2012

Systematic Reviews and Meta-Analysis - Course Syllabus 2011-2012

Washington University in St.Louis

M19-551 Spring 2012
Systematic Reviews and Meta-Analysis
in Public Health and Clinical Medicine

Course Description

Introduction to the use of meta-analysis and related methods used to synthesize and evaluate epidemiological and clinical research in public health and clinical medicine. Concepts introduced and illustrated through case studies of public health and medical issues.

Course Objectives

To learn how to use a variety of formal and informal methods for synthesizing epidemiological information on public health risks, to understand how to use these methods to assess the strength of the evidence in policy development and clinical contexts, and to appreciate how research synthesis can contribute to rational policy making in controversial areas.

Competencies

Principles consistent with epidemiology and biostatics competencies for the MPHS (www.mphs.wustl.edu)

Ability to design research synthesis and meta-analysis

- Define research question
- Define literature search strategy
- Conduct literature search and document the process
- Apply eligibility criteria, data extraction, and data quality scoring
- Develop data analysis plan
- Understand and interpret fixed-effects, random-effects, and meta-regression methods and results
- Recognize heterogeneity and approaches to quantification and reporting of among-study variation

Skills and experience to conduct analysis

- Master data analysis and model fitting in context of meta-analysis
- Quantitatively evaluate publication bias
- Be able to estimate combined results from reports of randomized trials, observational studies, and diagnostic test

Master the core reporting strategies

- Master reporting standards for RCTs and observational data in context of meta-analysis
- Master forest plot, summary tables, and publication bias presentations

Draw inferences from data to inform clinical and public health practices

- Correctly use reasoning for design and methodologies employed
- Present oral and written reports from analyses
- Place inference in context of clinical and public health implications for action and future research

Time and Location
Friday 9:00 AM to noon
Class location to be determined

Instructors
Graham A. Colditz, MD, colditzg@wudosis.wustl.edu
Methodius Tuuli, MD, tuulim@wudosis.wustl.edu
Office hours: By appointment and after class

Target audience
Clinicians interested in conducting research synthesis or meta-analysis to inform practice or policy, clinical training program participants, students enrolled in Genetic Epidemiology Master of Science program, students in MPH addressing application of epidemiologic data to prevention. Prior clinical or community research experience is helpful but not required.

Prerequisite
Introductory epidemiology and biostatistics 1 (or permission of the course master)

Credits 3

Class schedule
Most classes will involve case discussions, and students are expected to come to class prepared to discuss the readings. On one day to be determined --, the class will meet in the computer lab (STAT available in the Becker library) to review the use of Comprehensive Meta Analysis, a specialized computer program (or we could use Stata).

Students (working individually or in groups) will present their work according to the following schedule:

A. Study protocol: precise topic, search strategy, inclusion/exclusion criteria.
B. Search results, evidence table, statistical issues.
Last 2 days of class: Final presentation of results and conclusions.

Evaluation
Working individually or in groups of 2 individuals, students will be expected to carry out a written research synthesis of a public health or clinical topic of their own choosing. Intermediate results will be presented and discussed in class. Grades will be based on the written paper, presentations, and on class participation. The content of the written paper should be based on the QUORUM or MOOSE consensus statement as appropriate.

- Moher D, et al, Quality of reporting of meta-analyses (QUORUM) consensus statement, *Lancet* 1999, 354:1896-1900.
- Stroup DF, et al, Meta-analysis of observational studies in epidemiology (MOOSE) consensus statement, *JAMA* 2000, 283:2008-2012.

Software: We will be using STATA with the meta-analysis supplementary routines. It is available for purchase but can be used at the library where it is on 4 computers.
http://becker.wustl.edu/services/researchpod.html

Assignments and Grading

Homework 1	=	15%
Homework 2	=	15%
Final Paper	=	55%
Class Participation	=	15%

Readings

The primary text for the course is Systematic Reviews in Health Care: Meta-analysis in Context, 2nd Edition, Mattias Egger, George Davey Smith, and Douglas Altman, eds., BMJ Books, 2001. Supplemental readings from Introduction to Meta-Analysis, Michael Borenstein, Larry V Hedges, Julian PT Higgins, and Hannah R Rothstein, Wiley, 2009, are also given. Additional readings are indicated below and will be available through blackboard.

Additional Resources
BMJ methods http://www.bmj.com/search?submit=yes&tocsectionid=Research%20Methods*
Cochrane library http://www.thecochranelibrary.com/view/0/index.html

Cochrane methods group

UK NICE (National Institute for Health and Clinical Excellence) http://www.nice.org.uk/
Australia Handbook. How to use the evidence. NHMRC.
http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf
Berkeley Systematic Reviews Group, http://www.medepi.net/meta/

Date	*Topic*	Key Reading
January 20	**Introduction** **Defining the research question**	Egger 2001 Mosteller and Colditz 1996 Berlin and Colditz 1999 Stampfer 1982 (classic article) Cousell 1997
January 27	**Searching the literature; BCG and Stapling examples**	Egger 2001 Colditz 1994 Colditz 1995 Tuuli 2011 Lemeshow 2005 Dickersin 1994 (classic article)
February 3	**Statistical methods: effect sizes, basic meta-analysis calculations; BCG**	Egger 2001 Normand S-L 1999 Laird 1990
February 10	**Statistical methods, continued: cumulative meta-analysis, tools for publication bias; BCG**	Egger 2001 Tuuli 2011 Borenstein Chapter 11, Publication Bias
February 17	**Student presentations:** Homework 1: Topic and search protocol	
February 24	**Heterogeneity I: I^2, subgroup analysis; ETS, HIV counseling & testing NAC**	Egger 2001 Colditz 1995 Berlin 1995 Higgins 2003 Gonzales 2007

March 2	**Quality scores: application to research synthesis** GRADE **Computer lab**	Moher 1995 Moher 1996 Grade BMJ, 2004 Intro to STATA
March 9	**Heterogeneity II: Meta-regression; BCG, ETS, Alcohol and stroke, Vitamin E**	Egger 2001 Reynolds 2003 Miller 2005
March 16	**Epidemiology examples: ETS & EMF, physical activity** Homework 2 : data extraction write up	Egger 2001 Surgeon General's Report 2006 EMF National Academy Linet 1997 Campion 1997 Berlin 1990 Wolin 2009
March 23	**Student presentations**: **Results of literature search and preliminary results** **Applying results to policy and practice**	 Egger 2001 Ioannidis 2010 Kendrick 2009 Glaszious 2010 Bastian 2010 Grade 2008
March 30	**Drug safety** **Pros and Cons of meta-analysis** Class debate: meta-analysis vs. large trials Class teams will debate this topic using aspirin for prevention of preeclampsia as the topic	Jüni 2008 Bridge 2007 Kaizar 2006 Berlin and Colditz 1999
April 6	**Computer lab**	
April 13	***Combining diagnostic test results***	Egger 2001 Shapiro 1995 Rutter and Gatsomis 1995 Irwig 1994 Hovels 2008 Kwok 1999

April 20	**Comparing meta-analysis of published results with pooled analysis of individual level data**	Beral 2008 Whittemore 1992 Breast Cancer Collaborate 1996 Steinberg 1997 Hankinson 1992 Cholesterol Treatment Trialists' 2010
April 27	**Student presentations:** Summary and final results	
May 4	**Student presentations:** Summary and final results	

Readings

Week 1
Introduction and Defining the Question

Systematic Reviews in Health Care: Meta-analysis in Context, 2nd Edition, Mattias Egger, George Davey Smith and Douglas Altman eds, BMJ Books 2011; chapters 1 & 2.

Mosteller F, Colditz G. Understanding Research Synthesis (Meta-Analysis).Annual Rev Public Health 1996;17:1-23. Mosteller ARPH.pdf

Berlin JA, Colditz GA.The Role of Meta-Analysis in the Regulatory Process for Foods, Drugs, an Devices 1999: JAMA 281(9)830-934. Berlin - JAMA-1999-830-4.pdf

Counsell C. Formulating Questions and Locating Primary Studies for Incousion in Systematic Reviews. Ann Inter Med.1997;127:380-387. Counsell PICO.full.pdf

Classic article
Stampfer MJ, Goldhaber SZ, Yusuf S, Peto DPR, Hennekens CH. Effect of Intravenous Streptokinase on Acute Myocardial Infarction: Pooled Results from Randomized Trials. NEJM 1982;307(19):1180-82. Stampfer Streptokinase NEJM 1982.pdf

Week 2
Searching the literature
Example: BCG vaccine efficacy
Staples vs suture

Systematic Reviews in Health Care: Meta-analysis in Context, 2nd Edition, Mattias Egger, George Davey Smith and Douglas Altman eds, BMJ Books 2011;chapters 3, 4 & 5.

Colditz GA, Brewer TF, Berkey CS, Wilson ME, Burdick E, Fineberg HV, Mosteller F. Efficacy of BCG vaccine in the prevention of tuberculosis: Meta-analysis of the published literature. *JAMA* 1994; 271:698 colditz-bcg-jama-94.pdf

Colditz GA, Berkey CA, Mosteller F, Brewer TF, Wilson ME, Burdick E, Fineberg.The efficacy of Bacillus Calmette-Guérin vaccination of newborns and infants in the prevention of tuberculosis: Meta-analysis of the published literature, *Pediatrics* 1995;96:29-35. Colditz-bcg-kids peds 1995.pdf

Tuuli M G, Rampersad RM, Carbone JF, Stamilio D, Macones GA, Odibo AO. Staples Compared With Subcuticular Suture for Skin Closure After Cesarean Delivery *A Systematic Review and Meta-Analysis.* Obstet Gynec 2011; 117:682-90. Tuuli O&G 2011.pdf

Lemeshow AR, Blum RE, Berlin JA, Stoto MA, Colditz GA.Searching one or two databases was insufficient for meta-analysis of observational studies. J Clin Epidemiol 2005; 58:867-73 lemeshow-searching-05.pdf

Classic article
Dickersin K.Scherer R, Lefebvre C. Systematic Reviews: Identifying relevant studies for systematic reviews BMJ 1994;309:1286-91. Identifying relevant studies.bmj 00465-0048.pdf

Week 3
Statistical methods
Example: BCG vaccine efficacy (continued)

Systematic Reviews in Health Care: Meta-analysis in Context, 2nd Edition, Mattias Egger, George Davey Smith and Douglas Altman eds, BMJ Books 2011; chapters 15 & 16.

Normand S-L. Tutorial in Biostatistics Meta-Analysis: Formulating, Evaluating, Combining, and reporting. Statist.Med.1999;18:321-359. Normand-meta-tutorila stats med 1999.pdf

Laird NM, and Mosteller F. Some statistical methods for combining experimental results. Int J Technol Assess health Care 1990;6(1):5-30.Laird NM Some statistical methods for combining experimental results 1990.pdf

Additional readings:
Borenstein, Chapters 3-14
Using meta-analysis for research synthesis: pooling data from several studies. Biostatistics in Clinical Medicine, Chapter 14, 332-360.

Week 4
Statistical methods, continued: cumulative meta-analysis, tools for publication bias

Systematic Reviews in Health Care: Meta-analysis in Context, 2nd Edition, Mattias Egger, George Davey Smith and Douglas Altman eds, BMJ Books 2011; chapters 11,13-16.

Tuuli M G, Rampersad RM, Carbone JF, Stamilio D, Macones GA, Odibo AO. Staples Compared With Subcuticular Suture for Skin Closure After Cesarean Delivery *A Systematic Review and Meta-Analysis.* Obstet Gynec 2011; 117:682-90. Tuuli O&G 2011.pdf

Additional readings:

Borenstein M. Software for publication bias. Chapter 11 in Rothstein HR, Sutton AJ, Borenstein M, eds., *Publication Bias in Meta-Analysis – Prevention, Assessment and Adjustments,* Wiley 2005.

Week 5
***Student presentations**:* Study protocol precise topic, search strategy, inclusion/exclusion criteria.

Week 3-Class B
Heterogeneity I: I^2, subgroup analysis
Examples: ETS, HIV counseling & testing, NAC

Systematic Reviews in Health Care: Meta-analysis in Context, 2nd Edition, Mattias Egger, George Davey Smith and Douglas Altman eds, BMJ Books 2011; chapters 8,9

Colditz GA, Burdick E, Mosteller F. Heterogeneity in Meta-analysis of Data from Epidemiologic Studies: Reviews and Commentary. AJE 1995;371-81.Colditz Am. J. Epidemiol.-1995--371-hetero.pdf

Berlin JA. Invited Commentary: Benefits of Heterogeneity in Meta-analysis of Data from Epidemiologic Studies AJE 1995; 142: 385-8.berlin-commentaty-H aje 1995.pdf

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses, *BMJ* 2003;327:557-60. Higgins JT. Measuring inconsistency in meta-analysis.2003.pdf

Gonzales DA, Norsworthy KJ, Kern SJ, Banks S, Sieving PC, Staar RA, Natanson C, Danner RL. A meta-analysis of N-acetylcysteine in contrast-induced nephrotoxicity: unsupervised clustering to resolve heterogeneity, *BMC Medicine* 2007;5:32. A meta-analysis of N-acetylcysteine...1741-7015-5-32.pdf

Week 6
Quality scores application to research synthesis

Moher D, Olkin I. Meta-analysis of Randomized Control Trials. JAMA 1995:274(24)1962-64. Meta-analysis of Randomized Control Trials. JAMA 1995274(24)1962-64.pdf

Assessing the Quality of Randomized Control Trials: An Annotated Bibliography of Scales and Checklists. Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Controlled Clinical Trials 1995;16:62-73.

Assessing the quality of randomized control trials. Current issues and future directions. Moher D, Jadad AR, Tugwell P. Int'l J of Technology Assessment in Health Care 1996;12-1;196-208

Stewart LA, Palmer MK. Bias in the analysis and reporting of randomized controlled trials. Int'l J of Technology Assessment in Health Care 1996;12-2:264-275.

Computer lab

Comprehensive Meta Analysis Version 2.0: Introduction to the program

Additional readings:
Borenstein, Chapter 44

Week 8
Heterogeneity II: Meta-regression; BCG, ETS, Alcohol and stroke, Vitamin E

Systematic Reviews in Health Care: Meta-analysis in Context, 2nd Edition, Mattias Egger, George Davey Smith and Douglas Altman eds, BMJ Books 2011; chapters 9,10.

Reynolds K, Lewis BL, Nolen JDL, Kinney GL, Sathya B, He J. Alcohol consumption and risk of stroke: A meta-analysis, *JAMA* 2003, 289: 579-588. :Reynolds K. Alcohol Consumption and Risk of Stroke A Meta-Analysis. JAMA 2003.pdf

Miller ER, Pasdtor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: High-dosage Vitamin E supplementation may increase all-cause mortality, Ann Intern Med 2005;142:37-46 Miller ER et al. Meta-analysis High-dosage Vitamin E supplementation....pdf.

Additional readings:

Week 9
Epidemiology
Examples: Environmental tobacco smoke, electromagnetic fields, physical activity

Systematic Reviews in Health Care: Meta-analysis in Context, 2nd Edition, Mattias Egger, George Davey Smith and Douglas Altman eds, BMJ Books 2011; chapter 12.

The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General, U.S. Department of Health and Human Services, 2006 Focus on lung cancer section, chapter 7, pp. 423-445. Complete report available at: www.surgeongeneral.gov/library/secondhandsmoke/.Surgeon General's Report 2006.Physical Activity.pdf

Possible Health Effects of Exposure to Residential Electric and Magnetic Fields, National Research Council, Washington: National Academy Press, 1997. **Focus on research synthesis sections, pp. 1-8, 117-146.** Complete report available at: newton.nap.edu/catalog/5155.html.

Linet MS, Hatch EE, Kleinerman RA, Robison LL, Kaune W, Friedman DR, Severson R, Haines CM, Hartsock CT, Niwa S, Wacholder S, Tarone RE. Residential exposure to magnetic fields and acute lymphoplastic leukemia in children, *NEJM* 1997; 337:1-7 Linet MS. Residential exposure to magnetic fields...2007.pdf.

Campion EW.Power lines, cancer, and fear" (editorial), *NEJM*, 1997; 337:44-46 Campion EW. Power lines, cancer and fear NEJM 1997.pdf.
Berlin JA, Glasser SC, Ellenberg SS. Adverse Event Detection in Drug Development: Recommendations and Obligations Beyond Phase 3. Am J Public Health 2008:98;1366-1371.berlin-ae-trials.pdf

Wolin KY, Yan Y, Colditz GA, Lee I-M. Physical activity and colon cancer prevention: a meta-analysis. BJR 2009:100;611-616.wolin-ma-pa-colon-bjc09.pdf

Week 10

Student presentations

Search results, evidence table, statistical issues.

Applying results to policy and practice

Systematic Reviews in Health Care: Meta-analysis in Context, 2nd Edition, Mattias Egger, George Davey Smith and Douglas Altman eds, BMJ Books 2011;chapter 19, 21, 23

Ioannidis J, Karassa F. The need to consider the wider agenda in systematic reviews and meta-analysis. BMJ 2010;341:762-65.ioannidis - bmj - evidence 2010.pdf

Kendrick T, Dowrick C, McBride A, Howe A, Clarke P, Maisey S, Moore, Smith PW. Management of depression in UK general practice in relation to scores o depression severity questionnaires: analysis of medical record data. BMJ 2009;338:b750.Kendrick.bmj.b750.full.pdf

Glasziou P, Altman DG, Bastian H, Boutron I, Bride A, Jamtvedt G, Farmer A, Ghersi D, Groves T, Heneghan C, Hill S, Lewin S, Michie S, Perera R, Pomeroy V, Tilson J, Sheppard S, Williams JW. Taking healthcare interventions from trial to practice.BMJ 2010;341:c3852.Glasziou-bmj-Research_Methods_Reporting.full.pdf

Bastian H, Glasziou P, Chalmers I. Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will I Ever Keep Up? PLoS Medicine 2010;7(9):e1000326.bastian-glasziou- rct etc.pdf Bastian PLOS 2010

Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schunemann HJ. GRADE: going grom evidence to recommendations. BMJ 2008;336:1049-51.Grade-BMJ - 2008.pdf

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Week 11

Drug Safety

Examples: Vioxx, Avandia, vaccines, antidepressants

Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: Cumulative meta-analysis, *Lancet* 2004;364:2022-29. Juni, P. Risk of cardiovascular events.Lancet 2004.pdf

Bridge JA,Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA.Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: A meta-analysis of randomized clinical trials, *JAMA*, 2007;297:1683-1696. Bridge JA. Clinical response and risk fo suicidal ideation.JAMA. 2007683.full.pdf

Kaizar EE,Greenhouse JB, Seltman H, Kelleher K. Do antidepressants cause suicidality in children? A Bayesian meta-analysis, *Clinical Trials* 2006;3:73-98. Kaizar Clinical Trial 2007.pdf

Berlin JA, Colditz GA. The Role of Meta-analysis in the Regulatory Process for Foods, Drugs, and Devices. JAMA 1999;281(9):824-841.Berlin - JAMA-1999-830-4.pdf

Additional reading:

Stoto MA, Research synthesis for public health policy: Experience of the Institute of Medicine, in *Meta-Analysis in Medicine and Health Policy*, Stangl D and Berry D., eds., New York: Marcel Dekker, 2000, pp 321-357.

Week 12

Computer lab

Week 13
Combining Diagnostic Tests, Bayesian meta-analysis
Example: Exercise testing to detect coronary artery disease, mammography

Systematic Reviews in Health Care: Meta-analysis in Context, 2nd Edition, Mattias Egger, George Davey Smith and Douglas Altman eds, BMJ Books 201;chapter 14.

Issues in combining independent estimates of the sensitivity and specificity of a diagnostic test. Shapiro DE. Acad Radiol 1995;2:S37-S47.

Regression methods for meta-analysis of diagnostic test data.
Rutter CM, Gatsonis CA. Acad Radiol 1995;2:S48–S56.

Irwig L, Tosteson ANA, Gatsonis C, Lau J, Colditz GA, Chalmers TC, Mosteller F. Guidelines for Meta-analysis Evaluating Diagnostic Tests. Ann Intern Med 1994;120:667-676. Irwig- Ann INtern Med 1994.pdf

Examples:
Hövels AM et al., The diagnostic accuracy of CT and MRI in the staging of pelvic lymph noted in patients with prostate cancer: a meta-analysis. *Clinical Radiology* 2008; 63:387-395.Hovels AM. The diagnostic accuracy of CT and MRI 2008.pdf

Kwok Y et al., Meta-analysis of exercise testing to detect coronary artery disease in women, *American Journal of Cardiology* 1999; 83: 660-666.Kwok Y. Meta-Analysis of Exercise Testing to Detect Coronary Artery...1999.pdf

Additional reading:
Berry DA, Benefits and risks of screening mammography for women in their forties: A statistical approach, *JNCI* 1998; 90:1431-1439.

Week 14
Comparing meta-analysis of published results with pooled analysis of individual level data

Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23257 women with ovarian cancer and 87303 controls. Collaborative Group on Epidemiological Studies of Ovarian Cancer. Lancet 2008;371:303-14. beral-oc ovarian ca combined analysis lancet 2008.pdf

Characteristics Relating to Ovarian Cancer Risk: Collaborative Analysis of 12 US Case-Control Studies. II. Invasive Epithelial Ovarian Cancers in White Women.
Whittemore AS, Harris R, Itnyre J, and the Collaborative Ovarian Cancer Group.
Am J Epidemiol 1992;136:1184-1203.

Comparison of Effect Estimates from a Meta-Analysis of Summary Data from Published Studies and from a Meta-Analysis Using Individual Patient Data for Ovarian Cancer Studies.
Steinberg KK, Smith SJ, Stroup DF, Olkin I, Lee NC, Williamson D, Thacker SB.
Am J Epidemiol 1997;145:917-25. Steinberg KK Comparison of Effect Estimates from a Meta-Analysis 1997.pdf

A Quantitative Assessment of Oral Contraceptive Use and Risk of Ovarian Cancer. Hankinson SE, Colditz GA, Hunter DJ, Rosner BJ. Obstet Gynecol 1992;80:708-714. Hankinson SE. A quantitative assessment of oral contraceptive use and risk of ovarian cancer.1992.pdf

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials. Cholesterol Treatment Trialists. Lancet 2010;376:1670-81. cholesterol lowering lancet 2010.pdf

Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,238 women without breast cancer from 54 epidemiological studies. Lancet 1996;347:1713-27.Lancet

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Weeks 15 and 16
Student presentations:
Final presentation of results and conclusions.