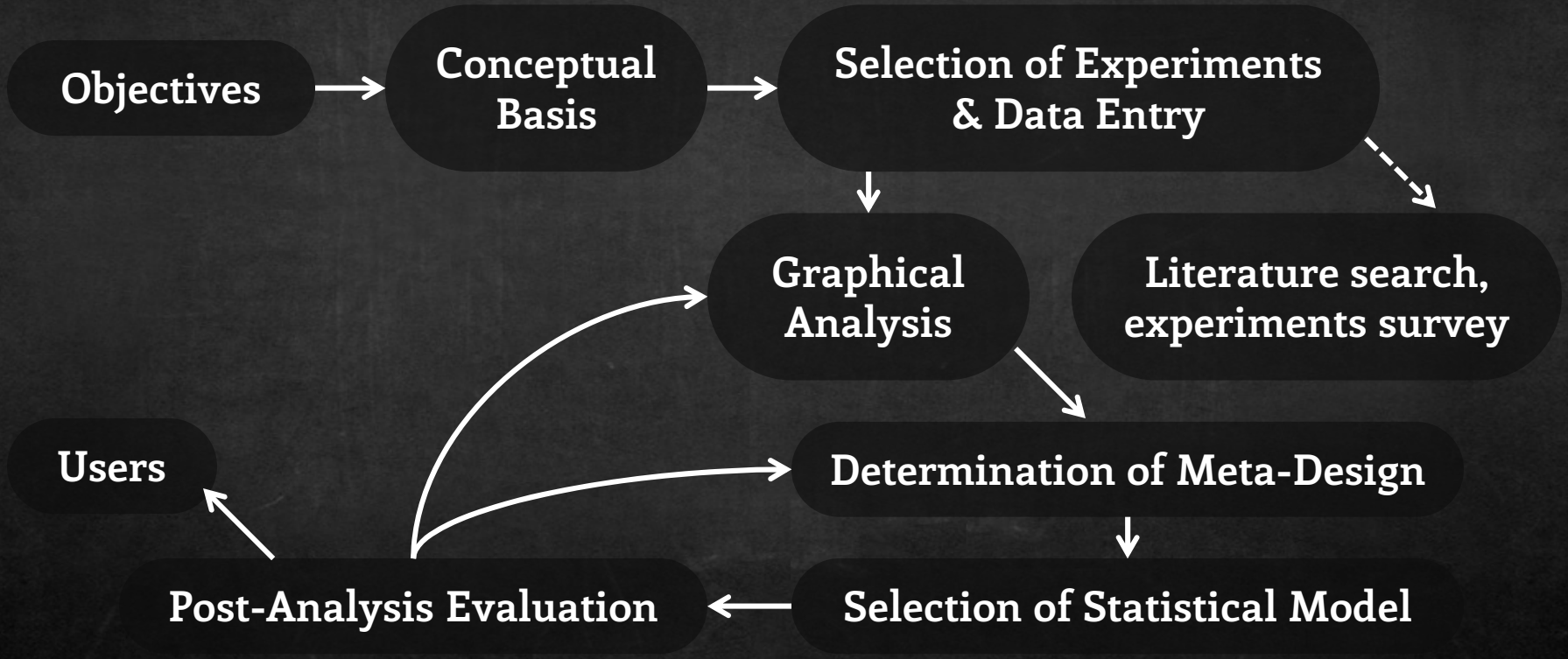
Meta Analyses: Benefits and Pitfalls

Why Do a Meta-Analysis?

- The analyses will also provide the basis to design experiments to answer new questions that were uncovered from the analyses – it is a research project in it's own right

Meta Analyses: Benefits and Pitfalls

Schematic Representation of the Meta-Analytic Process



Sauvant, Schmidely, Daudin and St-Pierre, 2008

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Selection of Studies to Use in Meta-Analyses

- If we are trying to understand the long term effects of an intervention on
  - Full Lactation, Early lactation, Transition
- Including studies with designs such as Latin squares is not suggested
  - Reduced variance will over-weight the studies
  - Unfortunately we are many times forced into the use of these studies due to a limited database for the intervention
- Randomized controlled studies preferred

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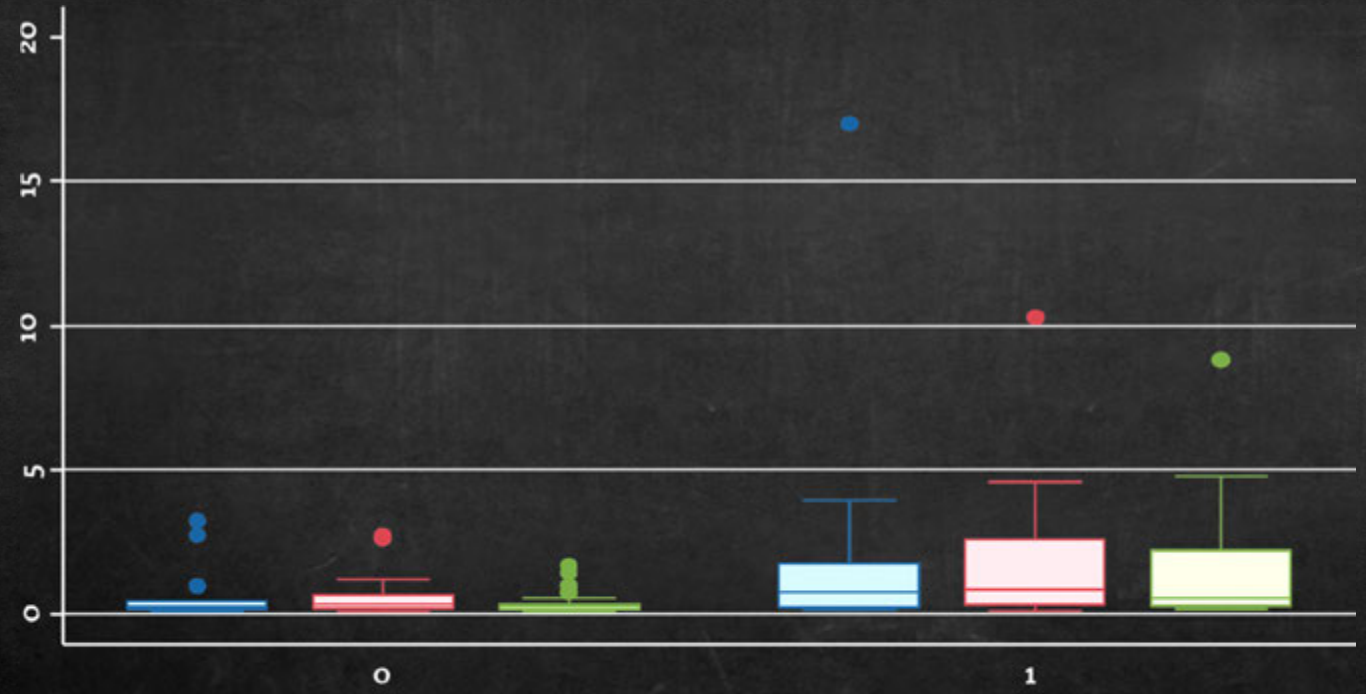
Differences in Weights from Randomized Controlled Studies[0] and Latin Squares[1]



Sniffen, et. Al (unpublished)

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Positive and Negative Attributes of Classical and Other Meta-Analyses

Positive Attributes	Classical	Other
A clear hypothesis	✓	✓
Comprehensive literature search at least three databases	✓	✓
Clearly defined criteria for inclusion or exclusion	✓	✓
Tables detailing studies extracted and data obtained	✓	✓
Measures of outcome analyzed	Odds ratios (OR), relative risk (RR), continuous variables, hazard ratios (from survival analysis), incidence rates	Continuous variables can be extended to logistic regression methods

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Positive and Negative Attributes of Classical and Other Meta-Analyses

Positive Attributes	Classical	Other
Outcomes	Pooled OR, RR, standard mean difference, meta regression, confidence intervals	Weighted, regression means, confidence intervals
Estimates of Heterogeneity (sources of variation)	✓	✓
Examination of Heterogeneity	✓	✓
Sensitivity analysis of powerful studies	✓	✓
Publication bias	Funnel plots	

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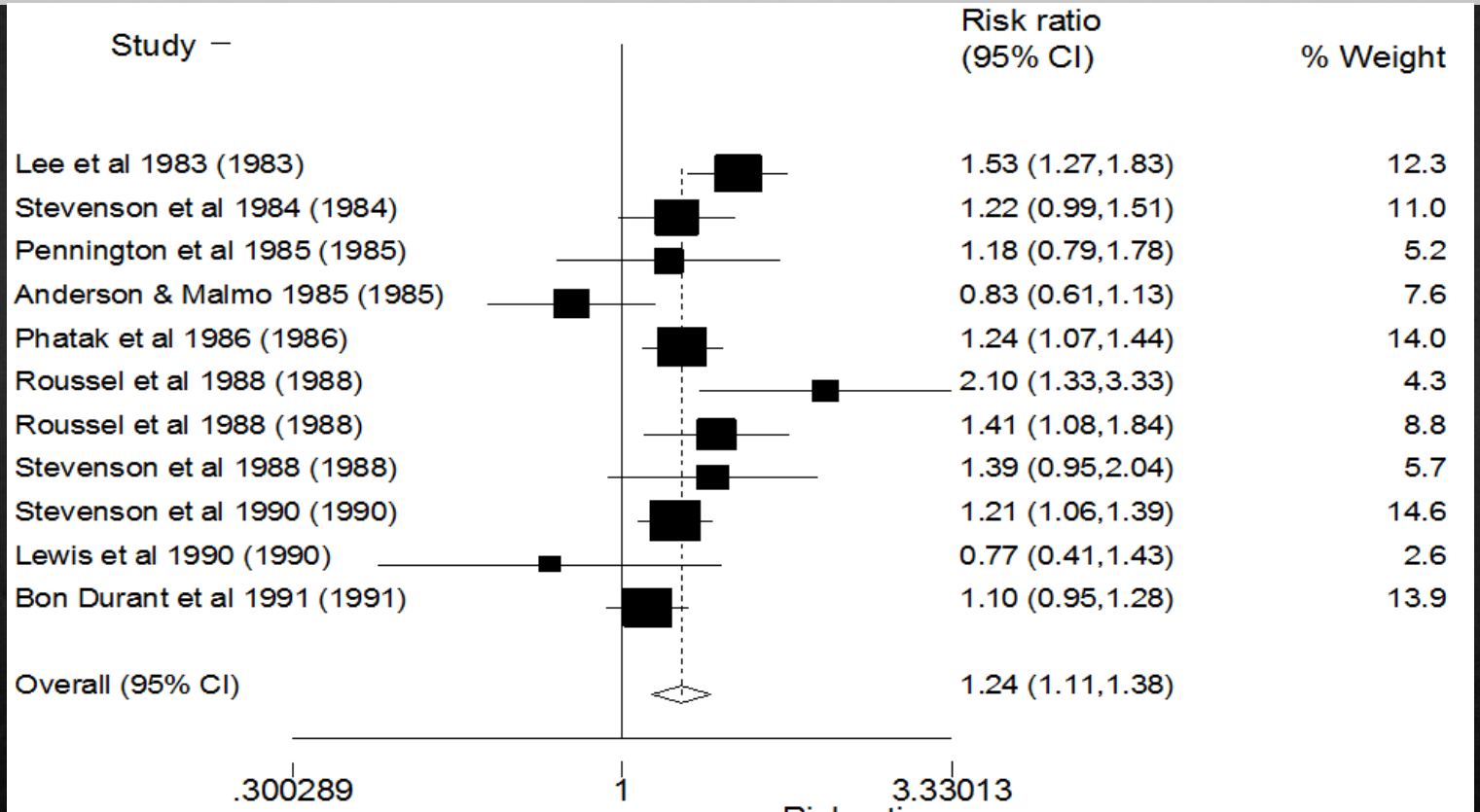
Forest Plot – Effect of GnRH on the RR for Pregnancy in Repeat Breeder Cows



Morgan and Lean, 1993

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Summary - GnRH

- A producer can use GnRH as an intervention that will provide a 24% increased chance of repeat breeder cows becoming pregnant
- Looking at the variance there were 4 studies that there was not a significant difference
- What other information can be obtained from these studies that would help the producer make a more informed decision for the use of GnRH?
- Would there be an opportunity get a better understanding of the biology to design new studies?

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Use of the Standardized Mean Difference (SMD)

- Useful in continuous trials such a milk production.
- SMD = (**Exp.** group mean – **control** group mean)/pooled SD of the groups
  - Accounts for study size and variance
- Can pool different measurement scales for the same measure

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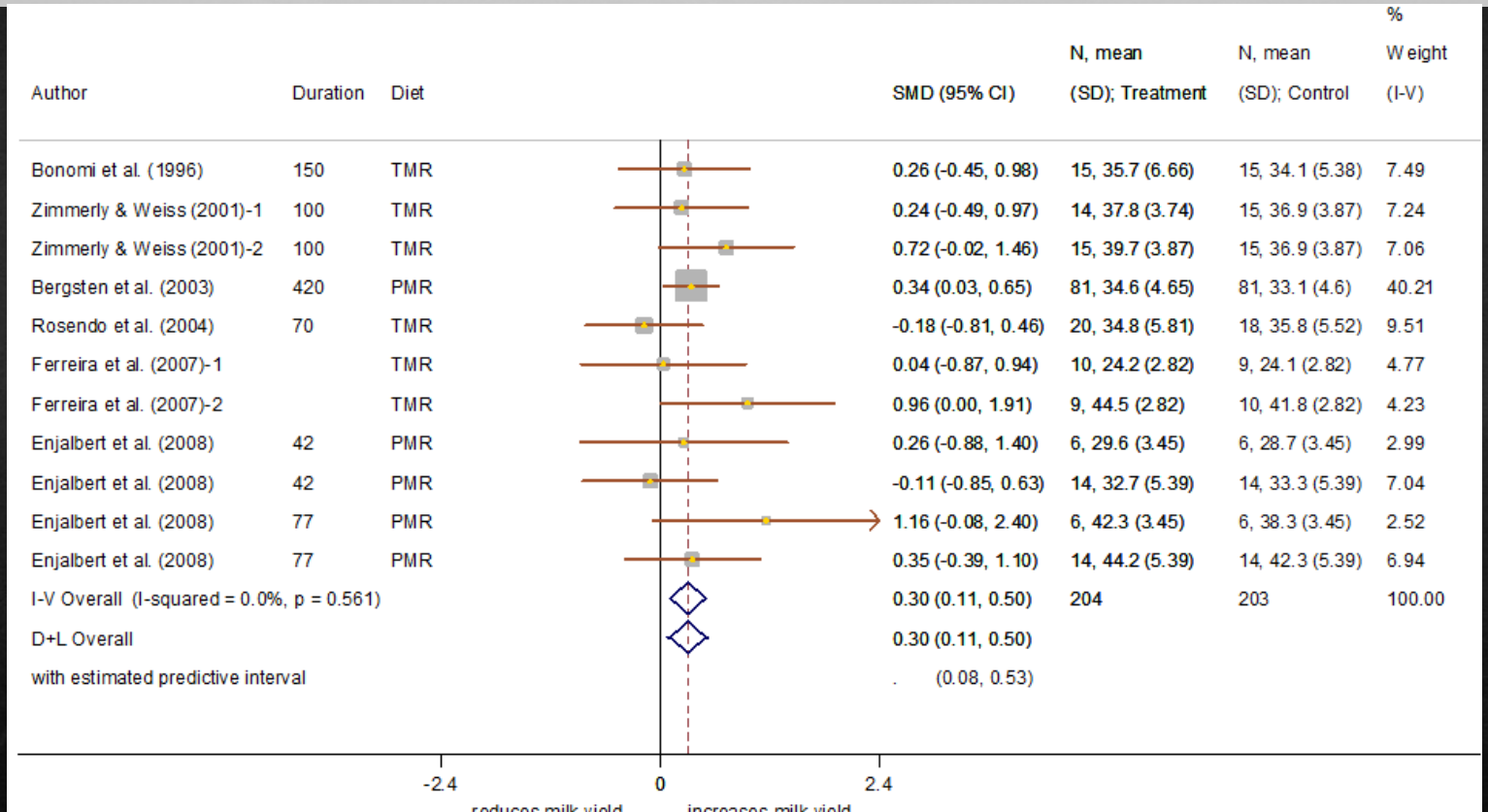
Forest Plot – SMD – Milk Production of Cows Supplemented with Biotin with Other Cows



Lean and Rabiee (2010)

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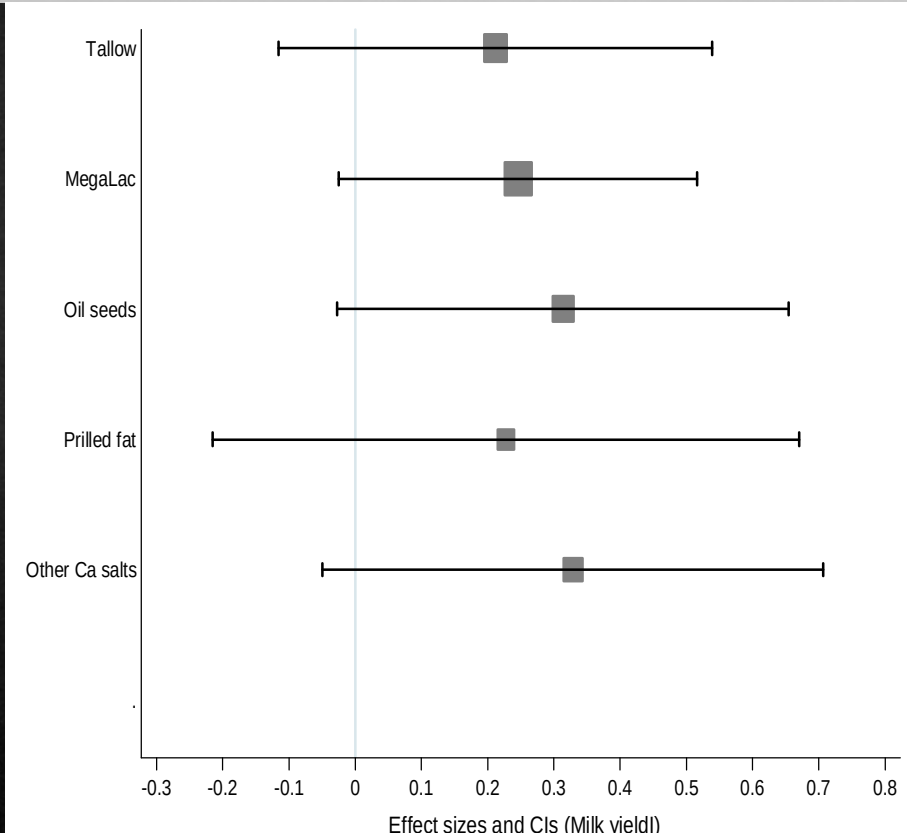
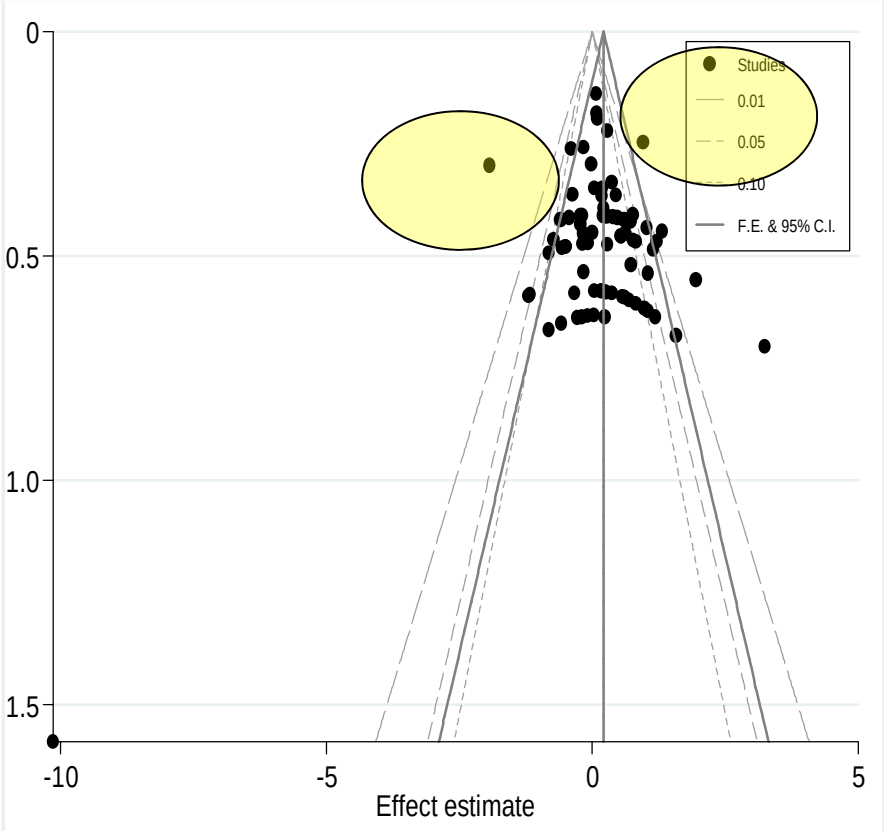
Forest and Funnel Plots:
Milk yield response to fats (Rabiee et al 2012)





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The Funnel Plot Use

- Used to examine publication bias
- The assumption is that the largest studies will be near the average effect
- The small studies will be spread on both sides of the average effect
  - Even distribution demonstrates no bias
  - An asymmetric distribution suggests bias
    - A relationship to study size and treatment effect

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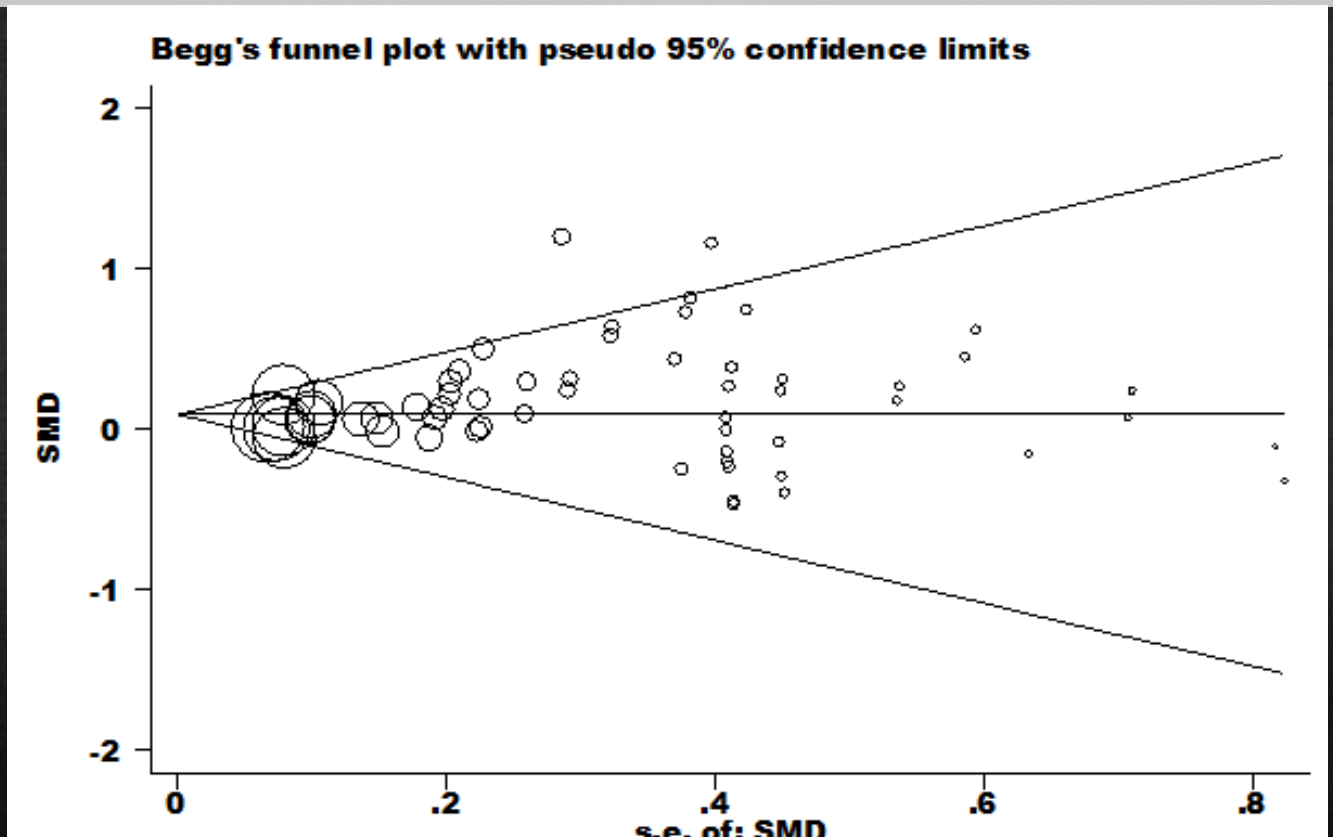
Begg's Funnel Plot – Effect of Monensin on Milk Yield



Duffield, et. Al (2008)

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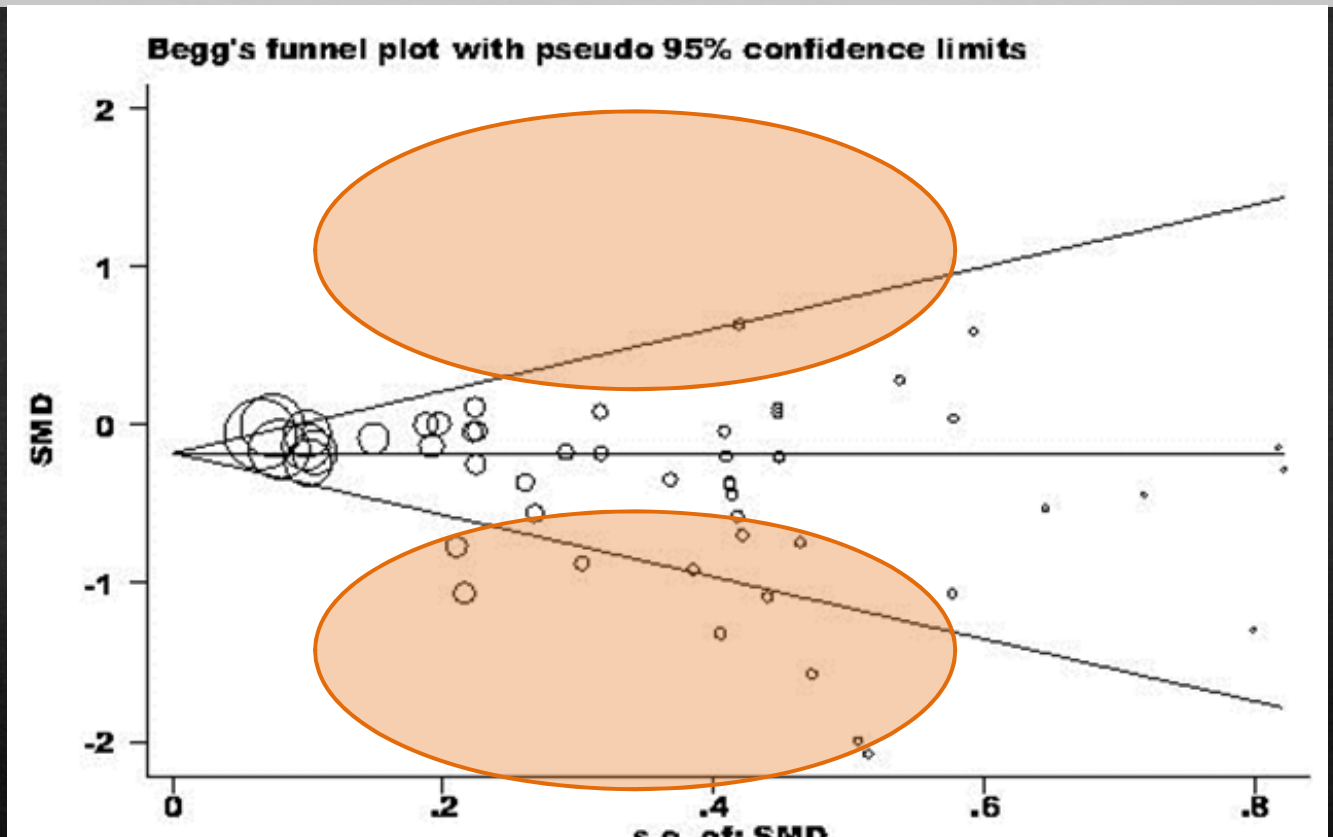
Begg's Funnel Plot – SE of the SMD – Effect of Monensin on Milk Fat Percentage



Duffield, et. Al (2008)

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Monesin Milk Fat Bias

- In this case there are a large number of negative small studies, but very few small positive studies –
- There are two possibilities:
  - That the small positive studies do not exist
  - That they exist, but were not published
    - Either because they were small, different and rejected by a journal
    - OR that the scientists decided to keep them in ‘the top drawer’ and did not submit.

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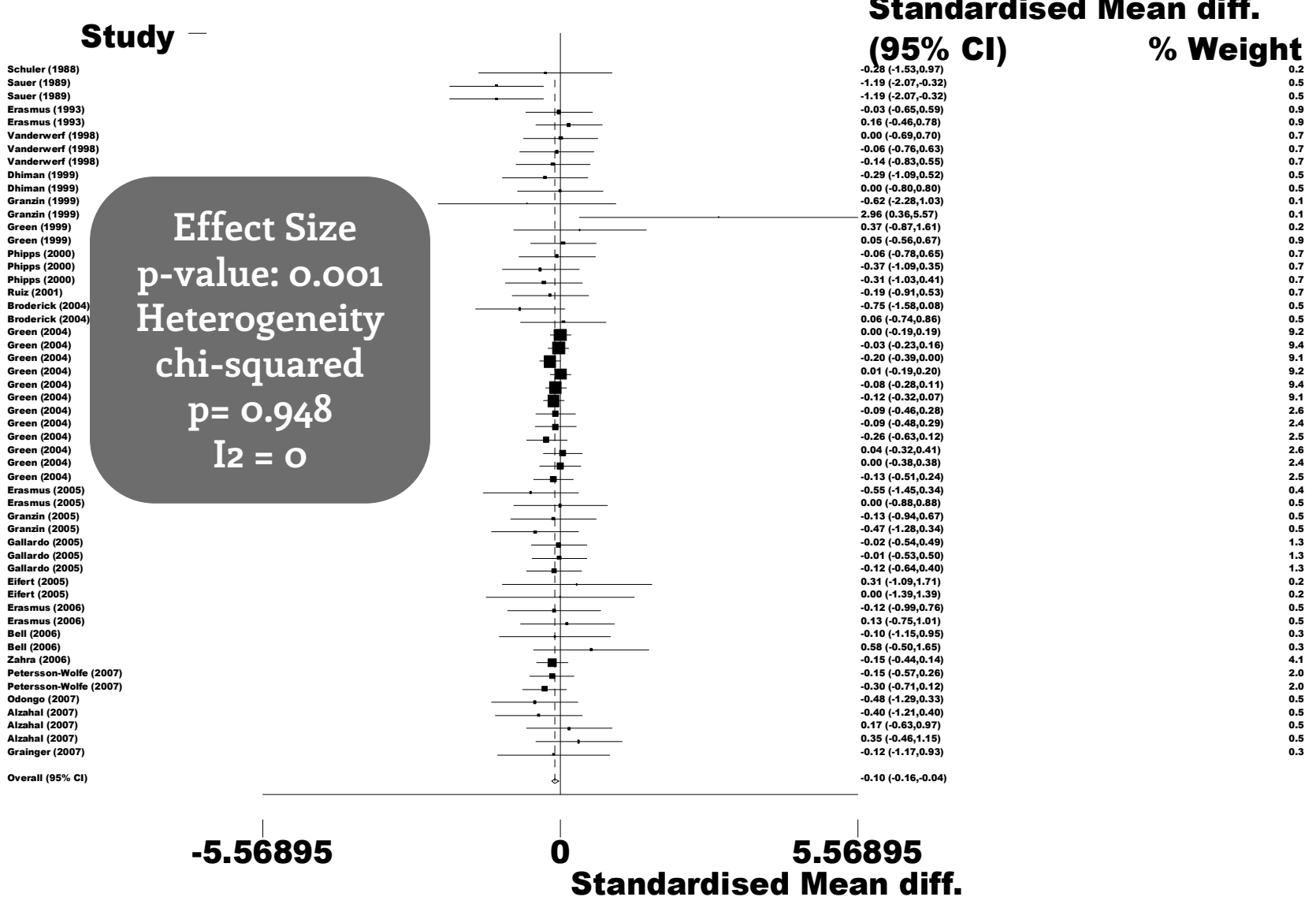
Heterogeneity – Variability

- Refers to the consistency of studies
- We consider this to be critical – the most important part of meta-analysis
- How is this measured – I2 (0 to 30 low; 30 -50 moderate, > 50 high) (based on Chi2 test)
- We know a lot about average responses! *Considerable progress will be made by understanding causes of variation*

Meta Analyses: Benefits and Pitfalls
Exploring Heterogeneity

- If clinical diversity (study/design or environment) causes statistical heterogeneity, meta-regression can be conducted
- Sub-group analysis can be used
  (Note: care if still heterogeneous)
- If the clinical diversity does not cause statistical heterogeneity then the point estimates are robust – i.e. really consistent results across a number of studies and environments


Study
Standardised Mean diff.
(95% CI)
% Weight
Schuler (1988) -0.28 (-1.53,0.97) 0.2
Sauer (1989) -1.19 (-2.07,-0.32) 0.5
Sauer (1989) -1.19 (-2.07,-0.32) 0.5
Erasmus (1993) -0.03 (-0.65,0.59) 0.9
Erasmus (1993) 0.16 (-0.46,0.78) 0.9
Vanderwerf (1998) 0.00 (-0.69,0.70) 0.7
Vanderwerf (1998) -0.06 (-0.76,0.63) 0.7
Vanderwerf (1998) -0.14 (-0.83,0.55) 0.7
Dhiman (1999) -0.29 (-1.09,0.52) 0.5
Dhiman (1999) 0.00 (-0.80,0.80) 0.5
Granzin (1999) -0.62 (-2.28,1.03) 0.1
Granzin (1999) 2.96 (0.36,5.57) 0.1
Green (1999) 0.37 (-0.87,1.61) 0.2
Green (1999) 0.05 (-0.56,0.67) 0.9
Phipps (2000) -0.06 (-0.78,0.65) 0.7
Phipps (2000) -0.37 (-1.09,0.35) 0.7
Phipps (2000) -0.31 (-1.03,0.41) 0.7
Ruiz (2001) -0.19 (-0.91,0.53) 0.7
Broderick (2004) -0.75 (-1.58,0.08) 0.5
Broderick (2004) 0.06 (-0.74,0.86) 0.5
Green (2004) 0.00 (-0.19,0.19) 9.2
Green (2004) -0.03 (-0.23,0.16) 9.4
Green (2004) -0.20 (-0.39,0.00) 9.1
Green (2004) 0.01 (-0.19,0.20) 9.2
Green (2004) -0.08 (-0.28,0.11) 9.4
Green (2004) -0.12 (-0.32,0.07) 9.1
Green (2004) -0.09 (-0.46,0.28) 2.6
Green (2004) -0.09 (-0.48,0.29) 2.4
Green (2004) -0.26 (-0.63,0.12) 2.5
Green (2004) 0.04 (-0.32,0.41) 2.6
Green (2004) 0.00 (-0.38,0.38) 2.4
Green (2004) -0.13 (-0.51,0.24) 2.5
Erasmus (2005) -0.55 (-1.45,0.34) 0.4
Erasmus (2005) 0.00 (-0.88,0.88) 0.5
Granzin (2005) -0.13 (-0.94,0.67) 0.5
Granzin (2005) -0.47 (-1.28,0.34) 0.5
Gallardo (2005) -0.02 (-0.54,0.49) 1.3
Gallardo (2005) -0.01 (-0.53,0.50) 1.3
Gallardo (2005) -0.12 (-0.64,0.40) 1.3
Eifert (2005) 0.31 (-1.09,1.71) 0.2
Eifert (2005) 0.00 (-1.39,1.39) 0.2
Erasmus (2006) -0.12 (-0.99,0.76) 0.5
Erasmus (2006) 0.13 (-0.75,1.01) 0.5
Bell (2006) -0.10 (-1.15,0.95) 0.3
Bell (2006) 0.58 (-0.50,1.65) 0.3
Zahra (2006) -0.15 (-0.44,0.14) 4.1
Petersson-Wolfe (2007) -0.15 (-0.57,0.26) 2.0
Petersson-Wolfe (2007) -0.30 (-0.71,0.12) 2.0
Odongo (2007) -0.48 (-1.29,0.33) 0.5
Alzahal (2007) -0.40 (-1.21,0.40) 0.5
Alzahal (2007) 0.17 (-0.63,0.97) 0.5
Alzahal (2007) 0.35 (-0.46,1.15) 0.5
Grainger (2007) -0.12 (-1.17,0.93) 0.3
Overall (95% CI) -0.10 (-0.16,-0.04)
Effect Size
p-value: 0.001
Heterogeneity
chi-squared
p= 0.948
I2 = 0
-5.56895
0
5.56895
Standardised Mean diff.

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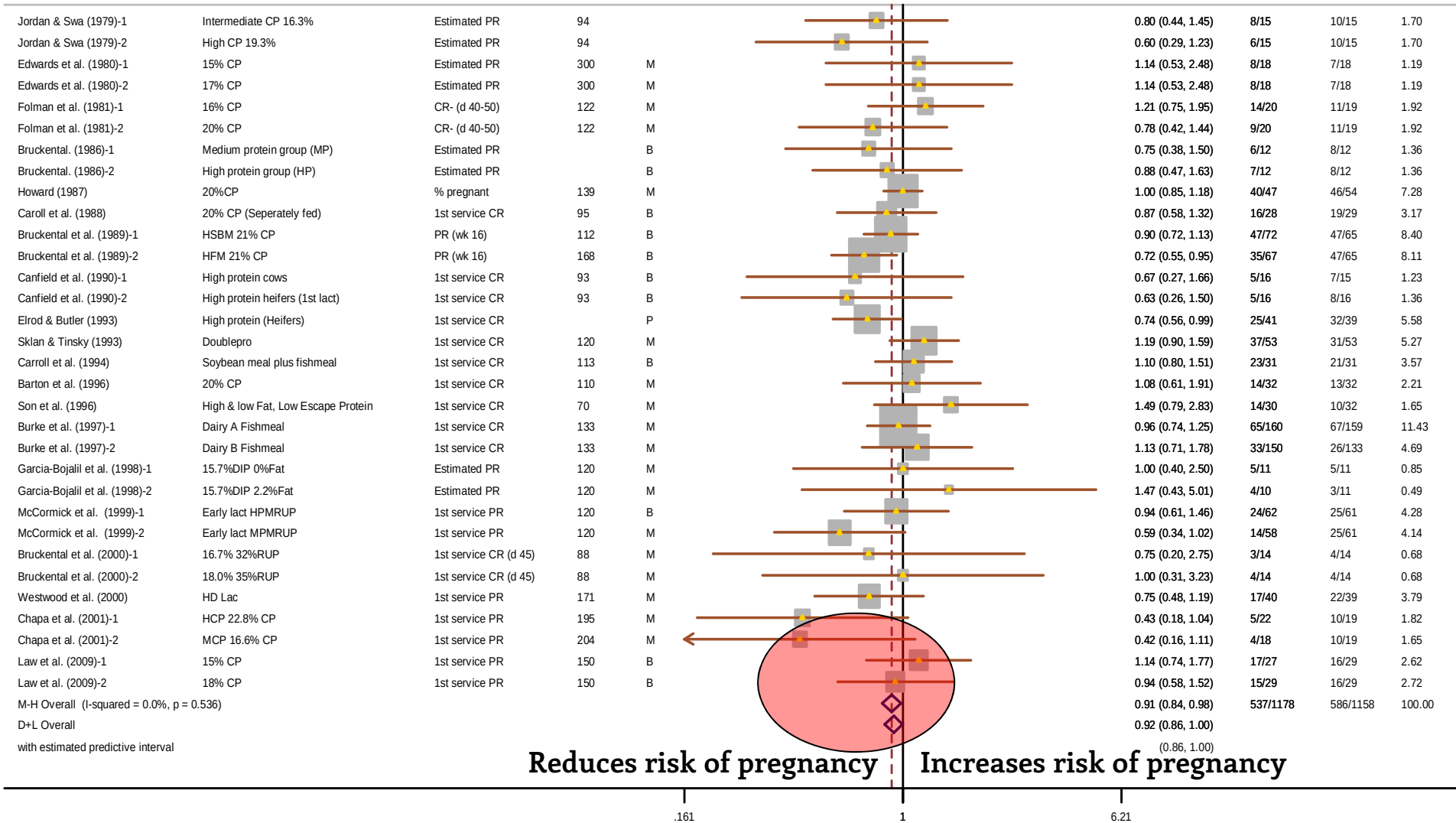
Meta-Regression

- To investigate whether heterogeneity is related to specific characteristics of the studies (e.g. dose rate)
- To investigate whether particular covariates (potential ‘effect modifier’) explain any of the heterogeneity
- To identify evidence of different effects in subgroups

Meta Analyses: Benefits and Pitfalls

Protein and Fertility (Lean et al, 2012)

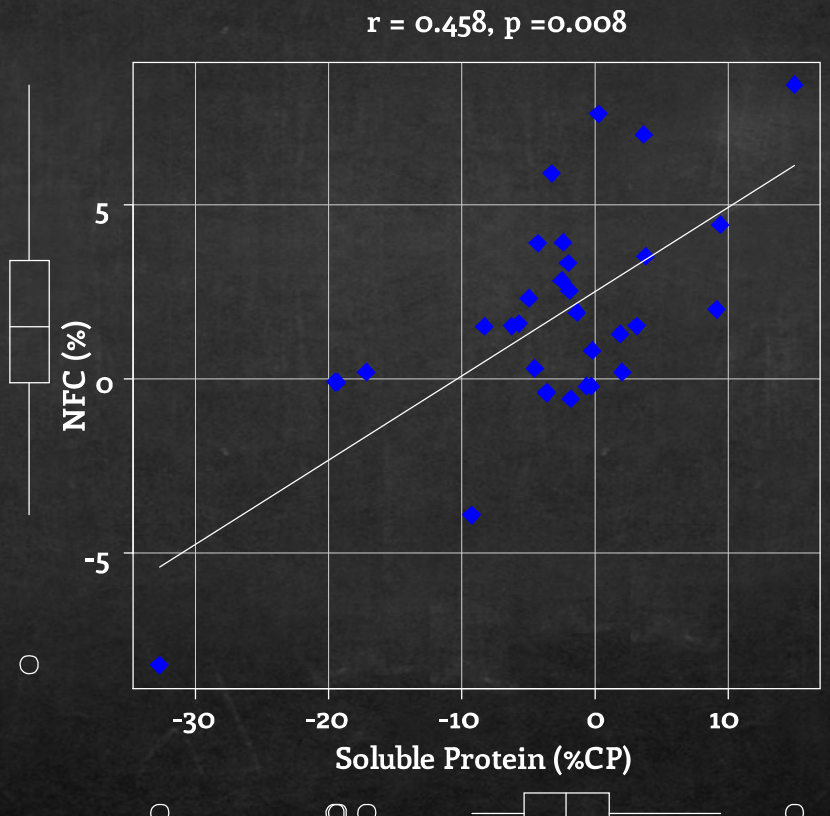
- This study highlighted two important matters
- Individual nutrition and fertility studies are almost inevitably confounded e.g. increase the protein meal do you change the NFC?
- There is benefit in exploring even consistent findings with meta-regression


Study
Diets
Preg
Duration
Parity
RR (95% CI)
Events, Treatment
Events, Control
Weight (M-H)
Jordan & Swa (1979)-1 Intermediate CP 16.3% Estimated PR 94 0.80 (0.44, 1.45) 8/15 10/15 1.70
Jordan & Swa (1979)-2 High CP 19.3% Estimated PR 94 0.60 (0.29, 1.23) 6/15 10/15 1.70
Edwards et al. (1980)-1 15% CP Estimated PR 300 M 1.14 (0.53, 2.48) 8/18 7/18 1.19
Edwards et al. (1980)-2 17% CP Estimated PR 300 M 1.14 (0.53, 2.48) 8/18 7/18 1.19
Folman et al. (1981)-1 16% CP CR- (d 40-50) 122 M 1.21 (0.75, 1.95) 14/20 11/19 1.92
Folman et al. (1981)-2 20% CP CR- (d 40-50) 122 M 0.78 (0.42, 1.44) 9/20 11/19 1.92
Bruckental. (1986)-1 Medium protein group (MP) Estimated PR B 0.75 (0.38, 1.50) 6/12 8/12 1.36
Bruckental. (1986)-2 High protein group (HP) Estimated PR B 0.88 (0.47, 1.63) 7/12 8/12 1.36
Howard (1987) 20%CP % pregnant 139 M 1.00 (0.85, 1.18) 40/47 46/54 7.28
Caroll et al. (1988) 20% CP (Seperately fed) 1st service CR 95 B 0.87 (0.58, 1.32) 16/28 19/29 3.17
Bruckental et al. (1989)-1 HSBM 21% CP PR (wk 16) 112 B 0.90 (0.72, 1.13) 47/72 47/65 8.40
Bruckental et al. (1989)-2 HFM 21% CP PR (wk 16) 168 B 0.72 (0.55, 0.95) 35/67 47/65 8.11
Canfield et al. (1990)-1 High protein cows 1st service CR 93 B 0.67 (0.27, 1.66) 5/16 7/15 1.23
Canfield et al. (1990)-2 High protein heifers (1st lact) 1st service CR 93 B 0.63 (0.26, 1.50) 5/16 8/16 1.36
Elrod & Butler (1993) High protein (Heifers) 1st service CR P 0.74 (0.56, 0.99) 25/41 32/39 5.58
Sklan & Tinsky (1993) Doublepro 1st service CR 120 M 1.19 (0.90, 1.59) 37/53 31/53 5.27
Carroll et al. (1994) Soybean meal plus fishmeal 1st service CR 113 B 1.10 (0.80, 1.51) 23/31 21/31 3.57
Barton et al. (1996) 20% CP 1st service CR 110 M 1.08 (0.61, 1.91) 14/32 13/32 2.21
Son et al. (1996) High & low Fat, Low Escape Protein 1st service CR 70 M 1.49 (0.79, 2.83) 14/30 10/32 1.65
Burke et al. (1997)-1 Dairy A Fishmeal 1st service CR 133 M 0.96 (0.74, 1.25) 65/160 67/159 11.43
Burke et al. (1997)-2 Dairy B Fishmeal 1st service CR 133 M 1.13 (0.71, 1.78) 33/150 26/133 4.69
Garcia-Bojalil et al. (1998)-1 15.7%DIP 0%Fat Estimated PR 120 M 1.00 (0.40, 2.50) 5/11 5/11 0.85
Garcia-Bojalil et al. (1998)-2 15.7%DIP 2.2%Fat Estimated PR 120 M 1.47 (0.43, 5.01) 4/10 3/11 0.49
McCormick et al. (1999)-1 Early lact HPMRUP 1st service PR 120 B 0.94 (0.61, 1.46) 24/62 25/61 4.28
McCormick et al. (1999)-2 Early lact MPMRUP 1st service PR 120 M 0.59 (0.34, 1.02) 14/58 25/61 4.14
Bruckental et al. (2000)-1 16.7% 32%RUP 1st service CR (d 45) 88 M 0.75 (0.20, 2.75) 3/14 4/14 0.68
Bruckental et al. (2000)-2 18.0% 35%RUP 1st service CR (d 45) 88 M 1.00 (0.31, 3.23) 4/14 4/14 0.68
Westwood et al. (2000) HD Lac 1st service PR 171 M 0.75 (0.48, 1.19) 17/40 22/39 3.79
Chapa et al. (2001)-1 HCP 22.8% CP 1st service PR 195 M 0.43 (0.18, 1.04) 5/22 10/19 1.82
Chapa et al. (2001)-2 MCP 16.6% CP 1st service PR 204 M 0.42 (0.16, 1.11) 4/18 10/19 1.65
Law et al. (2009)-1 15% CP 1st service PR 150 B 1.14 (0.74, 1.77) 17/27 16/29 2.62
Law et al. (2009)-2 18% CP 1st service PR 150 B 0.94 (0.58, 1.52) 15/29 16/29 2.72
M-H Overall (I-squared = 0.0%, p = 0.536) 0.91 (0.84, 0.98) 537/1178 586/1158 100.00
D+L Overall 0.92 (0.86, 1.00)
with estimated predictive interval (0.86, 1.00)
Reduces risk of pregnancy
Increases risk of pregnancy
.161
1
6.21

Meta Analyses: Benefits and Pitfalls

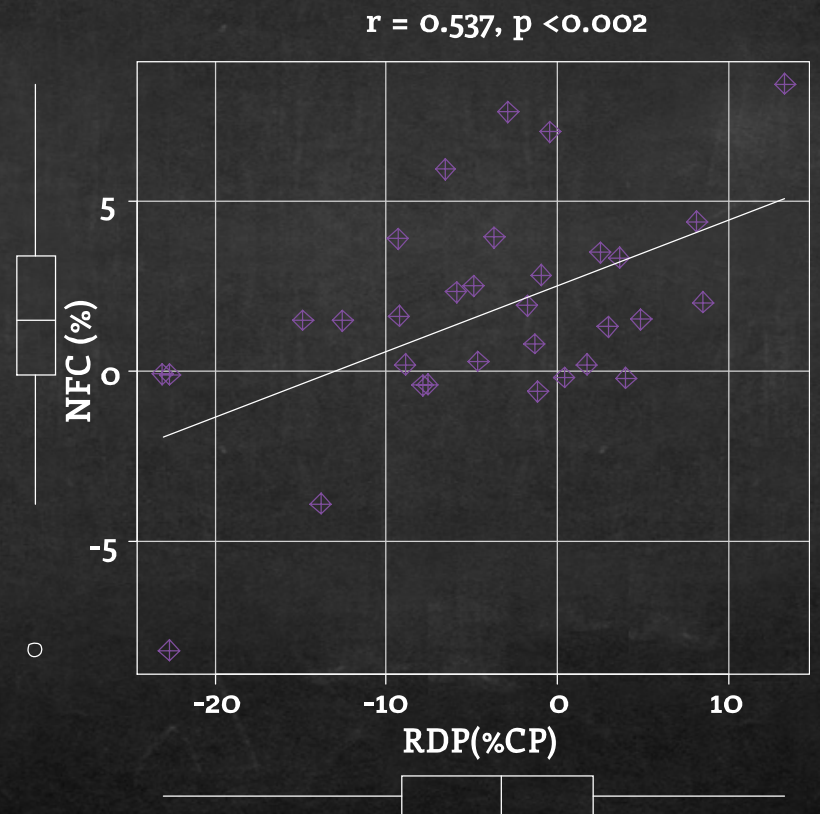
Protein and Reproduction

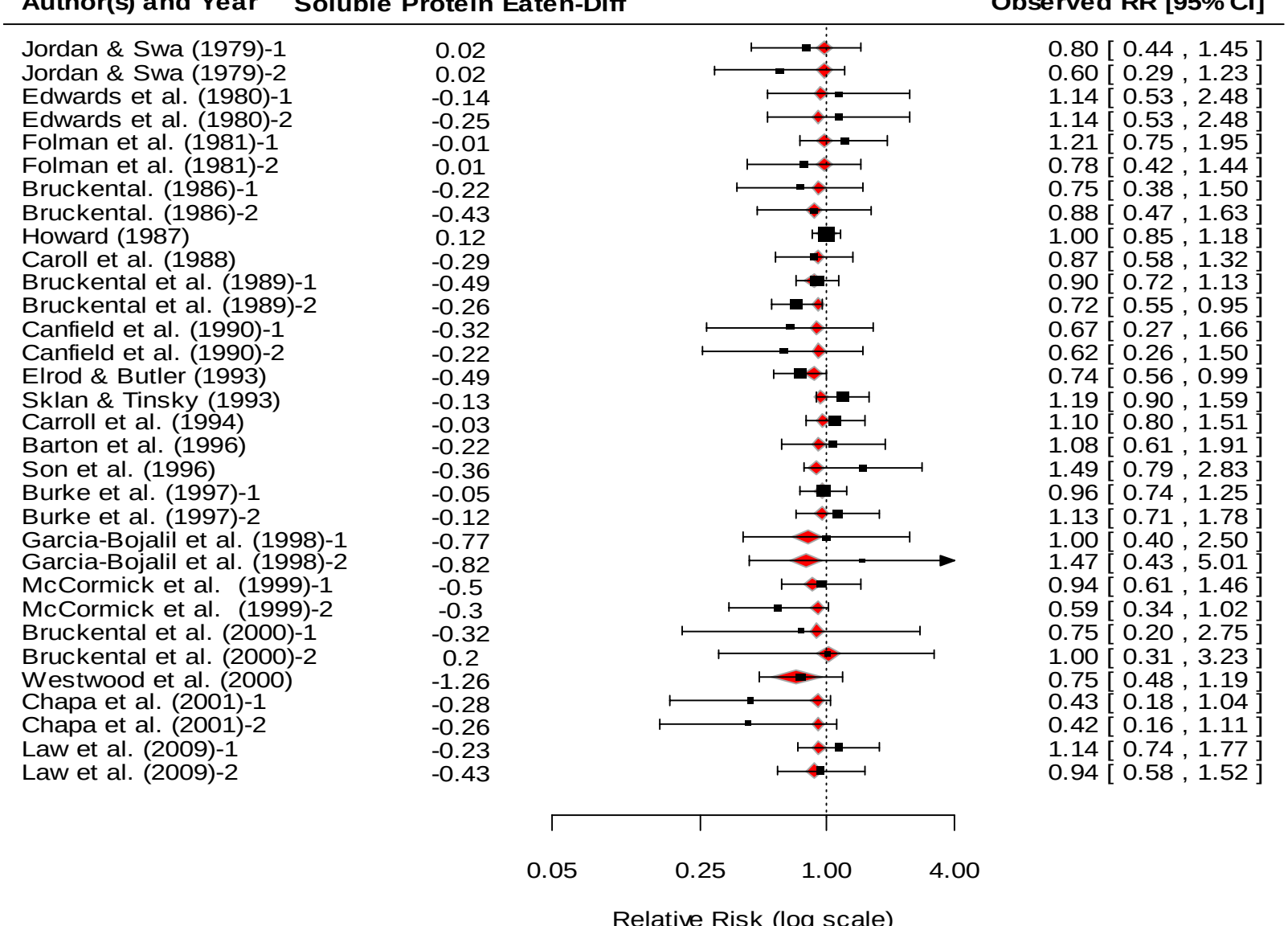
NFC and Soluble Protein % CP



Meta Analyses: Benefits and Pitfalls

Protein and Reproduction NFC and RDP




Author(s) and Year
Soluble Protein Eaten-Diff
Observed RR [95% CI]
Jordan & Swa (1979)-1 0.02 0.80 [0.44 , 1.45]
Jordan & Swa (1979)-2 0.02 0.60 [0.29 , 1.23]
Edwards et al. (1980)-1 -0.14 1.14 [0.53 , 2.48]
Edwards et al. (1980)-2 -0.25 1.14 [0.53 , 2.48]
Folman et al. (1981)-1 -0.01 1.21 [0.75 , 1.95]
Folman et al. (1981)-2 0.01 0.78 [0.42 , 1.44]
Bruckental. (1986)-1 -0.22 0.75 [0.38 , 1.50]
Bruckental. (1986)-2 -0.43 0.88 [0.47 , 1.63]
Howard (1987) 0.12 1.00 [0.85 , 1.18]
Caroll et al. (1988) -0.29 0.87 [0.58 , 1.32]
Bruckental et al. (1989)-1 -0.49 0.90 [0.72 , 1.13]
Bruckental et al. (1989)-2 -0.26 0.72 [0.55 , 0.95]
Canfield et al. (1990)-1 -0.32 0.67 [0.27 , 1.66]
Canfield et al. (1990)-2 -0.22 0.62 [0.26 , 1.50]
Elrod & Butler (1993) -0.49 0.74 [0.56 , 0.99]
Sklan & Tinsky (1993) -0.13 1.19 [0.90 , 1.59]
Carroll et al. (1994) -0.03 1.10 [0.80 , 1.51]
Barton et al. (1996) -0.22 1.08 [0.61 , 1.91]
Son et al. (1996) -0.36 1.49 [0.79 , 2.83]
Burke et al. (1997)-1 -0.05 0.96 [0.74 , 1.25]
Burke et al. (1997)-2 -0.12 1.13 [0.71 , 1.78]
Garcia-Bojalil et al. (1998)-1 -0.77 1.00 [0.40 , 2.50]
Garcia-Bojalil et al. (1998)-2 -0.82 1.47 [0.43 , 5.01]
McCormick et al. (1999)-1 -0.5 0.94 [0.61 , 1.46]
McCormick et al. (1999)-2 -0.3 0.59 [0.34 , 1.02]
Bruckental et al. (2000)-1 -0.32 0.75 [0.20 , 2.75]
Bruckental et al. (2000)-2 0.2 1.00 [0.31 , 3.23]
Westwood et al. (2000) -1.26 0.75 [0.48 , 1.19]
Chapa et al. (2001)-1 -0.28 0.43 [0.18 , 1.04]
Chapa et al. (2001)-2 -0.26 0.42 [0.16 , 1.11]
Law et al. (2009)-1 -0.23 1.14 [0.74 , 1.77]
Law et al. (2009)-2 -0.43 0.94 [0.58 , 1.52]
0.05
0.25
1.00
4.00
Relative Risk (log scale)

Meta Analyses: Benefits and Pitfalls
Summary

- The use of Meta-analyses is an excellent tool to identify the value of an intervention
  - With a proper analysis, one can:
    - Estimate the return on investment
    - Identify the conditions under which one will get the best responses
    - Ask the critical questions about the biology and what studies need to be done in the future
- As you look at meta-analyses for proposed interventions, follow the check lists to ensure that the intervention is valid and will be of value to the dairies you serve

Meta Analyses: Benefits and Pitfalls
Summary

- Boil it down and there is one simple message:
  - Proper pooling of all suitable studies is a lot more powerful than any one study and provides the best information on whether a product or a intervention works and under what circumstance

Meta Analyses: Benefits and Pitfalls

Questions & Answers

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