Table 8.4 Abilities of different approaches in providing treatment effect and heterogeneity information

Treatment effect and heterogeneity information provided	Approach	
	GLM	GLMM
Treatment effect		
• Estimated overall effect ($\hat{\theta}$)	X	X
• CI for θ	X	X
• Estimated component- specific effect ($\hat{\theta}_k$)	N/A	X
• SE of $\hat{\theta}_k$	N/A	X
Random effect		
• Estimated variance ($\hat{\tau}^2$)	X	X
• CI for τ^2	X	X*
• Estimated subgroup-variance and its SE	X	X*
Covariates effect		
• Estimated effect and its SE		
Categorical data	X	X
Continuous data	X	X

* results that can be obtained from the approach but not provided in the software used
N/A not applicable

8.3 Strengths and limitations for different approaches

Strengths and limitations of different approaches are discussed here in relation to their application to the meta-analyses involving cluster randomized trials. Summaries are presented in table 8.5.

For the GLM, it is the extension of simple conventional method of random effects model that naturally allows including covariates of trial level and individual level for the estimation. Application of the GLM to meta-analyses involving cluster randomized trials is logically straightforward. The approach provides all dimensions of the heterogeneity effects as mentioned earlier. Interpretation and inference on the treatment effect are also straightforward under the normal distributed assumption of random effect. However, this may lead to unreliable results if the assumption is misspecified. Another possible difficulty is that meta-analysts may need to have higher literate in modelling approach to implement the approach.

The GLMM provides greater heterogeneity information. The NPML estimate is a discrete mixing distribution on a finite component number implemented by the EM–algorithm. It is relatively simple to perform the mixture maximum likelihood computations. It has been shown(122) that the GLMM is robust against parametric model misspecification. It provides information of component(or subgroup)-specific treatment effects and trial classification according to the number of components where treatment heterogeneity is detected. This result gives useful information for further explanation on the heterogeneity effect Aitkin(122, 123) and Dietz (118) provide evidence on the theoretical and computational issues showing that the GLMM is a flexible method used to solve problems of treatment heterogeneity and random effects. However, there are some limitations. First, qualified meta-analysts may be needed in modelling the approach to the analyses. Second, convergence of the algorithm is often slow although consistent results are still obtained.

Third, the NPML estimates may produce unreliable results if the number of trials included in the meta-analysis is very small. Finally, difficulty in the interpretation of treatment effect from a discrete distribution of the NPML estimate may arise if the true random effects are likely to be a normal distribution. This is still an unsolved issue. Finally for the approach, qualified meta-analysts may be needed in modelling the approach to the analyses.

Table 8.5 Strengths and limitations for different approaches

Approach	Strengths	Limitations
• GLM with REML estimator	-Provide heterogeneity information from several sources, treatment effect, covariates effect and variance of random effects -Provide clear interpretation and inference on treatment effect	-Possibly difficult for non-literacy in modelling approaches -Possibly provide unreliable results when distribution of random effects is mis- specified.
• GLMM with NPML estimator	-Provide heterogeneity information from several sources; treatment effect, covariate effect and variance of unspecified random effects distribution -Provide subgroup-specific mean treatment effect -Provide posterior probability to classify trials to each subgroup	-Possibly difficult for non-literacy in modelling approaches -Convergence of algorithm is often slow -Results questionable for small number of trials in meta-analyses -Still questionable in reliability of interpretation of treatment effect

8.4 Comparison of numerical results for different approaches

8.4.1 Meta-analysis of vitamin A supplementation on child mortality trials

Summaries of parameter estimates for alternative approaches applied to the data are presented in table 8.6. The Q statistic for testing homogeneity ($\tau^2 = \mathbf{0}$) equals to 25.0 given p = 0.001 at 7 degree of freedom. This figure provides evidence of heterogeneity between the trials.

The GLMM for random treatment gives some higher estimated effect of the vitamin A supplementation with a wider confidence interval for the true treatment effect. The estimated variance of random effects obtained from the GLMM is 0.89, which is very large, compared to the estimated variances of 0.08 in the GLM.

To make a conclusion of this example under the preferred approach of GLMM, that is the log-relative risk of vitamin A supplementation about a mean of –0.43 (95 per cent CI – 1.37 to 0.51). The estimated variance of random effect is 0.89, which reflects huge variability between baseline characteristics. Some available information of various units of treatment allocation and control treatments across the trials may share in the reason of this huge variability of random effect. This result, however, does not correspond to the result from the original meta-analysis paper reports that there is evidence of significant benefit of vitamin A supplementation on child mortality by Dersimonian&Laird pooled overall log-odds ratio of -0.36 (95 per cent CI -0.54 to -0.16).

Table 8.6 Estimated vitamin A supplementation log-relative risk and variances of random effects, from the best model for different approaches

Approach	Log-relative risk (95 per cent CI)	Variance of random effect (95 per cent CI)
• GLM with REML estimator		
- Fixed treatment	-0.36 (-0.60, -0.15)	0.08 (0.0, 0.15)
• GLMM with NPML estimator		
- Random treatment (5 components)	-0.43 (-1.37, 0.51)	0.89

Q statistics: 25.00 ,p = 0.001 at 7 df for this example

8.4.2 Meta-analysis of mammographic screening on breast cancer mortality trials

In this example the Q statistic for testing homogeneity ($\tau^2 = \mathbf{0}$) equals to 14.58 given p=0.038 at 7 degree of freedom. This result shows evidence of heterogeneity between the trials but it is not strong as the probability is quite high.

The estimates of log-relative risk produced by alternative approaches are not much different. But the 95 per cent confidence interval for the true treatment effect is shown wider in the GLM for the fixed treatment effect model, as presented in table 8.7 The variances of random effects produced by the two approaches are rather similar in very small values. The two approaches do not show evidence of significant effect of randomized design on the breast cancer mortality. When allowing for random effects of randomized design for the GLM approach, the variance of random effect is somewhat larger in the group of individually randomized trials but still in a very small value.

So to conclude the results according to the GLMM approach, it shows that adjusted log-relative risk of mammographic screening effect about a mean of –0.23 (95 per cent CI – 0.55 to -0.11). The estimated variance of random effect is 0.07, which represents small variability between baseline characteristics. Even the estimated overall effect of mammographic screen is significant, the results obtained from component-specific mean effects, which is presented in Table 7.4, also show some heterogeneity effects of mammographic screening. Thus the estimate of overall treatment effect may be not appropriate for making a conclusion for this example.

Table 8.7 Estimated mammographic screening log-relative risk and variances of random effect , from the best model for different approaches

Approach	Log-relative risk (95 per cent CI)	Variance of random effect (95 per cent CI)
• GLM with REML estimator		
- Fixed treatment + Random design	-0.19 (-0.55, 0.15)	0.02 $(0,0.03)^{CRT}$ 0.06 $(0, 0.10)^{IRT}$
• GLMM with NPML estimator		
- Random treatment + Fixed design (3 components)	-0.23 (-0.35, -0.11)	0.07

Q statistics: 14.82 ,p = 0.038 at 7 df for this example, CRT= cluster randomized trial, IRT= individually randomized trial

8.4.3 Meta-analysis of multiple interventions on smoking prevalence trials

For the data of this example, Q statistic for testing treatment homogeneity equals to 75.93 given $p < 0.001$ at 13 degree of freedom. This results show that there is strong evidence of heterogeneity between the trials. Summaries of the estimates for individual approaches are presented in table 8.8.

The two alternative approaches provide relatively similar results of the adjusted effect of multiple interventions on smoking prevalence. But the GLMM gives much wider confidence interval and larger estimated variance of random effects, which is 0.28, compared to the variances of each category of the randomized design covariate, 0.005 for CRT and 0.013 for IRT, in the GLM. The GLM also produces no evidence of any covariate effects on the log-relative risk while the evidence of randomized design effect is provided by the GLMM.

In conclusion of this example by using the GLMM, it shows evidence of heterogeneity due to randomized design and random effects. The evidence of benefit of multiple interventions obtained from this approach is relevant to the results provided in the original meta-analysis.

Table 8.8 Estimated multiple interventions log-relative risk and variances of random effect from the best model , for adifferent approaches

Approach	Log-relative risk (95 per cent CI)	Variance of random effect (95 per cent CI)
• GLM with REML estimator		
- Fixed treatment + Random design	-0.12 (-0.20, - 0.02)	0.005 $(0, 0.01)^{CRT}$ 0.013 $(0, 0.03)^{IRT}$
• GLMM with NPML estimator		
- Random treatment(a) + Fixed design(b)+interacton a*b (4 components)	-0.19 (-0.35, -0.03)	0.28

Q statistics: 75.93 , $p < 0.001$ at 13 df for this example
CRT= cluster randomized trial, IRT= individually randomized trial

For these three examples, even they include all small number of trials, I believe that the results obtained from alternative approaches are reasonable for comparing their application. However the three examples are the biggest meta-analyses involving cluster randomized trials available in published literature.

Impression of the application of alternative approaches to the three examples is that they provide relatively consistent figures of treatment effect. The approaches of nonparametric maximum likelihood estimators mostly give stronger effect of treatment and wider confidence intervals for true treatment effects. This is reasonable because of the extra source of variability that comes from the interaction between treatment and random effect terms in the models.

8.5 Summary

According to all of these considerations, the GLMM are preferable for meta-analyses involving cluster randomized trials. The GLM and GLMM are, even compatible in terms of methodology and results provided for answering heterogeneity due to treatment effect, covariate effects and random effects. But in some aspects the GLMM is superior to the GLM. The GLMM provides component (or subgroup)-specific treatment effect and trial classification according to the optimal components, which is very useful in further explaining the heterogeneity effects of both treatment and baseline characteristics. Since the inference on the treatment effect obtained from a discrete mixing distribution has not been ruled out, it may be difficult to interpret the treatment effect by using the GLMM. Nevertheless, the approach will be much more efficient when they are applied to large meta-analyses.

Acknowledgements

I would like to express my thanks to the Thailand Research Fund for supporting this study. Part of this study was also carried out while I was spending several research visits at the Institute of International Health, Unit of Epidemiology and Biometery of the Joint Center of Health Sciences and Humanities at the Free University Berlin. I would like to thank Professor Dankmar Boehning, Professor Frank-Peter Schelp, Dr Ekkehart Dietz, Dr Martina Stallmann and Ms Yoong Moy Chew for their help, discussion and encouragement during this time in Berlin.

References

1. Fawzi WW, Chalmers T, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality: a meta-analysis. The Journal of the American Medical Association 1993;269(7):898-903.
2. Gotzsche P, Olsen O. Is screening for breast cancer with mammography justifiable? The Lancet 2000;355:129-134.
3. Ebrahim S, Davey SG. Multiple risk factor interventions for primary prevention of coronary heart disease (Cochrane Review). The Cochrane Libary 2001;I(Issue 3).
4. Villar J, Ba'aqeel H, Piaggio G, Lumbiganon P, Miguel BJ, al. e. WHO antenatal care randomized trial for the evaluation of a new model of routine antenatal care. Lancet 2001;357(9268):1551-1564.
5. Glass G. Primary, secondary and meta-analysis of research. Educational research 1976;5:3-8.
6. Thompson S, Sharp S. Explaining heterogeneity in meta-analysis: a comparison of methods. Statistics in Medicine 1999;18(20):2693-708.
7. Berry S. Understanding and testing for heterogeneity across 2 x 2 tables: application to meta-analysis. Statistics in Medicine 1998;17:2353-2369.
8. D' Agostino R, Weintraub M. Meta-analysis: A method for synthesizing research. Clinical Pharmacology & Therapeutics 1995;58(6):605-616.
9. Blettner M, Willi S, Schlehofer B, Scheuchenpflug T, Friedenreich C. Traditional reviews, meta-analyses and pooled analysis in epidemiology. International Epidemiological Association 1999;28:1-9.
10. Altman DG. Statistics in medical journals: some recent trend. Statistics in Medicine 2000;19:3275-3289.
11. Fleiss J. The Statistical Basis of Meta-Analysis. Statistical Methods in Medical Research 1993;2:121-145.
12. Smith TC, Spiegelhalter DJ, Thomas A. Bayesian Approaches to Random-Effects Meta-Analysis: A comparative study. Statistics in Medicine 1995;14:2685-2699.
13. Normand S. Tutorial in biostatistics meta-analysis: formulating, evaluating, combining and reporting. Statistics in Medicine 1999;18:321-359.
14. Thompson SG. Controversies in Meta-Analysis: the case of the trials of serum cholesterol reduction. Statistical Methods in Medical Research 1993;2:173-192.
15. Thompson SG. Meta-analysis of Clinical Trials. Dictionary in Biostatistics 1998:2570-2579.
16. Whitehead A, Jones NM. A Meta-Analysis of Clinical Trials Involving Different Classifications of Response into Ordered Categories. Statistics in Medicine 1994;13:2503-2515.
17. Edited by Stangl D, Berry D. Meta-Analysis in Medicine and Health Policy. New York: Marcel Dekker,Inc.; 2000.
18. Donner A, Klar N. Cluster randomization trials. Statistical Methods in Medical Research 2000;9(2):79-80.
19. Donner A, Klar N. Cluster Randomization Trials in Epidemiology: Theory and Application. Journal of Statistical Planning inference 1994;42:37-56.
20. Donner A. Some aspects of the design and analysis of cluster randomization trials. Applied Statistics 1998;47(1):95-113.
21. Buck C, Donner A. The Design of Controlled Experiments in the Evaluation of Non-therapeutic Interventons. Journal of Chronic Disease 1982;35:531-538.

22. Gail MH, Mark SD, Carroll RJ, Green SB, Pee D. On Design Considerations and Randomization-Based Inference for Community Intervention Trials. Statistics in Medicine 1996;15:1069-1092.
23. Ukoumunne OC, Gulliford MC, Chinn S, Sterne JA, GJ BP. Methods for Evaluating Area-Wide and Organisation-Based Interventions in Health and Health Care: A methodological systematic review for the NHS Research and Development Health Technology Assessment Programme. Health Technology Assessment 1999;3(3):1-110.
24. Hayes R, Alexander N, Bennett S, Cousens S. Design and analysis issues in cluster-randomized trials of interventions against infectious diseases. Statistical Methods in Medical Research 2000;9:95-116.
25. Wawer M, Sewankambo N, Serwadda D, al. e. Control of sexually transmitted diseases for AIDS prevention in Uganda: randomised community trial. Lancet 1999;353:525-535.
26. Curzin-Ouattara N, Van den Broek A, Habluetzel A, al. e. Wide-scale installation of insecticide-treated curtains confers high levels of protection against malaria transmission in a hyperendemic area of Burkina Faso. Transactions of the Royal Society of Tropical Medicine ad Hygiene 1999;93:473-479.
27. Hayes R, al. e. A community trial of the impact of improved sexually transmitted disease treatment on the HIV epidemic in rural Tanzania: 1 Design. AIDS 1995;9:919-926.
28. Kish L. Survey Sampling. London: Wiley; 1965.
29. Donner A, Klar N. Confidence Interval Construction for Effect Measures Arising from Cluster Randomization Trials. Journal of Clinical Epidemiology 1993;46 (2):123-131.
30. Mickey RM, Goodwin GD. The Magnitude and Variability of Design Effects for Community Intervention Studies. American Journal of Epidemiology 1993;137(1):9-18.
31. Murray D, Rooney B, Hannan P, et a. Intraclass correlation among common measures of adolescent smoking: Estimates, correlates and applications in smoking prevention studies. American Journal of Epidemiology 1994;140:1038-1050.
32. Simpson J, Klar N, Donnor A. Accounting for cluster randomization: a review of primary prevention trials, 1990 through 1993. American Journal of Public Health 1995;85(10):1378-1383.
33. Donner A, Eliasziw M, Klar N. A Comparison of Methods for Testing Homogeneity of Proportions in Teratologic Studies. Statistics in Medicine 1994;13:1253-1264.
34. Sommer A, Djunaedi E, Loeden A, Tarwotjo I, West KP, Tilden R. Impact of vitamin A supplementation on childhood mortality: A randomised controlled community trial. The Lancet 1986(24 May):1169-1173.
35. Donner A. Statistical Methodology for Paired Cluster Designs. American Journal of Epidemiology 1987;126(5):972-979.
36. Donner A, Hauck W. Estimation of A Common Odds Ratio in Paired-Cluster Randomization Designs. Statistics in Medicine 1989;8:599-607.
37. Donner A, Klar N. Statistical Considerations in the Design and Analysis of Community Intervention Trials. Journal of Clinical Epidemiology 1996;49(4):435-439.
38. Shipley MJ, Smith P, Dramix M. Calculation of Power for Matched Pair Studies when Randomization is by Group. International Journal of Epidemiology 1989;18 (2):457-461.

39. Grosskurth H, Mosha F, Todd J, Mwijarubi E, et a. Impact of Improved Treatment of Sexually Transmitted Disease on HIV Infection in Rural Tranzania: randomised controlled trial. The Lancet 1995;346:530-536.
40. Spiegelhalter DJ. Bayesian methods for cluster randomized trials with continuous responses. Statistics in Medicine. Statistics in Medicine 2001(20):435-452.
41. Donner A, Brown K, Brasher P. A methodological review of non-therapeutic intervention trials employing cluster randomization, 1979-1989. International Journal of Epidemiology 1990;19(4):795-800.
42. Sowden A, Arblaster L. Mass media interventions for preventing smoking among young people. The Cochrane Library 1999(Issue 1).
43. Hendrick R, Smith R, Rutledge IJ, Smart C. Benefit of screening mammography in women aged 40-49: a new meta-analysis of randomized controlled trials. Journal of the National Cancer Institute Monographs 1997;22:87-92.
44. Kramer M. Balanced protein/energy supplementation in pregnancy. The Cochrane Library 1999(Issue 1).
45. Glasziou PP, Woodward AJ, Mahon CM. Mammographic screening trials for women aged under 50: a quality assessment and meta-analysis. The Medical Journal of Australia 1995;162:625-629.
46. Roberts M, Alexander F, Anderson T, Chetty U, Donnan P, Forrest P, et al. Edinburgh trial of screening for breast cancer: mortality at seven years. The Lancet 1989;335(3 Feb.):241-246.
47. Tabar L, Fagerberg CG, Gad A, Holmberg L, Grontoft O, Ljungquist U, et al. Reduction in mortality from breast cancer after mass screening with mammography. The Lancet 1985(13 April):829-832.
48. Rao J, Scott AJ. A simple method for the analysis of clustered binary data. Biometrics 1992;48(june):577-585.
49. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-188.
50. Rahmathullah L. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. New England Journal of Medicine 1990;323:929-935.
51. West K, al e. Efficacy of vitamin A in reducing preschool child mortality in Nepal. Lancet 1991;338:67-71.
52. Daulaire N, al e. Childhood mortality after a high dose of vitamin A in a high risk population. British Medical Journal 1992;304:207-210.
53. The Vitamin A and Pneumonia Working Group. Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. Bulletin of the World Health Organization 1995;73(5):609-619.
54. Beaton G, Martorell R, Aronson K, Edmonston B, McCabe G, Ross A, et al. Effectiveness of Vitamin A supplementation in the control of young child morbidity and mortality in developing countries. The 1993;Paper No. 13(December).
55. Donner A, Piaggio G, Villar J. Statistical methods for the meta-analysis of cluster randomization trials. Statistical Methods in Medical Research 2001;10(5):325-338.
56. Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. Statistics in Medicine 2002;21:2971-2980.
57. Bauman KE, LaPrelle J, Brown JD, Koch GG, Padgett CA. The Influence of three mass media campaigns on variables related to adolescent cigarette smoking: results of a field experiment. American Journal of Public Health 1991;81(5):597-604.

58. Campbell M. Cluster Randomised Trials: time for improvement The implications of adopting a cluster design are still largely being ignored. British Medical Journal 1998;317(7167):1171-1172.
59. Elbourne D, Campbell M. Extending the CONSORT statement to cluster randomized trials: for discussion. Statistics in Medicine 2001;20(3):489-496.
60. Klar N, Donner A. Current and future challenges in the design and analysis of cluster randomization trials. Statistics in Medicine 2001;20(24):3729-3740.
61. Donner A, Klar N. Design and analysis of cluster randomization trials in health research. London: Arnold; 2000.
62. Panpanich R, Garner P. Growth monitoring in children. The Cochrane Library 1999 (Issue 1).
63. Garner P, Gulmezoglu A. Prevention versus treatment for malaria in pregnancy women. The Cochrane Library 1999(Issue 1).
64. Lumley J, Oliver S, Waters E. Intervention for promoting smoking cessation during pregnancy. The Cochrane Library 1999(ssue 1).
65. Thomson M, Oxman A, Davis D, Haynes R, Freemantle N, E H. Audit and feedback: effects on professional practice and health care outcomes. The Cochrane Library 1999 (Issue 1).
66. Thomson M, Oxman A, Haynes R, Davis D, Freemantle N, Harvey E. Local opinion leaders: effects on professional practice and health care outcomes. The Cochrane Libary 1999.
67. Jefferson T, Demicheli V, Deeks J, Graves P, Pratt M, Rivetti D. Vaccines for preventing anthrax Vaccines. The Cochrane Library 1999(Issue 1).
68. Villar J, D K-N. Patterns of routine antenatal care for low-risk pregnancy. The Cochrane Library 1999(Issue 1).
69. Howe R. Circumcision and HIV infection: a review of the literature and meta-analysis. International Journal of STD&Aids 1999;10:8-16.
70. Brunner E, White I, Thorogood M, Bristow A, Curle D, Marmot M. Can dietary interventions change diet and cardiovascular risk factors? A meta-analysis of randomized controlled trials. American Journal of Public Health 1997;87(9):1415-1422.
71. Mahomed K. Iron supplementation in pregnancy. The Cochrane Library 1999(Issue 1).
72. Silagy C, Ketteridge S. Physician advice for smoking cessation. The Cochrane Library 1999(Issue 1).
73. Lancaster T, Stead L. Self-help interventions for smoking cessation. The Cochrane Library 1999(Issue1).
74. Ebrahim S, Smith GD. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. British Medical Journal 1997;314:1666-1674.
75. Stead L, Lancaster T. Group behaviour therapy programmes for smoking cessation. The Cochrane Library 1999(Issue 1).
76. Dickson R, Awasthi S, Demellweek C, Williamson P. Anthelminthic drug for treating worms in children: effects on growth and cognitive performance. The Cochrane Library 1999(Issue 1).
77. Glasziou P, Mackerras D. Vitamin A supplementtation in infectious diseases: a meta-analysis. British Medical Journal 1993;306:366-370.
78. Gillespie L, Gillespie W, Robertson M, Cumming R, Lamb S, Rowe B. Interventions for preventing falls in elderly people. The Cochrane Library 2000(Issue 3).

79. Choi H, Breman J, Teutsch S, Liu S, Hightowe W, Sexton J. The effectiveness of insecticide-impregnated bed nets in reducing cases of maralia infection: a meta-analysis of published results. American Journal of Tropical Medicine and Hygiene 1995;52:377-382.
80. Lengeler C. Insecticide treated bednets and curtains for preventing malaria. The Cochrane Libary 1999(Issue 3).
81. Ringash J. Preventive health care, 2001 update: screening mammography among women aged 40-49 years at average risk of breast cancer. Canadian Medical Association Journal 2001;164(4):469-476.
82. Sutton A, Abrams K, Jones D. An illustrated guide to the methods of meta-analysis. Journal of Evaluation in Clinical Practice 2001;7(2):135-148.
83. Bailey KR. Inter-Study Differences: How should they influence the interpretation and analysis of results? Statistics in Medicine 1987;6:351-358.
84. Thompson S. Why sources of heterogeneity in meta-analysis should be investigated. British Medical Journal 1994;309(6965):1351-5.
85. Sutton A, Abrams K, Jones D, Sheldon T, Song F. Systematic reviews of trials and other studies. Health Technology Assessment 1998;2(19):1-275.
86. Thompson SG, Smith TC, Sharp SJ. Investigating Underlying Risk as a Source of Heterogeneity in Meta-Analysis. Statistics in Medicine 1997;16:2741-2758.
87. Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. Statistics in Medicine 2001;20:825-840.
88. Biggerstaff B, Tweedie R. Incoperating variability in estimates of heterogeneity in the random effects model in meta-analysis. Statistics in Medicine 1997;16:753-768.
89. Hardy RJ, Thompson SG. A Likelihood Approach to Meta-Analysis with Random Effects. Statistics in Medicine 1996;15:619-629.
90. Hardy RJ, Thompson SG. Detection and Describing Heterogeneity in Meta-analysis. Statistics in Medicine 1998;17:841-856.
91. Self S, Liang K-Y. Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions. Journal of the Amercan Statistical Association 1987;82:605-10.
92. Colditz G, Burdick E, Mosteller F. Heterogeneity in meta-analysis of data from epidemiologic studies: commentary. American Journal of Epidemiology 1995;142:371-382.
93. Dickersin K, Min Y, Meinert C. Factors influencing publication of research results. Journal of the American Medical Association 1992;267:374-378.
94. Staff BMJE. The editor regrets.....(editorial). British Medical Journal 1983;280:508.
95. Song F, Easterwood A, Gilbody S, Duley L, Sutton A. Publication and other selection biases in systematic reviews. Health Technology Assessment 2000;4(38):1-142.
96. Horton R. Medical editors trial amnestry. Lancet 1997;350:756.
97. Horton R, Smith R. Time to register randomised trials- the case is now unanswerable. British Medical Journal 1999;319:865-866.
98. Egger M, Davey S, Schneider M, Minder C. Bias in location and selection of studies. British Medical Journal 1997;315:629-634.
99. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Statistics in Medicine 2001;20:641-654.
100. Light R, Pillemar D. Summing Up: the science of reviewing research. Cambridge,MA: Harvard University Press; 1984.
101. Duval S, Tweedie R. Trim and Fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Bimetrics 2000;56:455-463.

102. Egger M, Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. British Medical Journal 1997;315:629-634.
103. Tang J-L, Liu JL. Misleading funnel plot for detection of bias in meta-analysis. Journal of Clinical Epidemiology 2000;53:477-484.
104. Ioannidis JP, Cappelleri JC, Lau J. Issues in Comparisons Between Meta-analyses and Large Trials. JAMA 1998;279(14):1089-1093.
105. Begg CB, Mazumdar M. Operating characteristic of a rank correlation test for publication bias. Bimetrics 1994;50:1088-1101.
106. Givens G, Smith D, Tweedie R. Publication bias in meta-analysis: a Bayesian data-augmentation approach to account for issues exemplified in the passive smoking debate. Statistical Sciences 1997;12:221-250.
107. Sutton AJ, Lambert PC, Hellmich MA, Abrams KR, Jones DR. Meta-Analysis in Practice: A critical review of available software. haven't know yet 1999:1-23.
108. Hasselblad V, Mccrory D. Meta-analytic tools for medical decision making: a practical guide. Medical Decision Making 1995;15:81-96.
109. Stram DO. Meta-Analysis of Published Data Using a Linear Mixed-Effects Model. Biometrics 1996;52(June):536-544.
110. Larholt K, Tsiatis A, Gelber R. Variability of coverage probabilities when applying a random effects methodology for meta-analysis. Unpublished 1994.
111. Berkey C, Hoaglin D, Mosteller F, Colditz G. A Random-Effect Regression Model for Meta-analysis. Statistics in Medicine 1995;14:395-411.
112. Chang B-H, Waternaux C, Lipsitz S. Meta-analysis of binary data: which within study variance estimate to use? Statistics in Medicine 2001;20:1947-1959.
113. Sullivan LM, Dukes KA, Losina E. Tutorial in Biostatistics An Introduction to Hierarchical Linear Modelling. Statistics in Medicine 1999;18:855-888.
114. Goldstein H, Rasbash J, Plewis I, Draper D, Browne W, Yang M, et al. A User's Guide to MLwiN. London: Institute of Education; 1998.
115. Goldstein H. Multilevel Statistical Models. London: Edward Arnold; 1995.
116. Turner RM, Omar RZ, Yang M, Goldstein H, SG T. A multilevel model framework for meta-analysis of clinical trials with binary outcomes. Statistics in Medicine 2000;19(24):3417-32.
117. Rasbash J, Browne W, Goldstein H, Yang M, Plewis I, Healy M, et al. A user's guide to MLwiN. London: Institute of Education; 2001.
118. Dietz E, Weist K. Meta-analysis in hospital and clinical epidemiology based on mixed generalized linear models. In: GLM; 2000: on publishing; 2000.
119. Aitkin M. A General Maximum Likelihood Analysis of Variance Components in Generalized Linear Models. Bimetrics 1999;55:117-128.
120. Platt RW, Leroux BG, Breslow N. Generalized Linear Mixed Models for Meta-analysis. Statistics in Medicine 1999;18:643-654.
121. Zhou X-H, Brizendine E, Pritz M. Methods for Combining Rates from Several Studies. Statistics in Medicine 1999;18:557-566.
122. Aitkin M. Meta-analysis by random effect modelling in generalized linear models. Statistics in Medicine 1999;18:2343-2351.
123. Aitkin M. A general maximum likelihood analysis of overdispersion in generalized linear models. Statistics and Computing 1996;6:251-262.
124. Hinde JP, Wood A. Binomial variance component models with a non-parametric assumption concerning random effects. In: R. Crouchley,ed. Longitudinal Data Analysis. Aldershot, Hants: Avebery; 1987.

125. Lindsay BG. Mixture Models: Theory, geometry and applications. Pennsylvania State: Institute of Mathematical Statistics and the American Statistical Association; 1995.
126. Boehning D. Chapter 2: Theory of nonparametric mixture models. In: Computer-Assisted Analysis of Mixtures and Applications: meta-analysis,disease mapping and others. New York: CHAPMANN&HALL/CRC; 1999. p. 31-42.
127. Boehning D. Chapter 5 C.A.MAN-application: meta-analysis. In: Computer-Assisted Analysis of Mixtures and Applications: meta-analysis,disease mapping and others. New York: CHAPMANN&HALL/CRC; 1999. p. 93-104.
128. Dietz E, Boehning D. Analysis of longitudinal data using a finite mixture model. Statistical Papers 1994;35:203-210.
129. Dietz E, Boehning D. Statistical inference based on a general model of unobserved heterogeneity. Lecture Notes in Statistics 1995;104:75-82.
130. Dietz E. PORML macro programe in S-plus software. In. Free University, Institute of Social Medicine, Berlin; 2001.
131. Bohning D. Mixture Models: Computational Aspects and Applications. Tutorials on Mixture Models, at the Conference on Recent Developments in Mixture Modeling, Hamburg Germany July,2001.
132. Celeux G. Different points of view for choosing the number of components in a mixture model. In: Govaert J, Janssen N, editors. 10th International Symposium on Applied Stochastic Models and Data Analysis; 2001; France; 2001. p. 21-28.
133. Hartzel J, Liu I-M, Alan A. Describing heterogeneous effects in stratified ordinal contingency tables, with application to multi-center clinical trials. Computational Statistics & Data Analysis 2001;35:429-449.
134. Aitkin M, Anderson D, Francis B, Hinde J. Statistical Modelling in GLIM. Oxford: Oxford University Press; 1990.

Appendix: References of meta-analyses and accessible cluster randomized trials for topic 3

1. George SM, Latham MC, Abel R, Ethirajan N, Frongillo EA, Jr. Evaluation of effectiveness of good growth monitoring in south Indian villages. Lancet 1993;342(8867):348-52.
2. Munjanja S, Lindmark G, Nystrom L. Randomised controlled trial of a reduced-visits programme of antenatal care in Harare, Zimbabwe. Lancet 1996; 348: 364-369.
3. Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Senkoro K, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. Lancet 1995;346(8974):530-6.
4. Roberts MM, Alexander FE, Anderson TJ, Chetty U, Donnan PT, Forrest P, et al. Edinburgh trial of screening for breast cancer: mortality at seven years. Lancet 1990;335(8684):241-6.
5. Ceesay SM, Prentice AM, Cole TJ, Foord F, Weaver LT, Poskitt EM, et al. Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. British Medical Journal 1997;315(7111):786-90.
6. Shulman CE, Dorman EK, Talisuna AO, Lowe BS, Nevill C, Snow RW, et al. A community randomized controlled trial of insecticide-treated bednets for the prevention of malaria and anaemia among primigravid women on the Kenyan coast. Tropical Medicina and Internal Health 1998;3(3):197-204.
7. Sorenson G, Morris DM, Hunt MK. Work-site nutrition intervention and employee's dietary habit: the Treatwell program. American Journal of Public Health 1992;82:877-880.
8. Menendez C, Todd J, Alonso PL, Francis N, Lulat S, Ceesay S, et al. The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene 1994;88(5):590-3.
9. Kendrick JS, Zahniser SC, Miller N, Salas N, Stine J, Gargiullo PM, et al. Integrating smoking cessation into routine public prenatal care: the Smoking Cessation in Pregnancy project. American Journal of Public Health 1995;85(2):217-22.
10. Tabar L, Fagerberg CJ, Gad A, Baldetorp L, Holmberg LH, Grontoft O, et al. Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. Lancet 1985;1(8433):829-32.
11. Bauman KE, LaPrelle J, Brown JD, Koch GG, Padgett CA. The influence of three mass media campaigns on variables related to adolescent cigarette smoking: results of a field experiment. American Journal of Public Health 1991;81(5):597-604.
12. Flay BR, Miller TQ, Hedeker D, Siddiqui O, Britton CF, Brannon BR, et al. The television, school, and family smoking prevention and cessation project. VIII. Student outcomes and mediating variables. Preventive Medicine 1995;24(1):29-40.
13. Flynn BS, Worden J, Secker-Walker RH, Badger GJ, Geller BM. Cigarette smoking prevention effects of mass media and school interventions targeted to gender and age groups. Journal of Health Education 1995;26(2):S45-S51.
14. Haug K, Fugelli P, Aaro LE, Foss OP. Is smoking intervention in general practice more successful among pregnant than non-pregnant women? Family Practice 1994;11:111-6.
15. Wilson DH, Wakefield MA, Steven ID, Rohrsheim RA, Esterman AJ, Graham NM. "Sick of Smoking": evaluation of a targeted minimal smoking cessation intervention in general practice. The Medical Journal of Australia 1990;152(10):518-21.
16. Janz NK, Becker MH, Kirscht JP, Eraker SA, Billi JE, Woolliscroft JO. Evaluation of a minimal-contact smoking cessation intervention in an outpatient setting. American Journal of Public Health 1987;77(7):805-9.
17. Lomas J, Enkin M, Anderson GM, Hannah WJ, Vayda E, Singer J. Opinion leaders vs audit and feedback to implement practice guidelines. Delivery after previous cesarean section. Journal of the American Medical Association 1991;265(17):2202-7.
18. Brown LF, Keily PA, Spencer AJ. Evaluation of a continuing education intervention "Periodontics in General Practice". Community Dental Oral Epidermiology 1994;22:441-447.
19. Howe A. Detecting psychological distress: can general practitioners improve their performance? British Journal of General Practice 1996; 46: 407-410.
20. Lando HA, McGovern PG. The influence of group cohesion on the behavioral treatment of smoking: a failure to replicate. Addictive Behavior 1991;16(3-4):111-21.
21. Resnicow K, Vaughan R, Futterman R. A self-help smoking cessation program for inner-city African Americans: results from the Harlem Health Connection Project. Health Education & Behavior 1997; 24(2): p. 201-217.
22. Group W. Multifactorial trial in the prevention of coronary heart disease. II Risk factor changes at two and four years. European Heart Journal 1982; 3: 184-190.

23. Group I C R F Ë S. Effectiveness of health checks conducted by nurses in primary care: results of the OXCHECK study after one year. British Medical Journal 1994; 308: 308-312.
24. Group FHS. Randomised controlled trial evaluating cardiovascular screening and intervention in general practice: principal results of the British family heart study. British Medical Journal 1994;308: 313-320.
25. Glasgow RE, Terborg JR, Hollis JF, Severson HH, Boles SM. Take heart: results from the initial phase of a work-site wellness program. American Journal of Public Health 1995;85(2):209-16.
26. Hill R, Rigdon M, Johnson S. Behavioral smoking cessation treatment for older chronic smokers. Behavior Therapy 1993; 24: 321-9.
27. Jason LA, Lesowitz T, Michaels M, Blitz C, Victors L, Dean L, et al. A worksite smoking cessation intervention involving the media and incentives. American Journal of Community Psychology 1989;17 (6):785-99.
28. Jason LA, McMahon SD, Salina D, Hedeker D, Stockton M, Dunson, K, et al. Assessing a smoking cessation intervention involving groups, incentives, and self-help manuals. Behavior Therapy 1995; 26: 393-408.
29. Thein-Hlaing, Thane-Toe, Than-Saw. A controlled chemotherapeutic intervention trial on the relationship between Ascaris lumbricoides infection and mulnutrition in children. Transections of the Royal Society of Tropical Medicine and Hygiene 1991; 85: 523-528.
30. Rousham E, Mascie-Taylor C. An 18-month study of the effect of periodic anthelminthic treatment on the growth and nutritional status of pre-school children in Bangladesh. Annals of Human Biology 1994; 21: 315-324.
31. Stoltzfus RJ, Albonico M, Tielsch JM, Chwaya HM, Savioli L. School-based deworming program yields small improvement in growth of Zanzibari school children after one year. Journal of Nutrition 1997;127 (11):2187-93.
32. Hodnett ED, Kaufman K, O'Brien-Pallas L, Chipman M, Watson-MacDonell J, Hunsburger W. A strategy to promote research-based nursing care: effects on childbirth outcomes. Research in Nursing & Health 1996;19(1):13-20
33. Sommer A, Tarwotjo I, Djunaedi E, West KP, Jr., Loeden AA, Tilden R, et al. Impact of vitamin A supplementation on childhood mortality. A randomised controlled community trial. Lancet 1986;1 (8491):1169-73.
34. Rahmathullah L. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. New England Journal of Medicine 1990; 323: 929-935.
35. West KP, Jr., Pokhrel RP, Katz J, LeClerq SC, Khatry SK, Shrestha SR, et al. Efficacy of vitamin A in reducing preschool child mortality in Nepal. Lancet 1991;338(8759):67-71.
36. Daulaire NM, Starbuck ES, Houston RM, Church MS, Stukel TA, Pandey MR. Childhood mortality after a high dose of vitamin A in a high risk population. British Medical Journal 1992;304(6821):207-10.
37. Muhilal, Murdiana A, Azis I, Saidin S, Jahari AB, Karyadi D. Vitamin A-fortified monosodium glutamate and vitamin A status: a controlled field trial. American Journal of Clinical Nutrition 1988;48(5):1265-70.
38. Herrera MG, Nestel P, el Amin A, Fawzi WW, Mohamed KA, Weld L. Vitamin A supplementation and child survival. Lancet 1992;340(8814):267-71.
39. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effect on clinic attendances, hospital admissions, and child mortality. Lancet 1993; 342: 7-12.
40. Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M, et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. New England Journal of Medicine 1994;331(13):821-7.
41. Tinetti M, McAvay G, Claus E. Does multiple risk factor reduction explain the reduction in fall rate in the Yale FICSIT trial? American Journal of Epidemiology 1996; 144: 389-399.
42. Vetter N, Lewis P, Ford D. Can health visitors prevent fractures in elderly people? British Medical Journal 1992; 304: 888-890.
43. Hornbrook MC, Stevens VJ, Wingfield DJ, Hollis JF, Greenlick MR, Ory MG. Preventing falls among community-dwelling older persons: results from a randomized trial. Gerontologist 1994;34(1):16-23.
44. Reinsch S, MacRae P, Lachenbruch PA, Tobis JS. Attempts to prevent falls and injury: a prospective community study. Gerontologist 1992; 32: 450-6.
45. Stross JK, Bole GG. Evaluation of a continuing education program in rheumatoid arthritis. Arthritis and Rheumatism 1980;23:846-849.
46. Stross JK, Hiss RG, Watts CM, Davis WK, Macdonald R. Continuing education in pulmonary disease for primary-care physicians. American Review in Respiratory Disease 1983;127(6):739-46.
47. Stross J, Bole G. Evaluation of an educational program for primary care practitioners, on the management of osteoarthritis. Arthritis and Rheumatism 1985; 28: 108-111.

48. Elliott TE, Murray DM, Oken MM, Johnson KM, Braun BL, Elliott BA, et al. Improving cancer pain management in communities: main results from a randomized controlled trial. Journal of Pain and Symptom Management 1997;13(4):191-203.
49. Snow R, Rowan K, Greenwood B. A trial of permetrin-treated bed nets in the prevention of malaria in Gambian children. Transactions of The Royal Society of Tropical Medicine and Hygiene 1987; 81: 563-567.
50. Snow R, Rowan K, Lindsay S, Greenwood B. A trial of bed nets (mosquito nets) as a malaria control strategy in a rural area of the Gambia, West Africa. Transactions of The Royal Society of Tropical Medicine and Hygiene 1988; 82: 212-215.
51. Sexton JD, Ruebush TK, Brandling-Benett AD. Permethrin-impregnated curtains and bed-nets prevent maralia in western Kenya. American Journal of Tropical Medicine and Hygiene 1990;43:11-18.
52 Kamol-ratanakul P, Prasittisuk C. The effectiveness of permethrin-impregnated bed nets against malaria for migrant workers in Eastern Thailand. American Journal of Tropical Medicine and Hygiene 1992;47:305-309.
53 Beach RF, Ruebush TK, 2nd, Sexton JD, Bright PL, Hightower AW, Breman JG, et al. Effectiveness of permethrin-impregnated bed nets and curtains for malaria control in a holoendemic area of western Kenya. American Journal of Tropical Medicine and Hygiene 1993;49(3):290-300.
54 Graves PM, Brabin BJ, Charlwood JD, Burkot TR, Cattani JA, Ginny M, et al. Reduction in incidence and prevalence of Plasmodium falciparum in under- 5-year-old children by permethrin impregnation of mosquito nets. Bulletin of the World Health Organization 1987;65(6):869-77.
55 Kothari G. The effect of vitamin A prophylaxis on morbidity and mortality among children in urban slums in Bombay. Journal of Tropical Pediatrics 1991;37: 141.
56 D'Alessandro U, Olaleye BO, McGuire W, Langerock P, Bennett S, Aikins MK, et al. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. Lancet 1995;345(8948):479-83.
57 Habluetzel A, Diallo DA, Esposito F, Lamizana L, Pagnoni F, Lengeler C, et al. Do insecticide-treated curtains reduce all-cause child mortality in Burkina Faso? Tropical Medicine and International Health 1997;2(9):855-62.
58 Kroeger A, Manchcheno M, Alarcon J, Pesse K. Insecticide-impregnated bed nets for maralia control: varying experiences from Ecuador, Colombia, and Peru concerning acceptability and effectiveness. American Journal of Tropical Medicine and Hygiene 1995; 53: 313-323.
59 Moyou-Somo R, Lehman LG, Awahmukalah S, Ayuk Enyong P. Deltamethrin impregnated bednets for the control of urban malaria in Kumba Town, South-West Province of Cameroon. Journal of Tropical Medicine and Hygiene 1995; 98(5): 319-324.
60 Rowland M, Bouma M, Ducornez D, Durrani N, Rozendaal J, Schapira A, et al. Pyrethroid-impregnated bed nets for personal protection against malaria for Afghan refugees. Transactions of the Royal Society of Tropical Medicine and Hygiene 1996;90(4):357-61.
61 Nevill CG, Some ES, Mung'ala VO, Mutemi W, New L, Marsh K, et al. Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. Tropical Medicine and International Health 1996;1(2):139-46.
62 Binka FN, Kubaje A, Adjuik M, Williams LA, Lengeler C, Maude GH, et al. Impact of permethrin impregnated bednets on child mortality in Kassena- Nankana district, Ghana: a randomized controlled trial. Tropical Medicine and International Health 1996;1(2):147-54.

Output of the study

1. Presentations at national and international meeting:

1.1 Oral presentation of 'Describing Heterogeneity in Meta-analysis Involving Cluster Randomized Trials: Normal versus Nonparametric Approaches of Random Effects Models' at the 4th Applied Statistics Conference of Northern Thailand during May 23-24, 2002 in Chiang Mai. This presentation is funded by the faculty of Public Health Khon Kaen University.Schedule of the conference is on the attached document no.1.

1.2 Poster presentation of 'Describing Heterogeneity in Meta-analysis Involving luster Randomized Trials: Normal versus Nonparametric Approaches of Random Effects Models' at the 10th Cochrane Colloquium during 31 July – 3 August 2002 in Stavanger, Norway. This presentation is funded by the developing country stipend of the Cochrane Collaboration. Schedule of the Colloquium is on the attached document no.2.

1.3 Poster presentation of 'Overview of Meta-analyses Involving Cluster Randomized Trials'at the XVI International Epidemiology Association World Congress of Epidemiology during August 18-22, 2002 in Montreal, Canada. This presentation is funded by the Thailand Research Fund and the faculty of Public Health Khon Kaen University. Schedule of the Congress is on the attached document no.3.

1.4 Oral presentation of 'Describing Heterogeneity in Meta-analysis Involving Cluster Randomized Trials: Normal versus Nonparametric Approaches of Random Effects Models' at the 23rd Annual Conference The International Society for Clinical Biostatistics (ISCB) during September 9-13, 2002 in Dijon, France.

This presentation is funded by the ISCB Scientist Award and the Khon Kaen University. Schedule of the conference is on the attached document no.4.

2. Publication:

2.1 Laopaiboon M. Meta-analyses involving cluster randomization trials: a review of published literature in health care. StatisticalMethods in Medical Research 2003;in press for the last issue of this year.

Attached document no.5 is the paper

Attached document no. 1

การประชุมวิชาการ สถิติประยุกต์ ภาคเหนือ ครั้งที่ 4

23-24 พฤษภาคม 2545

ณ โรงแรมธาริน อ.เมือง จ.เชียงใหม่

4th Applied Statistics Conference of Northern Thailand

May 23-24 , 2002

Tarin Hotel, Chiang Mai, Thailand

ภาควิชาสถิติ คณะวิทยาศาสตร์ มหาวิทยาลัยเชียงใหม่

สมาคมสถิติแห่งประเทศไทย

โปรแกรมวิชาสถิติประยุกต์
สถาบันราชภัฏเชียงใหม่

ภาควิชาคณิตศาสตร์และสถิติ
มหาวิทยาลัยแม่โจ้

ภาควิชาสถิติ
มหาวิทยาลัยพายัพ

ISBN 974-657-690-9

กำหนดการประชุม

กำหนดการวันพฤหัสบดีที่ 23 พฤษภาคม 2545

เวลา	กิจกรรม
08.00-08.45 น.	ลงทะเบียน
08.45-09.00 น.	พิธีเปิด โดยคณบดี คณะวิทยาศาสตร์ มหาวิทยาลัยเชียงใหม่
09.00-10.30 น.	บรรยายพิเศษเรื่อง ทิศทางการวิจัยทางด้านสถิติ : อดีต ปัจจุบัน และอนาคต ศ.ดร สุชาดา กีระนันทน์ นายกสมาคมสถิติแห่งประเทศไทย
10.30-10.45 น.	อาหารว่าง
10.45-12.00 น.	**เสนองานวิจัยรับเชิญ 2 เรื่อง** 1. ความสัมพันธ์ระหว่างข้อมูลจากการตอบกับข้อมูลที่สะท้อนความเป็นจริง เสนอโดย รศ.ดร สรชัย พิศาลบุตร มหาวิทยาลัยธุรกิจบัณฑิตย์ 2. การวัดประสิทธิภาพของการไฟฟ้าฝ่ายจำหน่ายในประเทศไทย เสนอโดย รศ.ดร. วิชิต หล่อจีระชุณห์กุล สถาบันบัณฑิตพัฒนบริหารศาสตร์
12.00-13.00 น.	รับประทานอาหาร
13.00-14.30 น.	**เสนอผลงานวิจัย** • **สถิติประยุกต์ (ห้องประชุม 1)**
13.00-13.20 น.	1. การสำรวจแรงงานเด็กในภาคประมงและเกษตรจังหวัดสงขลาและนราธิวาส เสนอโดย ผศ.ดร. จิราพร ชมพิกุล มหาวิทยาลัยสงขลานครินทร์
13.20.13.40 น.	2. องค์ประกอบที่มีความสัมพันธ์กับการตัดสินใจของนักศึกษาในการเลือกอันดับเข้าศึกษา ปริญญาตรีสาขาคณิตศาสตร์ เสนอโดย อ. ภูชงค์ แพรขาว มหาวิทยาลัยเทคโนโลยีพระจอมเกล้าธนบุรี
13.40-14.00 น.	3. สถิติวิเคราะห์ปริมาณน้ำตาลในเนื้อผลสับปะรด เสนอโดย นางสาวพีณา สลีวงศ์ มหาวิทยาลัยพายัพ
14.00-14.20 น.	4. สถิติวิเคราะห์ปัจจัยที่มีอิทธิพลต่อจริยธรรมของนักเรียนชั้นมัธยมศึกษาตอนปลาย จังหวั เสนอโดย นางสาว เกสินี วงศ์พนัสสัก มหาวิทยาลัยเชียงใหม่ ผู้ดำเนินรายการ อ.ลักษณา นุศย์น้ำเพชร สถาบันราชภัฏเชียงใหม่
	• **ทฤษฎีสถิติและคณิตศาสตร์ประยุกต์ (ห้องประชุม 2)**
13.00-13.20 น.	1. การเปรียบเทียบวิธีการแก้ปัญหาข้อมูลที่ขาดหายไป 6 วิธีภายใต้บริบทของการวิเคราะห์ เสนอโดย ผศ.ดร.สุนันทา วีรกุลเทวัญ สถาบันราชภัฏสุรินทร์
13.20.13.40 น.	2. A Zero-inflated Negative Binomial Model Applied to a Set of Tissue Culture Data เสนอโดย อ. ดร. นราทิพย์ จั่นสกุล มหาวิทยาลัยสงขลานครินทร์
13.40-14.00 น.	3. An Age-sex Specific EMS backcalculation model and the penalized maximum likelih estimation เสนอโดย ผศ.ดร สุวาณี สุรเสียงสังข์ จุฬาลงกรณ์มหาวิทยาลัย

เวลา	กิจกรรม
14.00-14.20 น.	4. การเปรียบเทียบความแกร่งระหว่างแผนภูมิค่าเฉลี่ยแบบถ่วงน้ำหนักแบบเอกซ์โปเนนเชียล (ENMA) ชิวฮาร์ทและซินเทติก กรณีข้อมูลไม่เป็นการแจกแจงปกติ เสนอโดย รศ. อดิศักดิ์ พงษ์พูลผลศักดิ์ มหาวิทยาลัยเทคโนโลยีพระจอมเกล้าธนบุรี ผู้ดำเนินรายการ อ.อุทิตย์ แก้วบุญเรือง มหาวิยาลัยพายัพ
14.30-15.00 น.	อาหารว่างและชมโปสเตอร์
15.00-16.30 น.	**เสนอผลงานวิจัย (ต่อ)** • **สถิติประยุกต์ (ห้องประชุม 1)**
15.00-15.20 น.	5. Chiang Mai Birthweight Study เสนอโดย อ. ดร.ศักดา พรึงลำภู สถาบันวิจัยวิทยาศาสตร์สุขภาพ มหาวิทยาลัยเชียงใหม่
15.20-15.40 น.	6. แนวคิดพื้นฐานในการเรียนการสอนสถิติศาสตร์ เสนอโดย อ. ดร. ยงยุทธ ไชยพงศ์ จุฬาลงกรณ์มหาวิทยาลัย
15.40-16.00 น.	7. การสำรวจความคิดเห็นของบุคลากรในมหาวิทยาลัยเชียงใหม่ที่มีต่อการปรับเปลี่ยนมหาวิทยาลัยของรัฐให้เป็นมหาวิทยาลัยในกำกับของรัฐบาล เสนอโดย รศ. วัฒนาวดี ศรีวัฒนพงศ์ มหาวิทยาลัยเชียงใหม่
16.00-16.20 น	8. ดัชนีคุณภาพชีวิตและค่าวัดความยากจนในประเทศไทย เสนอโดย ผศ.สุเทพ พันประสิทธิ์ มหาวิทยาลัยธุรกิจบัณฑิตย์ ผู้ดำเนินรายการ อ.สุรีย์ ชูประทีป มหาวิทยาลัยเชียงใหม่
	• **ทฤษฎีสถิติและคณิตศาสตร์ประยุกต์ (ห้องประชุม 2)**
15.00-15.20 น.	5. ช่วงการทำนายค่าสำหรับค่าสังเกตหนึ่งหน่วยในอนาคต เสนอโดย อ. กฤษณะ ลาน้ำเที่ยง มหาวิทยาลัยแม่โจ้
15.20-15.40 น.	6. Describing Heterogeneity in Meta-analysis Involving Cluster Randomized Trials : Normality Versus Nonparametric Approaches of Random Effects Models เสนอโดย รศ. มาลินี เหล่าไพบูลย์ มหาวิทยาลัยขอนแก่น
15.40-16.00 น.	7. การศึกษาตัวสถิติทดสอบสำหรับข้อมูลกระบวนการปัวส์ซอง เสนอโดย อ.อรัญญาพร ไชยสิทธิ์ สถาบันราชภัฏสวนดุสิต
16.00-16.20 น..	8. การประมาณค่าสัมประสิทธิ์การถดถอยเชิงพหุกรณีปัญหามีความสัมพันธ์ระหว่างตัวแปรอิสระและมีค่าผิดปกติ เสนอโดย นางสาวจินดา สุวินัยตระกูล มหาวิทยาลัยเชียงใหม่ ผู้ดำเนินรายการ อ.รุ่งกานต์ ใจวงศ์ยะ มหาวิทยาลัยแม่โจ้

การเสนอผลงานวิจัย

เรื่องที่ 10 : Describing Heterogeneity in Meta-analysis Involving Cluster Randomized Trials: Normality Versus Nonparametric Approaches of Random Effects Models

Malinee Laopaiboon

ment of Biostatistics&Demography, Faculty of Public Health, Khon Kaen University, Khon Kaen 40002, Thailand

66-0-4334-7637 Fax: 66-0-4336-2075 Email: malinee@kku.ac.th

Describing Heterogeneity in Meta-analysis Involving Cluster Randomized Trials: Normality Versus Nonparametric Approaches of Random Effects Models

orresponding author's contact details:

Malinee Laopaiboon,

Department of Biostatistics&Demography,

Faculty of Public Health, Khon Kaen University,

Khon Kaen 40002, Thailand

Tel: 66-0-4334-7637

Fax: 66-0-4336-2075

Email: malinee@kku.ac.th

Describing Heterogeneity in Meta-analysis Involving Cluster Randomized Trials: Normality Versus Nonparametric Approaches of Random Effects Models

Malinee Laopaiboon, Dankmar Böhning, Department of Biostatistics&Demography, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand

Rationale: Meta-analyses involving cluster randomized trials may lead to additional sources of heterogeneity beyond those elevated by meta-analyses involving only individually randomized trials. The general linear mixed model (GLM) has been proposed to explain heterogeneity in meta-analysis where the treatment effect is measured in binary outcome. Log-relative measure is used as a response variable. The parameter estimation is based on assumption of normal distribution of random effects, which has been discussed that it may be difficult to verify in meta-analysis situation. Furthermore, the treatment random effects cannot be measured. The generalized linear mixed model (GLMM) under unspecified distribution of random effects may be an alternative choice.

Objective: This study is done to compare the GLM with the GLMM for describing heterogeneity in meta-analysis involving cluster randomized trials in binary outcome.

Methods: The GLM and GLMM approaches are exemplified in two published meta-analyses involving cluster randomized trials. The first meta-analysis of 14 trials included is done to assess the effectiveness of multiple risk factor interventions to reduce cardiovascular risk factors from coronary heart disease.

The second meta-analysis comprises of 8 trials, which is performed to evaluate the effect mammographic screening on reduction of breast cancer mortality. Observed log-relative risks individual trials are fitted to the GLM as a continuous response. The trials included are classified to categories of randomization units, clusters and individually. This provides a covariate of the model. model parameters are estimated with the restricted maximum likelihood (REML) under the norm assumption of random effects. For the GLMM, observed frequencies of the outcome for each treatm group are used for individual trials. A canonical link function of the observed mean proportion associated with linear predictors model of which treatment and randomization design are treated covariates. Here, the treatment random effects can be measured. The maximum likelihood estimate the model parameters are obtained non-parametrically under a discrete mixture distribution of rand effects for K components, which is implemented by the EM-algorithm procedure. Maximum poster probability is used to classified trials to each component.

Results: The two approaches shown that the covariates effects and variability of random effects f the models easily explained heterogeneity between trials. Results of numerical example will presented at the conference. The GLMM is superior to the GLM in some aspects. The GLMM g further heterogeneity information from random treatment effects. In addition, the approach prov component -specific treatment effect and trial classification according to the optimal components. is very useful in further explaining the heterogeneity that might be beyond the effects found in model.

Conclusions: The GLMM approach provides more information for explaining heterogene effect in the meta-analyses studied. However, care should be taken when interpreting covariates effects of the model because inference on these effects obtained from a discrete mix distribution has not been ruled out. Nevertheless, the GLMM would be much more efficient w it is applied to large meta-analyses.

488words

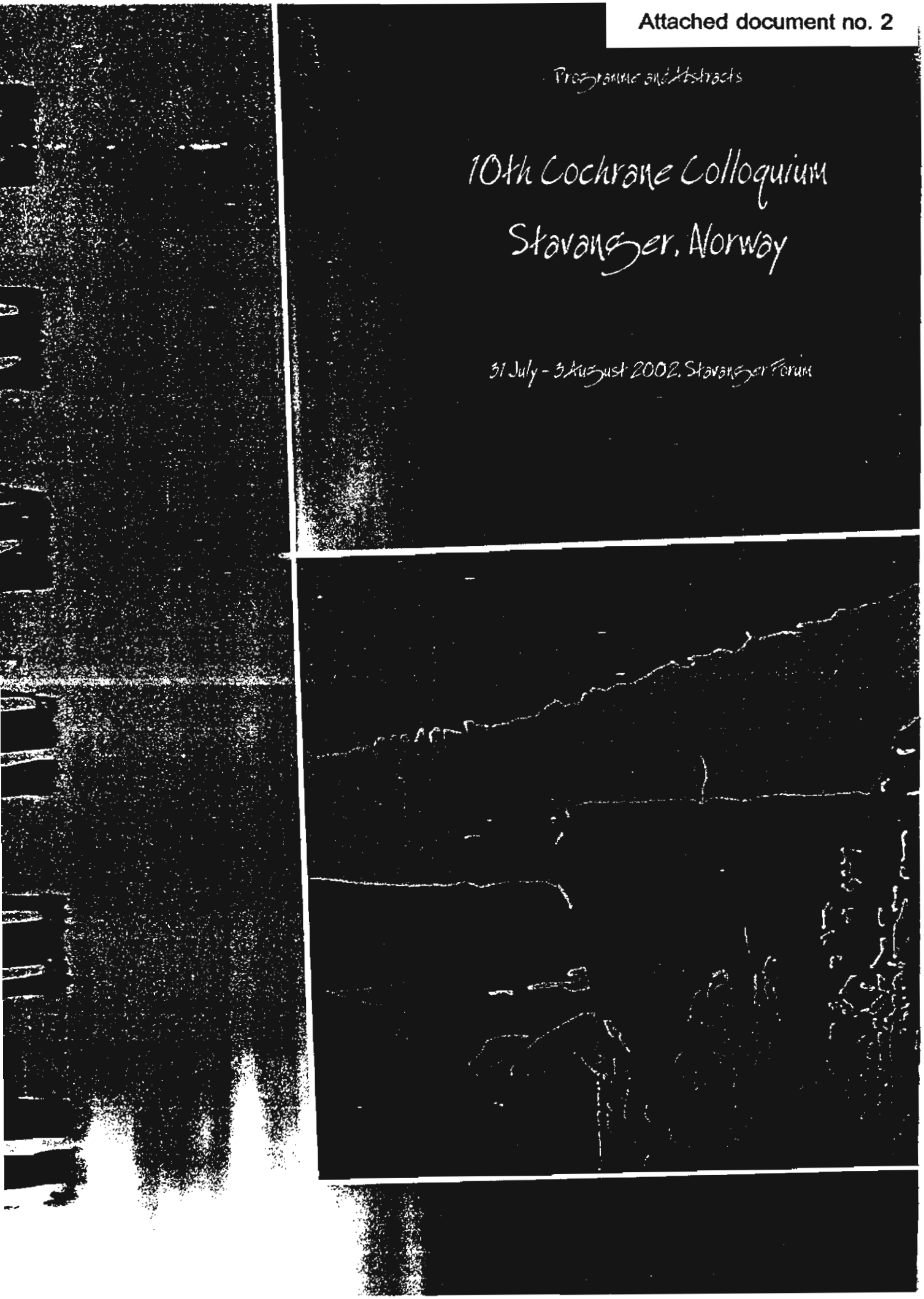
Attached document no. 2

Programme and Abstracts

10th Cochrane Colloquium

Stavanger, Norway

31 July - 3 August 2002, Stavanger Forum



Daily schedule

Tuesday, July 30th

09:00 – 17:00	Meetings
13:00 - 17:00	Funders´ Forum Workshop

Wednesday, July 31st

09:00 – 16:45	Meetings
09:00 - 16:00	Funders´ Forum Workshop
09:00 ~16:00	Hike to Pulpit Rock
09:00 ~16:00	Sightseeing by boat and bus
09:20 - 16:30	Pre-Colloquium Consumer Workshop
12:30 ~16:00	Utstein Monastery
17:00 - 18:15	**Plenary session**
18:30 - 20:00	**Welcome reception at the Rogaland Art Museum**

Thursday, August 1st

07:45 - 09:15	Meetings
09:30 - 10:30	**Plenary session**
10:30 - 10:50	Coffee
11:00 - 12:30	**Entity exchange & Meet the Steering Group**
12:30 - 14:15	Meetings
12:30 - 13:30	Lunch
13:00 – 13:30	**Formal Annual General Meeting (for entity representatives)**
14:10 - 14:30	Coffee
14:30 - 16:30	**Workshops**
16:45 - 17:45	Meetings
18:00 - 23:00	Fjord Cruise on the Lysefjord

Friday, August 2nd

07:45 - 09:15	Meetings
09:30 - 10:30	**Plenary session**
10:30 - 10:50	Coffee
11:00 - 14:15	Meetings
12:00 - 14:00	**Poster presentations session A**
12:30 - 13:30	Lunch
14:10 - 14:30	Coffee
14:30 - 16:30	**Workshops**
16:45 - 17:45	Meetings
18:00 - 23:00	Fjord Cruise on the Lysefjord

Saturday, August 3rd

07:45 - 09:15	Meetings
09:30 - 10:30	**Plenary session**
10:30 - 10:50	Coffee
11:00 - 14:15	Meetings
12:00 - 14:00	**Poster presentations session B**
12:30 - 13:30	Lunch
14:10 - 14:30	Coffee
14:30 - 16:30	**Workshops**
16:45 - 17:45	Meetings
19:30 – 02:00	**Conference party**

Sunday, August 4th

09:00 ~16:00	Hike to Pulpit Rock
09:00 ~16:00	Sightseeing by boat and bus
12:30 ~16:00	Utstein Monastery

(Critical Skills Training in Appraisal for Librarians), created by Anne Brice et al. at Oxford University. The following information will be extracted from relevant articles: study objectives, databases and other electronic resources searched, subject being searched, comparisons made, number of RCTs identified from each source, numerical summaries presented and conclusions. A qualitative analysis will be conducted and, if possible, a quantitative analysis will be done.
Results: Results will be available by July 2002.
Conclusions: This study will aid in developing recommendations for which sources to search in order to identify RCTs and CCTs for systematic reviews. The next step is to conduct a systematic review of search strategies for the databases identified in this review.

[P18] A Typical Cochrane Review: How Many More are Needed to Cover Existing Evidence?

Susan Mallett and Mike Clarke. UK Cochrane Centre, NHS Research and Development Programme, Oxford, OX2 7LG, UK.

Objective: To describe a typical Cochrane review in terms of the number of studies listed as included studies, ongoing studies and studies awaiting assessment. To use this information to provide an estimate of how many Cochrane reviews would be needed to assess all studies currently listed in *The Cochrane Controlled Trials Register (CENTRAL).*
Methods: 989 reviews from *The Cochrane Database of Systematic Reviews* in *The Cochrane Library,* Issue 1, 2001 were analysed for the number of included studies, ongoing studies and studies awaiting assessment per review. Included studies are those meeting eligibility criteria for the review, and where information is included. The number of references cited per study was extracted from a random sample of reviews.
Results: The 989 Cochrane reviews contained 9,778 included studies, with the typical Cochrane review containing 6 studies (based on the median number per review). 17% of reviews listed ongoing studies that met review criteria but where the results of the study were not yet available for inclusion. 29% of reviews listed studies awaiting assessment of whether these should be included in the review. The number of references per study within Cochrane reviews was used to provide an estimate of the number of trials referenced by 300,00 reports in *CENTRAL.* This was used to provide an estimate of the number of additional Cochrane reviews that would be needed for systematic reviews to cover all these studies.
Conclusions: 9,778 trials were included in 989 Cochrane reviews in *The Cochrane Library*, Issue 1, 2001. A typical Cochrane review included 6 studies and 6.6 references. With an average Cochrane review containing six studies, this would correspond to 45,000 Cochrane reviews being needed to cover the more than 300,000 references in *CENTRAL* (approximately 270,000 studies). It is, however, possible that 1.1 references per study is an underestimate. For example, the Cochrane Stroke Group found an average of 2.1 in their Specialized Register of Stroke Trials (4,525 reports corresponding to 2,132 studies). On the basis of this figure, the number of additional Cochrane reviews would be estimated as 24,000. In addition not all references in *CENTRAL* or the studies they report, might be suitable for new Cochrane reviews. There will be references to studies already within Cochrane reviews and some references appear more than once. In addition some of the studies will relate to interventions that are no longer used or information that is not relevant to health care decisions, and some studies may be eligible, but not yet included, in existing Cochrane reviews. Given that 45,000 may be a gross overestimate, it is difficult to know how many Cochrane reviews would be needed, but we predict that at least another 10,000 Cochrane reviews are needed to cover a substantial proportion of the studies relevant to health care that have already been identified.

[P19] Describing Heterogeneity in Meta-analysis Involving Cluster Randomized Trials: Normality versus Nonparametric Approaches of Random Effects Models

Malinee Laopaiboon, Dankmar Böhning, Department of Biostatistics & Demography, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand

Objective: The purpose of this study was to compare the general linear mixed model (GLM) with the generalized linear mixed model (GLMM) for describing heterogeneity in meta-analysis involving cluster randomized trials in binary outcome.
Methods: The two approaches of GLM and GLMM were exemplified in two published meta-analyses involving cluster randomized trials. The first meta-analysis was done to assess the effectiveness of multiple risk factor interventions to reduce cardiovascular risk factors from coronary heart disease. Analysis was performed in the 14 trials included that provided smoking prevalence outcome. The second meta-analysis comprised fewer trials of 8, which was performed to evaluate the effect of mammographic screening on reduction of breast cancer mortality. Observed log-relative risks for individual trials are fitted to the GLM as a continuous response. Randomization design was treated as a covariate of the model. The model parameters were estimated with the restricted maximum likelihood (REML) under the normality assumption of random effects. For the GLMM, observed frequencies of the outcome for each treatment group that approached to poisson distribution were used rather than the observed log-relative risks for individual trials. A canonical link function of the observed mean proportions was associated with linear predictors model of which treatment and randomization design were treated as covariates. The model parameters were estimated non-parametrically under a discrete mixture distribution of random effects for K components. Maximum posterior probability were used to classified trials to each component.
Results: The two approaches shown that the covariates effects and variability of random effects from the models easily explained heterogeneity between trials. The GLMM was superior to the GLM in some aspects. The GLMM gave further heterogeneity information from random treatment effects. In addition, it provided component (or subgroup)-specific treatment effect and trial classification according to the optimal components. This was very useful in further explaining the heterogeneity that might be beyond the effects found in the model.
Conclusions: The GLM and GLMM approaches were preferable for meta-analyses involving cluster randomized trials. However, care should be taken when using the GLM because the GLM needed a strong assumption of normality distribution of random effects components. It was also difficult to verify validity of the assumption. For the GLMM, care should be taken when interpreting treatment effect in terms of risk since the inference on treatment effect obtained from a discrete mixing distribution had not been ruled out. Nevertheless, these two approaches would be much more efficient when they were applied to large meta-analyses.

[P20] Impact of Grey Literature on Meta-Analyses of Randomized Trials – A Systematic Review

Sally Hopewell, Steve McDonald, Mike Clarke, Matthias Egger. The UK Cochrane Centre, Oxford, United Kingdom.

Background: The inclusion of grey literature (i.e. literature that has not been formally published) in systematic reviews may help to overcome some of the problems of publication bias, which can arise due to the selective availability of data. There is now some evidence in support of this, suggesting that the exclusion of grey literature from meta-analyses can lead to an exaggeration of the effect of treatment.
Objective: This study aims to review systematically research studies, which have investigated the impact of grey literature in meta-analyses of randomized trials. A study will be considered eligible for this review if it compares the effect of the inclusion and exclusion of grey literature on the results of meta-analyses of randomized trials.
Methods: Studies will be identified by searching the *Cochrane Methodology Register*, MEDLINE, EMBASE, Science Citation Index and by handsearching journals and conference proceedings. The main outcome measure will be an estimate of the impact of trials from the grey literature on the pooled effect estimates of the meta-analyses. Information will also be collected on the area of health care, the number of meta-analyses, the number of trials, the number of trial participants, the year of publication of the trials, the language and country of publication of the trials, the number and type of grey and published literature, and methodological quality.
Results and Conclusions: As of February 2002, two studies have been identified which assess the impact of including grey literature in meta-analyses of randomized trials. The results of these studies and any other studies identified in the interim will be reviewed.

Attached document no. 3

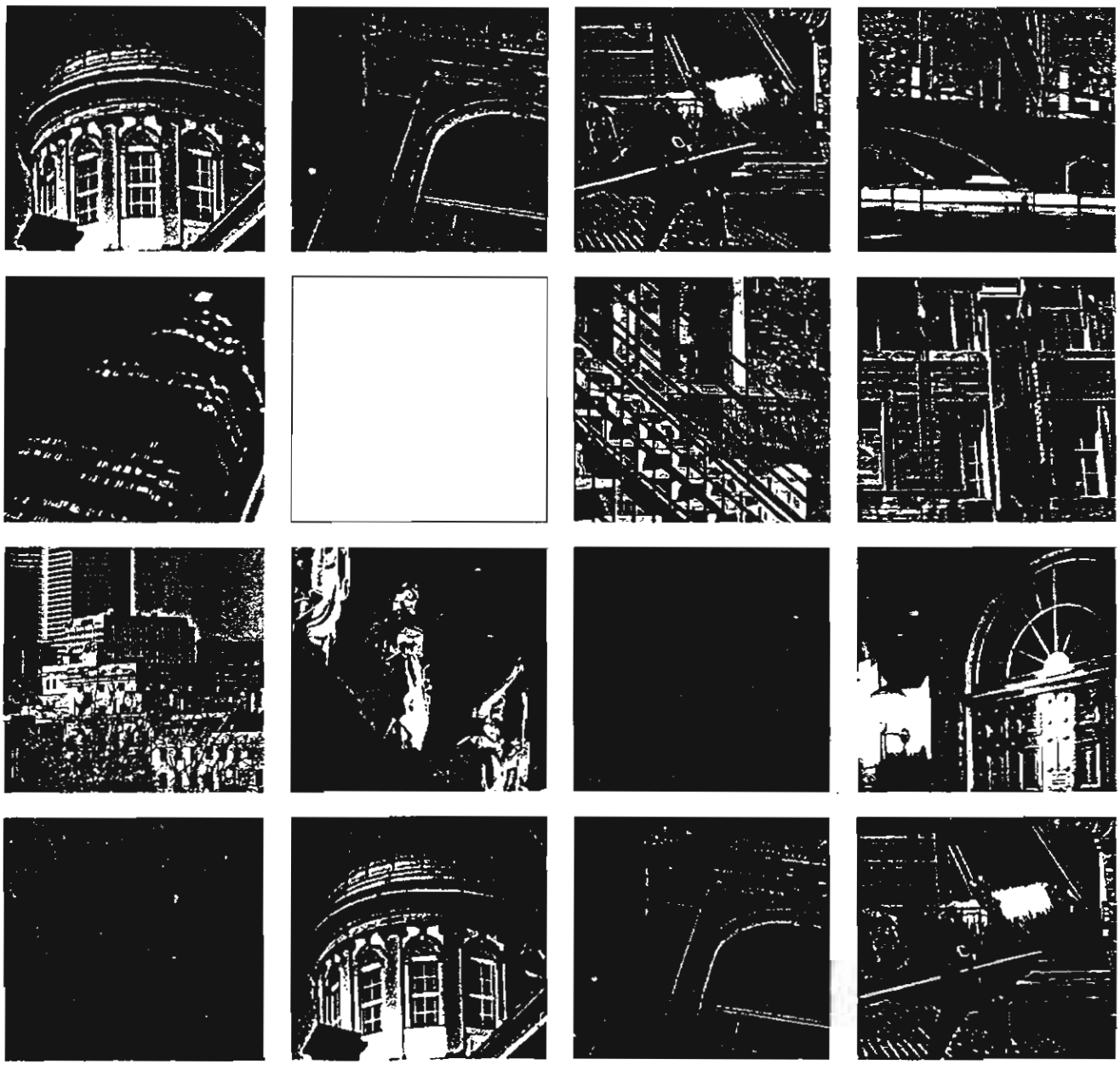
XVI IEA World Congress of Epidemiology

International Epidemiological Association

Montreal, Canada, August 18 - 22, 2002

Palais des Congrès

Final Programme & Book of Abstracts



PROGRAMME AT A GLANCE

	Sunday, Aug. 18	Monday, Aug. 19	Tuesday, Aug. 20	Wednesday, Aug. 21	Thursday, Aug. 22
8:30 - 10:30	Pre-Congress Workshops: IGES Workshop/Training Course: Association Studies in Genetic Epidemiology (13:00-16:00) - Room 514C Effectiveness of Prevention - What Is the Evidence? (10:00-16:30) - Room 514AB Design and Analysis of Matching Data (9:00-17:00) - Room 513DE	Plenary: Global Health Concerns for Epidemiology - Room 517BC	Plenary: International Health and International Epidemiology - Room 517BC	Plenary: Epidemiology as a Trans-disciplinary Science - Room 517BC	Plenary: Molecular and Genetic Epidemiology: Opinions at Odds - Room 517BC
10:30 - 11:00		Break and Poster Viewing			Break
11:00 - 12:30		Evidence to Action: Science, Ethics, and Precautionary Preventive Interventions - Room 516CD Biomarkers of Exposures and Risk - Room 516AB Satellite Workshop: New Developments in the Epidemiology of Sexually Transmitted Infections - Room 513 ABC	Evaluating the Impact of Large Scale Population Interventions: The Role of Randomization and Other Approaches - Room 516AB Environmental and Occupational Exposures: Under-Studied Populations and Under-Studied Risks - Room 516CD WHO Satellite Symposium: Global Health Security: Epidemic Alert and Response - Room 513ABC	Application of Epidemiology to Cancer Prevention - Room 516CD Infectious Diseases - Room 516AB The Epidemiological Study of Social and Psychological Determinants - Room 513ABC	Expanding Analytic Methods to Account for Biases in Observational Studies - Room 516AB Summaries of Regional Workshops - Room 513ABC
11:00 - 13:00		Oral Communications			
12:30 - 14:00	Registration	Lunch Break and Poster Discussions			
14:00 - 15:30		Epid-Internet-ology: Internet at the Center of Our Field - 516AB HIV in Developing Countries: What Is the Link between Current Prevention Programmes and the Epidemiologic Evidence? - Room 516CD Occupation, Cancer and Aging - Room 514 Health Canada Satellite Symposium on Chonic Disease Control - Room 513 ABC	Indicators for Estimates of the Burden of Illness: Framework and Practice in Developing Countries - Room 514 Publishing in Epidemiology Journals - Room 516CD Epidemiology of Arthritis and Rheumatic Diseases - Room 513ABC Assessment of Population and Individual Risk from Epidemiologic Data - Room 516AB	ADELF Workshop: Les bases scientifiques des liens cancer-environnement - Room 516CD Regional Workshop: Control of Chagas' Disease in Latin America - Room 513ABC Regional Workshop: Tobacco Control in the Eastern Mediterranean Region - Room 516AB Region-Specific Workshop: Developing Community-based Programmes to Mange Impact of HIV/AIDS Epidemic - Room 514	
15:30 - 16:00		Oral Communications Break and Poster Viewing			
16:00 - 17:30		Longitudinal Study of Aging Cohorts: What Have We Learned About Chronic Diseases? - Room 513ABC The Role of Clinical Trials in Nutritional Epidemiology - 516CD Satellite Workshop: New Developments in the Epidemiology of Diseases Caused by Blood-borne Pathogens - Room 516AB WHO Symposium: Reproductive Health Library - Room 514	Breast and Prostate Cancers - Room 513 ABC Cardiovascular Diseases - Room 514 Personal Character, Virtue and the Ethical Epidemiologist - Room 516CD Community Intervention Trials - 516AB	ADELF Workshop *(continued)* Regional Workshop: Eastern Mediterranean *(continued)* Regional Workshop: Africa *(continued)* Regional Workshop: Status of Medical Biostatistics in Southeast Asia - Room 513ABC	Closing Ceremony (12:30)
16:00 - 18:00		Oral Communications			
17:30 - 19:00	Opening Ceremony and Keynote Lecture - Room 517BC	IEA Business Meeting (17:45-19:15)		IEA Business Meeting (17:45-19:45)	
19:00 - 20:00	Welcome Reception - Exhibit Hall	Concert at Notre-Dame Basilica (19:30)		Gala Banquet (20:00)	

WP153 **Informal Work and Common Mental Disorders**
Ana Ludermir, Federal University of Pernambuco, Recife, Brazil

WP154 **The Prevalence of Depression and Suicidal Thoughts in Iranian Students**
Mohammad Reza Sargolzaee, Mashad University of Medical Sciences, Mashad, Iran

WP155 **The Associations between Discomfort and Psychological Symptoms, in the Greater Athens Area, during the Maximum of the Solar Cycle No 22**
Athanasios Paliatsos, TEI of Piraeus, Glyfada, Greece

WP156 **Overview of Meta-Analyses Involving Cluster Randomized Trials**
Malinee Laopaiboon, University of Khon Kaen, Faculty of Public Health, Khon Kaen, Thailand

WP157 **Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational studies**
Michael Huncharek, Meta-analysis Research Group, Stevens Point, USA

WP158 **Hepatitis B Immune Globulin for Prevention of Post-transplantation Hepatitis B (Cochrane Review)**
Zhiyong Hong, Blood-borne Pathogens Division, CIDPC, Ottawa, Canada

WP159 **The Mammography Controversy: Our Unsupportable Claims of Certainty Catch Up with Us**
Carl V. Phillips, University of Texas School of Public Health, Houston, USA

WP160 **A Survey on the Knowledge, Attitudes and Practices of Married Women of 15-49 Years Old to Contraceptive Devices in Shiraz, Iran, 2000**
Leila Malekjamshidi, Shiraz University of Medical Sciences, Shiraz, Iran

WP161 **Social Epidemiology: An Essential Aspect of Inter-Disciplinary Professional Training**
Fredric Daniell, State University of New York at Brockport, Brockport, USA

WP162 **Teaching Epidemiology On-Line: Overview of Course with an Emphasis on On-Line Discussions and Practicals Correction**
Pierre Philippe, University of Montréal, Montréal, Canada

WP163 **Problem-Based Learning as a Tool for Teaching Epidemiology**
Jane Heyworth, The University of Western Australia, Crawley, Australia

WP164 **Clinicians and Epidemiology**
Shyam Chirravoori, DRRML Hospital, Dwarka, India

WP165 **Teaching Postgraduate Epidemiology in a Time of Transition–The Polish Experience**
Miroslaw Wysocki, National Institute of Hygiene, Warsaw, Poland

WP167 **Association of Time Spent Watching Television and Physical Activity with Obesity in Ahwaz-Iran**
Hamid Soori, Ahwaz University of Medical Sciences, Ahwaz, Iran

WP168 **Hygiene Characteristics of Households in an Epidemic of Acute Diarrhoeal Disease in Rural Nigeria**
Christian Chibuzo Ibeh, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria

WP169 **Determination of Marital Satisfaction and Its Contributing Factors in Shiraz.**
Ramin Shafieian, Shiraz University of Medical Sciences, Shiraz, Iran

WP153

INFORMAL WORK AND COMMON MENTAL DISORDERS

Ludermir A.
Department of Social Medicine. Federal University of Pernambuco, Brazil.

Background:

Understanding causes of common mental disorders in different societies requires an understanding of the differing socio-economic circumstances around the world. One of the significant differences between employment status in developed and developing world is that a large proportion of people work outside the formal labour market in the latter.

Objectives:

This paper investigates the association between informal work and common mental disorders in an impoverished area of Brazil.

Methods:

A cross-sectional survey of a random sample of private households included 683 adults aged 15 years and over living in area II of Olinda, Recife Metropolitan Region, Pernambuco, Brazil. The self-reporting questionnaire (SRQ) was used to estimate the prevalence of common mental disorders.

Results:

Informal workers had a higher prevalence of common mental disorders compared to those in formal employment. This was true before and after adjustment for sex, age, marital status and migration (OR 2.16, 95% CI 1.3-3.7, respectively) and for education and household *per capita* monthly income (OR 1.83, 95% CI 1.1-3.1).

Conclusions:

Working outside the protection of employment legislation is very common in many poorer countries and have adverse consequences for psychological health.

E-mail abl@npd.ufpe.br

WP154

THE PREVALENCE OF DEPRESSION AND SUICIDAL THOUGHTS IN IRANIAN STUDENTS

Sargolzaee, M.R , Keikhaee , M.R.
Department of psychiatry, Mashad University of Medical sciences Mashad. Iran.

Background:

Previous reports have suggested high point prevalence of Depression, Hopelessness and Suicidal thoughts in Iranian students

Objective;

We tested the hypothesis of high prevalence of Depression in the students and the correlation between it and the worries of in the students.

Methods:

We conducted the study on 680 students in four universities in Iran. Our instruments were Beck's Depression inventory and Demographic and psychosocial Questionnaire.

Results:

Over 25 % of the students had Moderate to severe Depression. The prevalence of Depression was not correlated with sex. About 15 % of the students had suicidal thoughts

Conclusion:

High prevalence of Depression and suicidal thought in the students support the notion that they need special Mental Health professional care and social support.

E-mail: isssp@yahoo.com

WP155

THE ASSOCIATIONS BETWEEN DISCOMFORT AND PSYCHOLOGICAL SYMPTOMS, IN THE GREATER ATHENS AREA, DURING THE MAXIMUM OF THE SOLAR CYCLE No 22

Paliatsos A.G., Panagiotakos A.G., Nastos A.G., Korbakis G. K., Tritakis V., Bergiannaki J, Psarros C, Papavrigopoulos T, Stefanis C.N.
General Department of Mathematics, Technological Education Institute of Piraeus; Laboratory of Climatology, Department of Geology, University of Athens; Research Center for Astronomy and Applied Mathematics, Academy of Athens; Mental Health Research Institute, University of Athens, Greece.

Background.

The fact that environmental conditions play a role in the pathogenesis of physical disease was known as early as the time of Hippocrates (430 B.C.). The aim of this study is to evaluate the associations between an environmental index with the presence of psychopathological symptoms observed during the maximum of the solar cycle No 22, on the Greater Athens Area (GAA) inhabitants.

Methods.

We studied a sample of 3569 outpatients (48% were females, 41.96 ± 17.5 years old, 52% were males, 37.45 ± 16.5 years old) that visited the Athens University Medical School during 1989. The investigated psychological symptoms were: aggressive behavior, self-destruction, sleep disorder, acute stress and anxiety, euphoria, feeling of fatigue and depressive mood. In order to evaluate the association between the previous psychopathological symptoms and both the environmental index suggested by Giles, we applied generalized linear models.

Results.

A significant seasonal variation of the DI and the sequence of hospital visits were observed. In particular, 10-unit increases in the DI raise by 25% the probability of having psychopathological symptoms (95% CI: 11% to 45%, $p < 0.001$), while DI > 24 (moderate-to-intense) 2folds the risk (odds ratio = 1.86, 95% CI 1.065 – 3.158, significant level = 0.029) of observing the daily number of outpatients in the upper quartile (i.e. > 13 cases with patho-physiological symptoms per day) compared to the lower quartile (i.e. < 5 cases with patho-physiological symptoms per day).

Conclusions.

In conclusion, our findings suggest that an association between discomfort and the daily number of the outpatients' visits in the psychiatric emergency unit seems to exist. However, it is hard to claim that our findings support causal evidence and a prospective cohort in different time periods may be conducted in order to confirm or refute our findings.

E-mail: dbpanag@math.uoa.gr

WP156

OVERVIEW OF META-ANALYSES INVOLVING CLUSTER RANDOMIZED TRIALS

Laopaiboon M.
Department of Biostatistics and Demography, University of Khon Kaen, Faculty of Public Health, Mueng District, Khon Kaen, Thailand.

Background:

Meta-analysis is commonly used as a tool to evaluate the effectiveness of therapeutic and preventive interventions in many areas of health care. Cluster randomized trials have been increasingly used to evaluate the effectiveness of health interventions in the past two decades. Meta-analysts are being faced with inclusion of such trials in the synthesis approach.

Objective:

To identify and describe current practice of meta-analysis involving cluster randomized trials in the published literature on health care.

Search strategy:

Electronic databases were searched for meta-analyses involving cluster randomized trials from the earliest date available to July 2000.

Selection criteria:
Meta-analyses that included trials where all or some trials had clusters (groups of individuals) as randomization units.
Data collection and analysis:
Each meta-analysis was selected and detail of quantitative synthesis was evaluated regarding the estimation approached for an overall treatment effect, heterogeneity consideration and the concern of inclusion of cluster-randomized trials. The original papers of included cluster randomized trials of the meta-analyses, which were available, were also examined for their randomized designs and data analysis regarding to adjustment for the clustering effect.
Main results:
Twenty-five meta-analyses were reviewed. Fifteen included more than one cluster randomized trial. Each of the fifteen meta-analyses included cluster randomized trials with a mixture of randomized designs and units of analysis. These mixture situations were not considered in any of the meta-analysis. There were three meta-analyses that attempted to estimate the clustering effects for some unadjusted cluster randomized trial results before pooling them in the synthesis, but were arbitrary approaches. Fifty-seven percent of the cluster-randomized trials, which were available, reported their results adjusted for clustering effects.
Conclusions:
No well-established methods used in the meta-analyses involving cluster randomized trials have been proposed. The problem of heterogeneity resulting from complex situations in randomized designs and units of analysis that may be beyond the heterogeneity results obtained from individually randomized trials is still to be considered. Thus, issues in these areas need to be investigated further.

E-mail: malinee@kku.ac.th

WP157
PERINEAL APPLICATION OF COSMETIC TALC AND RISK OF INVASIVE EPITHELIAL OVARIAN CANCER: A META-ANALYSIS OF 11,933 SUBJECTS FROM SIXTEEN OBSERVATIONAL STUDIES
Huncharek M., Kupelnick B.
Meta-analysis Research Group, Stevens Point, WI, United States.

Background:
Prior epidemiological studies suggest an association between perineal cosmetic talc use and increased risk of ovarian cancer. A meta-analysis was performed to evaluate this association.
Methods:
Literature search techniques, study inclusion criteria and statistical procedures were prospectively defined. Data from observational studies were pooled using a general variance based meta-analytic method employing confidence intervals. The outcome of interest was a summary odds ratio (ORp) reflecting the risk of ovarian cancer development associated with perineal talc use versus non-use.
Results:
Sixteen studies meeting protocol inclusion criteria were located enrolling 11,933 subjects. Pooling all 16 studies yielded a ORp of 1.33(1.16-1.45) suggesting a 33% increased risk of ovarian cancer with perineal talc use (no statistical heterogeneity was found). The data showed a lack of a clear dose-response relationship making the ORp of questionable validity. Further analyses showed that hospital based studies demonstrated no relationship between talc use and ovarian cancer risk, i.e. ORp 1.19(0.99-1.41) versus population-based studies, 1.38(1.25-1.52). This suggests that selection bias and/or uncontrolled confounding may result in a spurious positive association.
Conclusion:
The available data do not support the existence of a causal relationship between perineal talc exposure and an increased risk of epithelial ovarian cancer.
E-mail: metaresearch@hotmail.com

WP158
HEPATITIS B IMMUNE GLOBULIN FOR PREVENTION OF POSTTRANSPLANTATION HEPATITIS B (COCHRANE REVIEW)
Hong Z., Zou S., Gao R., Giulivi A.
FPHB, Health Canada, Blood-borne Pathogens Division, CIDPC, Ottawa, ON, Canada.

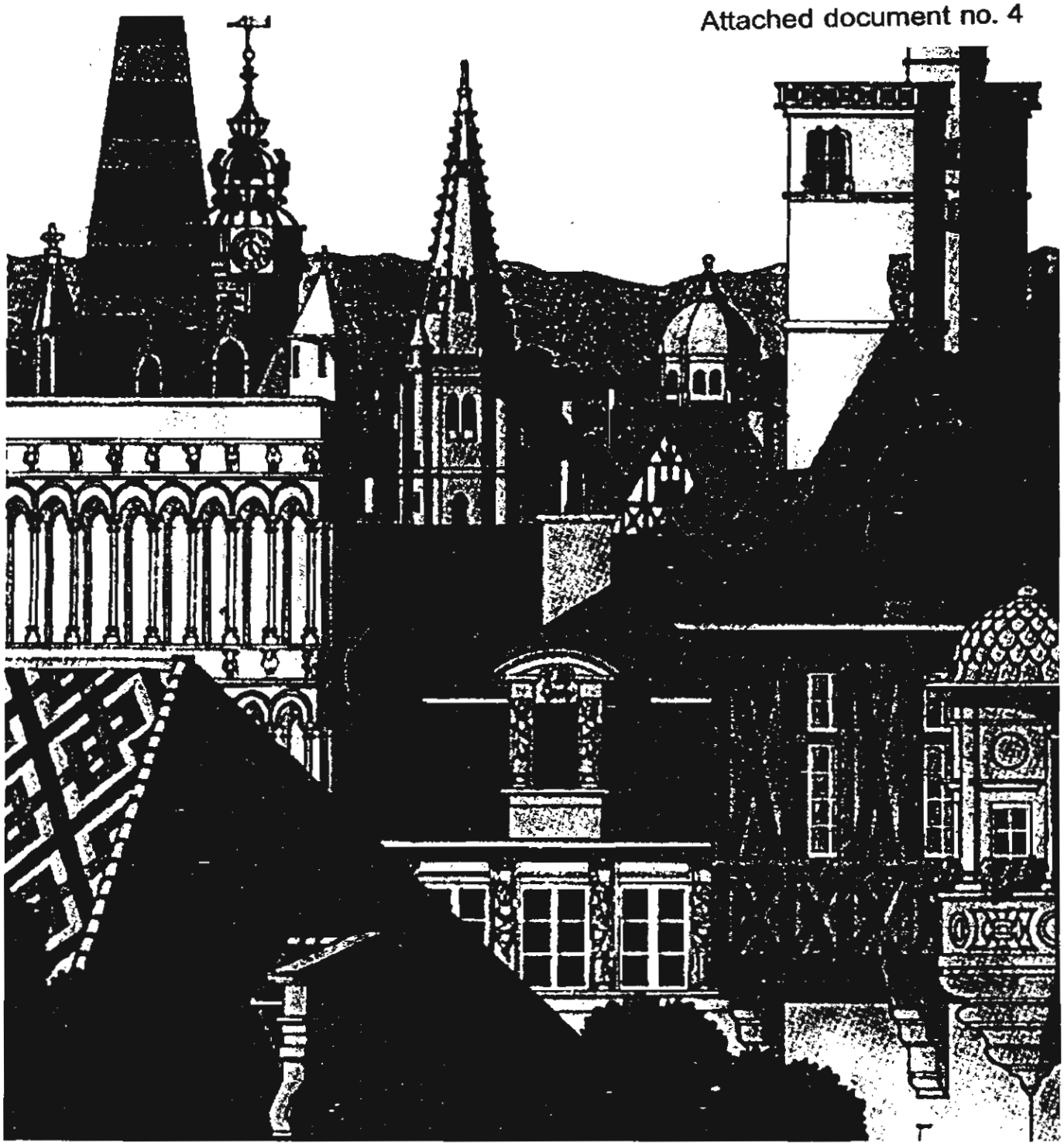
Objectives:
Since the early 1990s, hepatitis B immune globulin (HBIG) was used to prevent hepatitis B recurrence for liver transplantation patients with previous hepatitis B history. The results of Liver transplantation (LT) have improved significantly for this indication.
The objective is to assess the efficacy and safety of optimum schedule and duration of HBIG for prevention of post transplantation hepatitis B infection in patients with pre-transplantation hepatitis B infection.
Method:
The review will include randomized clinical trials (RCTs) regardless of publication status or language. The trials could be double blind, single blind, or not blind. Only trials with a minimum follow-up of three months will be included. Patients with liver transplantation diagnosed as having pre-transplantation hepatitis B will be included. Patients of gender, any age, or ethnic origin will be included. The outcome indicators include mortality, morbidity, clearance and recurrence of hepatitis B, adverse event of HBIG administration.
Results:
We use the key words " HBIG" and "Liver transplantation" as the key words for our literature search in MEDLINE (1975 - 2002) and get 129 articles, including 33 reviews (1991-2001).
We use RevMan(4.1) to make statistical analyses. Dichotomous outcomes results are expressed as relative risk (RR) with 95% confidence intervals. Continuous outcomes results are expressed as weighted mean difference with 95% confidence intervals.
Primary Conclusions:
1. The regimen of 10,000 IU HBIG administrated during the anhepatic phase, and during the first postoperative week, then 2,000 IU daily for 3 months can reach the best preventive efficacy;
2. Combination therapy with HBIG and lamivudine appears to be a promising strategy for prevention of HB recurrence.

E-mail: Zhiyong_Hong@hc-sc.gc.ca

WP159
THE MAMMOGRAPHY CONTROVERSY: OUR UNSUPPORTABLE CLAIMS OF CERTAINTY CATCH UP WITH US
Phillips C V.
Department of Management and Policy Sciences, University of Texas School of Public Health, Houston, Texas, United States.

Much of the sound and fury surrounding the current mammography controversy is driven by failure to recognize and quantify our uncertainty. Debates rage about whether to accept or disregard a particular study's findings based on its quality, ignoring the fact that no study is either perfect or worthless. Recent findings should indeed lower our confidence in mammography, perhaps quite a lot. But the public did not perceive a moderate adjustment of our point estimate for effectiveness, along with a widening of our distribution. Instead they feel like there was a dichotomous shift: one week the experts were implying that we have absolute proof, and the next they are claiming total ignorance. Indeed, based on what has been said in the debate, many of the experts seem to believe this too. Clinicians, with no definitive word from the research community, increasingly tell patients they must decide about mammography for themselves. To put it bluntly, this means that despite decades of research data, we have delegated

Attached document no. 4



PROGRAMME AND ABSTRACTS

23rd Annual Conference
The International Society for Clinical Biostatistics

September 9-13 2002 Dijon, France

Department of Biostatistics and Demography

http://www.iscb-dijon.u-bourgogne.fr

http://www.iscb-homepage.org

PROGRAMME OVERWIEW

	MONDAY (9 Sept.)	TUESDAY (10 Sept.)
08:30-17.30		Poster session (P01-P04) *Foyer*
08:45-09:00		**OPENING**
09:00-10:30	**Pre-conference Course 1** Adaptive and Sequential Procedures for Clinical Trials *Santenay-Chablis* **Pre-conference Course 2** Methods for Interval Censored Data *Morey St. Denis*	**Invited Session** Statistical Modelling (I01) *Romanée Conti*
10:30-11:00	**COFFEE**	**COFFEE**
11:00-12:30	**Pre-conference Course 1** Adaptive and Sequential Procedures for Clinical Trials *Santenay-Chablis* **Pre-conference Course 2** Methods for Interval Censored Data *Morey St. Denis*	**Invited Session** Sample Size Determination in Clinical Trials (I02) *Romanée Conti*
12:30-14:00	**LUNCH**	**LUNCH**
13:30-14:00		**Poster Session Presentation** (P01-P04) *Foyer*
14:00-15:30	**Pre-conference Course 1** Adaptive and Sequential Procedures for Clinical Trials *Santenay-Chablis* **Pre-conference Course 2** Methods for Interval Censored Data *Morey St. Denis*	**Invited Session** Thirty Years of the Cox Model (I03) *Romanée Conti* **Contributed Oral Sessions** Survival Models 1 (O01) *Morey St. Denis* Epidemiology 1 (O02) *Santenay-Chablis* Statistical Modelling 1 (O03) *Musigny*
15:30-16:00	**COFFEE**	**COFFEE**
16:00-17:30	**Pre-conference Course 1** Adaptive and Sequential Procedures for Clinical Trials *Santenay-Chablis* **Pre-conference Course 2** Methods for Interval Censored Data *Morey St. Denis*	**Contributed Oral Sessions** Missing Data 1 (O04) *Romanée Conti* Epidemiology 2 (O05) *Santenay-Chablis* Survival Models 2 (O06) *Morey St. Denis* Design and Modelling (O07) *Musigny*
18:30		**Reception Dijon City Hall**
19.00		

PROGRAMME OVERWIEW

WEDNESDAY (11 Sept.)	THURSDAY (12 Sept.)	FRIDAY (13 Sept.)
Poster session (P05-P10) *Foyer*	Poster session (P11-P15) *Foyer*	
Contributed Oral Sessions (09:00-10:15) Statistical Modelling 2 (O08) *Musigny* Phase II Clinical Trials (O09) *Romanée Conti* PK/PD Modelling (O10) *Morey St. Denis* Planning and Decision Making (O11) *Santenay-Chablis*	**Invited Session** Infectious Diseases (I04) *Romanée Conti* **Contributed Oral Sessions** Survival Models 3 (O12) *Morey St. Denis* Statistical Modelling 3 (O13) *Musigny* Epidemiology 3 (O14) *Santenay Chablis*	**Mini Symposium** Human Fertility and Fecundity *Romanée Conti*
COFFEE (10:15-10:45)	**COFFEE**	**COFFEE**
Keynote Leture Judgement in errors: handling measurment error in Biostatitics *Romanée Conti* **Annual General Meeting** *Romanée Conti* **(10:45-12:45)**	**Invited Session** Causality Assessment and Observational Studies (I05) *Romanée Conti* **Contributed Oral Sessions** Survival and Modelling (O15) *Musigny* Survival Models 4 (O16) *Morey St. Denis* Genetics and Bioinformatics (O17) *Santenay- Chablis*	**Mini Symposium** Human Fertility and Fecundity *Romanée Conti*
LUNCH	**LUNCH**	**CLOSING**
Poster Session Presentation (P05-P10) *Foyer*	**Poster Session Presentation** (P11-P15) *Foyer*	
Excursions	**Contributed Oral Sessions** Statistical Modelling 4 (O18) *Musigny* Meta-Analysis 1(O19) *Romanée Conti* Missing Data 2 / Genetics and Bioinformatics (O20) *Santenay-Chablis* Planning and Decision Making / Meta-Analysis 2 (O21) *Morey St. Denis*	
Excursions	**COFFEE**	
Excursions	**Contributed Oral Sessions** Survival Models 5 (O22) *Morey St. Denis* Statistical Modelling 5 (O23) *Musigny* Clinical Trials (O24) *Romanée Conti* Miscellaneous (O25) *Santenay-Chablis*	
	Conference Dinner at Bastion de Beaune	

16.00-17.30 O22 **SURVIVAL MODELS 5** Morey St. Denis

O:81 **Smits Jacqueline :** Who is most in need of a heart transplant ? Validation and calibration of a prognostic survival model - **P. 114**

O:82 **Giorgi Roch, Astruc K, Bolard P, Quantin C, Abrahamowicz M, Faivre J, Gouvernet J :** A @ flexible relative survival regression model using B-splines : application to stomach cancer - **P. 115**

O:83 **Parrinello Giovanni, Cimino A, Girelli A, Valentini U, Decarli A :** Long-survivors in Type II diabetes mellitus patients - **P. 116**

O:84 **Ghilagaber Gebrenegus :** Correcting for selection biases in evaluating the effects of health inputs on child survival - **P. 117**

CONTRIBUTED ORAL SESSIONS

16.00 -17.30 O23 **STATISTICAL MODELLING 5** Musigny

O:85 **Mansmann Ulrich, Friede T :** Planning clinical trials with correlated binary response - **P. 118**

O:86 **Fidler Vaclav :** Is occupancy rate of intensive care units related to the mortality ? - **P. 119**

O:87 **Robertson Chris, Mazzetta C, Ecob R :** Modelling trends in regional variation - **P. 120**

O:88 **Spiessens Bart, Verbeke G, Komarek A :** Classification of longitudinal profiles using mixtures of normal distributions in nonlinear and generalised linear mixed models - **P. 121**

16:00 - 17:30 O24 **CLINICAL TRIALS** Romanée Conti

O:89 **Posch Martin, Bauer P, Brannath W :** Sample size reassessment and estimation in adaptive designs - **P. 122**

O:90 **Graveland Wilfried, van Putten WLJ :** Obtaining an interim analysis plan in complex designs using simulation - **P. 123**

O:91 **Franzén Stefan :** Fixed length sequential exact confidence intervals for the probability of response - **P. 124**

O:92 **Müller Hans-Helge :** Sample size recalculation in optimized group sequential designs with stop in favour of the null-hypothesis - **P. 125**

16:00 - 17:30 O25 **MISCELLANEOUS** Santenay-Chablis

O:93 **Lachenbruch Peter :** Protecting an analysis from non-normal data - **P. 126**

O:94 **Laopaiboon Malinee, Boehning D :** Describing heterogeneity in meta-analysis involving cluster randomized trials: normality versus nonparametric approach to random effects models - **P. 127**

O:95 **Chappell Rick, Cheung K :** Examples of three new designs for Phase I cancer clinical trials - **P. 128**

CONTRIBUTED POSTER SESSIONS

08:30 - 17:30 P11 **SURVIVAL MODELS 2** Foyer

P:58 **Kawalec Ewa, Pajak A :** Are psychological factors associated with risk of cardiovascular diseases (CVD) and coronary heart disease (CHD) deaths ? results of the PolMonica Cracow project - **P. 185**

P:59 **Biganzoli Elia, Ambrogi F, Boracchi P :** Selection of artificial neural network models for sur vival data - **P. 186**

P:60 **Hopirtean Vincent, Mejean A, Chauchat J-H, Bazin JP, Roupret M, Hubert B, Balian C, Chretien Y, Thiounn N, Dufour B :** Interest of bootstrapping to analyze and compute the odds ratio's confidence intervals in the Cox proportional hazards. Application in bilateral renal cell carcinoma - **P. 187**

DESCRIBING HETEROGENEITY IN META-ANALYSIS INVOLVING CLUSTER RANDOMIZED TRIALS : NORMALITY VERSUS NONPARAMETRIC APPROACHES OF RANDOM EFFECTS MODELS

M. Laopaiboon [1], *D. Boehning* [2]
1 Khon Kaen University, Faculty of Public Health, Department of Biostatistics, Khon Kaen, Thailand
2 Free University, Institute of International Health, Berlin, Germany

Rationale : Most of statistical methods used in meta-analysis assume individual subjects as units of randomization. Meta-analyses involving cluster randomized trials may lead to additional sources of heterogeneity beyond those elevated by meta-analyses involving only individually randomized trials. The appropriate statistical analysis to these meta-analyses must take into account potential heterogeneity in the cluster randomized trials. Currently, the general linear mixed model (GLM) has been proposed to explain heterogeneity in meta-analysis where the treatment effect is measured in binary outcome. Log-relative measure is used as a response variable. The parameter estimation is based on assumption of normal distribution of random effects. However, this assumption has been discussed that it may be difficult to verify in meta-analysis situation. In addition, the treatment effect cannot be measured as random effects. The generalized linear mixed model (GLMM) under unspecified distribution of random effects may be an alternative choice that is interesting to be investigated.

Objective : The purpose of this study is to compare the GLM with the GLMM for describing heterogeneity in meta-analysis involving cluster randomized trials in binary outcome.

Methods : The two approaches of GLM and GLMM are exemplified in two published meta-analyses involving cluster randomized trials. The first meta-analysis is done to assess the effectiveness of multiple risk factor interventions to reduce cardiovascular risk factors from coronary heart disease. Analysis is performed in the 14 trials included that provided smoking prevalence outcome. The second meta-analysis comprises fewer trials of 8, which is performed to evaluate the effect of mammographic screening on reduction of breast cancer mortality. For each meta-analysis, observed log-relative risks for individual trials are fitted to the GLM as a continuous response. The trials included are classified to two categories according to randomization units, clusters and individually, and called randomization design variable. This variable is treated as a covariate of the model. The model parameters are estimated with the restricted maximum likelihood (REML) under the normality assumption of random effects via MLwiN software. For the GLMM, observed frequencies of the outcome for each treatment group are used rather than the observed log-relative risks for individual trials. A canonical link function of the observed mean proportions is associated with linear predictors model of which treatment and randomization design are treated as covariates. Here, the treatment effect can be treated as random treatment effects. The maximum likelihood estimates of the model parameters are obtained non-parametrically under a discrete mixture distribution of random effects for K components, which is implemented by the EM-algorithm procedure via S-plus software. Maximum posterior probability is used to classified trials to each component.

Results : The two approaches shown that the covariates effects and variability of random effects from the models easily explained heterogeneity between trials. Results of numerical example will be presented at the conference. The GLMM is superior to the GLM in some aspects. The GLMM gives further heterogeneity information from random treatment effects. In addition, the approach provides component (or subgroup)-specific treatment effect and trial classification according to the optimal components. This is very useful in further explaining the heterogeneity that might be beyond the effects found in the model.

Conclusions: The GLMM approach provides more information for explaining heterogeneity effect in meta-analyses involving cluster randomized trials. However, care should be taken when interpreting the covariates effects of the model because inference on these effects obtained from a discrete mixing distribution have not been ruled out. Nevertheless, the GLMM would be much more efficient when it is applied to large meta-analyses.

Statistical Methods in Medical Research 2003; **00**: 1–16

Meta-analyses involving cluster randomization trials: a review of published literature in health care

M Laopaiboon Department of Biostatistics and Demography, Khon Kaen University, Khon Kaen, Thailand

Over the past two decades cluster randomization trials have been increasingly used to evaluate effectiveness of health care intervention. Such trials have raised several methodologic challenges in analysis. Meta-analyses involving cluster randomization trials are becoming common in the area of health care intervention. However, as yet there has been no empirical evidence of current practice in the meta-analyses. Thus a review was performed to identify and examine synthesis approaches of meta-analyses involving cluster randomization trials in the published literature. Electronic databases were searched for meta-analyses involving cluster randomization trials from the earliest date available to 2000. Once a meta-analysis was identified, papers on the relevant cluster randomization trials included were also requested. Each of the original papers of cluster randomization trials included was examined for its randomized design and unit, and adjustment for clustering effect in analysis. Each of the selected meta-analyses was then evaluated as to its synthesis concerning clustering effect. In total, 25 eligible meta-analyses were reviewed. Of these, 15 meta-analyses reported simple conventional methods of the fixed-effect model as method of analysis, while Six did not incorporate the cluster randomization trial results in the synthesis methods but described the trial results individually. Three meta-analyses attempted to account for the clustering effect in the synthesis methods but they were in arbitrary approaches. Fifteen meta-analyses included more than one cluster randomization trial, each of which included cluster randomization trials with a mixture of randomized designs and units, and units of analysis. These mixture situations might increase heterogeneity, but have not been considered in any meta-analysis. Some methods dealing with a binary outcome for some specific situations have been discussed. In conclusion, some difficulties in the quantitative synthesis procedures were found in the meta-analyses involving cluster randomization trials. Recommendations in the applications of approaches to some specific situations in a binary outcome variable have also been provided. There are still, however, several methodologic issues of the meta-analyses involving cluster randomization trials that need to be investigated further.

Q2

1 Introduction

Meta-analysis of trial results is a common tool used in health care research. There is substantial literature covering the statistical methodology used in meta-analyses. Most is related to meta-analyses of trials, which randomize individual subjects to receive treatments.

Throughout the 1990s cluster randomization trials, in which treatments are randomly assigned to clusters (or groups) of individuals, have become widely used for the evaluation of health care interventions.[1,2] Such trials raise special methodologic challenges in analysis. Cluster randomization trials, however, have received little research attention in the literature on meta-analysis. Thus, to obtain empirical evidence of recent practices, a review has been conducted of published meta-analyses involving

Q3

Address for correspondence: M Laopaiboon, Department of Biostatistics and Demography, Faculty of Public Health, Khon Kaen University, Khon Kaen 40002, Thailand. E-mail: malinee@kku.ac.th

10.1191/0962280203sm347oa

cluster randomization trials. The objective of this review was to describe statistical approaches for handling heterogeneity and estimation of treatment effects that have been used in meta-analyses involving cluster randomization trials.

2 Methods

2.1 Study search and identification

An electronic search was performed to find reports in English on meta-analyses involving cluster randomization trials. We were aware of the difficulty in searching for reports related to cluster randomization trials because using the keywords 'cluster randomization' might not be able to identify some of the meta-analyses involving such trials. Therefore, other keywords related to 'cluster randomization' were also combined with the keywords of meta-analyses. These search keywords are presented in Table 1. The following electronic databases were used: Medline, Health Star, Embase, SCIsearch and the Cochrane Library. The SCIsearch database was used to identify further references that cited the relevant papers. The search was carried out from the first year of each electronic database to 2000.

Once a meta-analysis was identified, papers on the relevant cluster randomization trials included were also requested.

2.2 Review process

Each cluster randomization trial was reviewed with respect to designs of randomization and adjustment for clustering effect in the analysis. Each meta-analysis was then reviewed with respect to number of trials included, particularly the number of cluster randomization trials, types of intervention of interest, outcome measure, methods to obtain an overall treatment effect, and heterogeneity consideration regarding the inclusion of cluster randomization trials. The interventions of interest were classified into three main types, *educational*, *health care* and *screening*. The educational intervention referred to the interventions related to health promotion or nontherapeutic treatments, such as mass media, group behavior therapy, and so on. Health care intervention referred to the interventions related to therapeutic or preventive treatments, such as routine antenatal care, vitamin A supplementation, and so on. Screening

Table 1 Keywords used for electronic databases searching

1 meta-analysis	11 randomization
2 randomized controlled trials	12 randomisation
3 randomised controlled trials	13 (11) OR (12)
4 (2) OR (3)	14 (10) AND (13)
5 (1) AND (4)	15 (10) AND (4)
6 cluster	16 trials
7 group	17 intervention trials
8 community	18 (16) OR (17)
9 field	19 (10) AND (18)
10 (6) OR (7) OR (8) OR (9)	20 (14) OR (15) OR (19)
	21 (1) AND (20)

referred to the interventions related to investigation of disease in the general population, for example mammographic screening, and so on.

3 Results

The search identified 25 eligible meta-analysis reports published between January 1990 and 2000. Sixteen reports were from the Cochrane Library, and two were from the *British Medical Journal*. One each of the remaining seven was from the *American Journal of Public Health*, *American Journal of Tropical Medicine and Hygiene*, *Bulletin of the World Health Organization*, *International Journal of STD&AIDS*, *Journal of American Medical Association*, *Journal of the National Cancer Institute Monographs* and *The Medical Journal of Australia*, respectively.

Table 2 presents the types of intervention studied and trials included in each of the 25 meta-analyses. Health care interventions formed the majority, accounting for 64% (16/25) of the meta-analyses. A total of 89 cluster randomization trials and 297 individually randomization trials were included in these 25 meta-analyses. A mean number of 15 trials was found for individual meta-analyses, ranging from 2 to 41. For the cluster randomization trials included, a mean of 4, ranging from 1 to 17, was found. There were 15 meta-analyses that included more than one cluster randomization trial. The randomized units of cluster randomization trials within the same meta-analysis were for the most case different. For example, in a meta-analysis on mass media interventions to prevent smoking among children,[3] the three included cluster randomization trials were area, school and community as randomized unit, respectively. Moreover, eligibility criteria at both cluster and individual levels of the trials included in the same meta-analysis were quite different. These differences among the cluster randomization trials might lead to extra sources of heterogeneity beyond those already existing in meta-analyses including only individually randomization trials. Consequently, they might raise more difficulties regarding methodologic issues.

From the 89 cluster randomization trials, 83 original papers could be reviewed. In two of the remaining six cluster randomization trials, the required information was extracted from the meta-analyses in which they were included. One of them was an unpublished paper, and the other was written in Russian. The remaining four cluster randomization trials could not be accessed as they were referenced incorrectly. We attempted to search for these four trial papers but did not succeed in accessing the correct papers. Consequently, a total of 85 cluster randomization trials could be reviewed. References to the trials reviewed are presented in the Appendix. The following results were thus based only on the accessible papers.

Twenty-two meta-analyses had a binary endpoint as the primary outcome. One meta-analysis had binary and continuous endpoints as the co-primary outcomes. Fifteen meta-analyses reported simple conventional methods of the fixed effect model as method of analysis. They treated the cluster randomization trial results as individual randomization trial results. Six meta-analyses did not incorporate the cluster randomization trial results in the quantitative synthesis and described the results of cluster randomization trials separately. Three meta-analyses reported the synthesis methods that account for clustering effect. One was unclear, as it did not report the synthesis method.

Table 2 Numbers of individual and cluster randomization trials included for the individual meta-analyses reviewed

Meta-analysis reference[d]	Type of intervention	Number of trials included[a]	
		Individual randomization	Cluster randomization
32	Health care	1	(1)[b]
26	Health care	1	1[1]
33	Health care	6	1[2]
34	Health care	6	1[3]
4	Screening	7	1[4]
5	Health care	13	1[5]
27	Health care	14	1[6]
35	Health care	16	1[7]
36	Health care	28	1[8]
28	Educational	39	1[9]
6	Screening	6	2[4,10]
3	Educational	2	3[11–13]
37	Educational	13	3[14–16]
29	Educational	34	3[17–19]
38	Educational	38	3[15,20,21]
39	Health care	10	4[22–25]
40	Educational	15	4[20,26–28]
41	Health care	23	4[29–32]
42	Health care	—	5[33–37]
16	Health care	—	5[35–39]
43	Health care	13	5[40–44]
30	Educational	2	6[17,32,45–48]
44	Health care	3	7[49–54](1)[c]
10	Health care	—	8[33–39,55]
45	Health care	1	17[49–52,56–62](3)[c]
Total		297	89 (5)

[a]Numbers in parentheses were papers on cluster randomization trials for which original papers could not be retrieved. Superscript numbers are references of trials reviewed, presented in the Appendix.
[b]Paper is in Russian; its details were extracted from the meta-analysis.
[c]Missing papers that were incorrectly referenced.
[d]Reference details provided in reference list.

Q3

Details of the randomized design and unit of analysis for each cluster randomization trial included in each meta-analysis and the combining methods are presented in Table 3. Here the last three columns were considered together. In the group of 15 meta-analyses that reported simple conventional methods in the quantitative synthesis, two meta-analyses[4,5] likely provided reasonable evidence because the results of cluster randomization trials included were analysed as individual unit adjusted for clustering effect. Nine of the fifteen meta-analyses included cluster randomization trials with a mixture of different randomized designs: completely randomized, matched-pair randomized and stratified randomized. The cluster randomization trials included in the nine meta-analyses also had a mixture of different units of analysis, some at cluster level and some at individual level. These mixtures certainly raised additional heterogeneity in the meta-analyses and needed to be considered in the synthesis procedures. However, none of these meta-analyses reported any concern regarding heterogeneity that might be due to cluster randomization trials.

Table 3 Details of individual cluster randomized trials (CRT) for each meta-analysis in terms of randomization design and analysis level, and combining method of meta-analysis

Meta-analysis reference	No. of CRT included	Randomization design	Analysis level	Combining method
36	1	1 C	1 IU	T
33	1	1 C	1 IU	T
5	1	1 S	1 IA	T[a]
32	1	1 U	1 U	T
4	1	1 S	1 IA	T[a]
35	1	1 S	1 C	T
37	3	1 C, 1M, 1 U	2 IU, 1 U	T
38	3	1 S, 1 U	1 IA, 2 U	T
39	4	1 C, 3 M	2 C, 2 IU	T
40	4	1 C, 1 M, 2 U	1 C, 1 IA, 1 IU, 1 U	T
41	4	2 C, 1 S, 1 U	1 IA, 3 IU	T
16	5	4 C, 1 M	1 C, 3 IA, 1 IU	T
43	5	3 C, 1 M, 1 S	2 IA, 3 IU	T
44	6	1 C, 2 M, 3 S	1 C, 5 IU	T
45	14	4 C, 6 M, 4 S	9 C, 5 IU	T
26	1	1 M	1 C	D[a]
27	1	1 C	1 C	D[a]
28	1	1 S	1 IA	D[a]
3	3	2 C, 1 M	3 IA	D[a]
29	3	3 C	2 C, 1 IA	D[a]
30	6	5 C, 1 M	1 C, 2 IA, 3 U	D[a]
6	2	1 M, 1 S	1 IA, 1 IU	A
42	5	4 C, 1 M	2 C, 2 IA, 1 IU	A
10	8	6 C, 1 M, 1 U	1 C, 3 IA, 4 IU	A
34	1	1 M	1 C	U
Total	85			

Randomization designs: C, completely randomized; M, matched-pair; S, stratified randomized.
Analysis level: C, cluster; IA, individual adjusted for clustering effect; IU, individual unadjusted for clustering effect; U, unclear.
Combining method: A, account for clustering effect; D, describe CRT results separately; T, treated CRT results as if of IRT and use fixed effect models; U, unclear method.
[a]Reasonable method.

For the six meta-analyses that did not incorporate the results of cluster randomization trials into the quantitative synthesis, three included more than one cluster randomization trial. The trials for each meta-analysis were mixed up with different randomized designs and units of analysis. These meta-analyses were probably the ones that used sensible methods because the reviewers were aware of the heterogeneity that might be due to cluster randomization trials.

Three meta-analyses that included cluster randomization trials with a mixture of different randomized designs and units of analysis attempted to adjust for clustering effect in the quantitative synthesis. Details of adjustment for each meta-analysis are presented in Table 4. The outcome measures of these three meta-analyses were binary data. Individual explanations for clustering effect adjustment in the meta-analyses are outlined in the following three paragraphs.

First was the meta-analysis evaluating the value of mammographic screening for women under 50 years of age.[6] It included six individual randomization trials and two

Table 4 Design of randomization and analyses level of the individual included cluster randomization trial (CRT) of the three meta-analyses managing clustering effect in the combination

Number of CRTs reviewed				Management of clustering effect in the combination
Randomized design		Analyses level		
(A) Meta-analysis on mammographic screening trials[6]				
Stratified	1	Adjusted at individual level	1	Proposed method of Mantel–Haenszel by Rao and Scott[9] for clustered binary data is used in a sensitivity analysis to examine the clustering effect of the two included CRTs
Matched-pair	1	Unadjusted at individual level	1	
Total	2	Total	2	
(B) Meta-analysis on vitamin A supplementation[10]				
Completely randomized	6	Adjusted at individual level	3	DerSimonian and Laird method[11] adjusted for clustering effect by increasing variance of each pooled log-odds ratio with a fixed estimate of 30%
Matched-pair	1	Unadjusted at individual level	4	
		Cluster level	1	The estimate is determined from some included CRTs which provided sufficient clustering effect
Unclear	1			
Total	8	Total	8	
(C) Meta-analysis on vitamin A supplementation[16]				
Completely randomized	4	Adjusted at individual level	2	Mantel–Haenszel method adjusted for clustering effect for each pooled result differently
Matched-pair	1	Unadjusted at individual level	1	The adjusted effects are estimated from the external CRT study done in a similar topic to the included CRTs
		Cluster level	2	
Total	5	Total	5	

cluster randomization trials. For the two cluster randomization trials, one[7] used the design of stratified randomization and individual level as the unit of analysis adjusted for the clustering effect. The other[8] used a matched-pair design and also individual level as the unit of analysis, but ignored clustering effect. The applied technique of Mantel–Haenszel for clustered binary data, proposed by Rao and Scott,[9] was used in the sensitivity analysis. The technique aimed at estimating an overall odds ratio of K 2×2 tables of independent clustered data in the binary outcome. By using Rao and Scott's method, each included trial of the meta-analysis was taken to represent an independent group of the clustered binary data. The method required the clustering effect of each

treatment group for each trial to be adjusted for in the analysis. Since there was less information on this process in the methodology part of the meta-analysis, it was unclear exactly how the authors managed this issue. But they reported that each of the two cluster randomization trial results allowed for the same degree of clustering effect of a relative 90% (=100(1/design effect)) in the synthesis without any explanation for the adjustment. This might elevate the problem of inappropriate adjustment. Only one cluster randomization trial[7] reported the estimate of relative efficiency due to cluster sampling of 87%. In addition, the six individual randomization trials seemed to be treated as having one cluster in each arm of the trial. This issue did not satisfy the requirement of the method, which needed a large number of clusters in each arm of each trial to provide valid results. Thus Rao and Scott's method would be inappropriate for estimating an overall odds ratio of any meta-analysis including a mixture of individual and cluster randomization trials, which was the case for this meta-analysis.

Second was the meta-analysis assessing the effect of vitamin A supplementation on child mortality.[10] All eight trials included were cluster randomized. Six of them used a completely randomized design, one used matched-pair and the other reported unclear information on the randomized design. The analyses were reported at cluster level in one trial and at individual level in seven trials, of which three trials were adjusted for clustering effect. The meta-analysis reported the common method of DerSimonian and Laird,[11] which was the random effects model, used to estimate an overall odds ratio. Each pooled odds ratio was adjusted for clustering effect by increasing the variance with an equal estimate of 30%. The report noted that this figure was determined from some included cluster randomization trials that provided sufficient information on the clustering effect ranging from 10 to 44%. In fact, the cluster randomization trials were quite different in terms of types of unit of treatment allocation, such as wards, household, clusters, villages, districts areas and slums, and number of clusters of each trial. Thus it seemed to be unfair to account for clustering effect with the same degree for individual pooled odds ratio. In addition, some results of the cluster randomization trials[12–14] were already adjusted for clustering effect, and one[15] had the result at cluster level. The approach of adjustment for clustering effects used in this meta-analysis might be reasonable if the trials included have quite similar units of treatment allocation and number of clusters of each arm for each trial.

The third meta-analysis was on vitamin A supplementation on childhood pneumonia mortality.[16] This meta-analysis included five cluster randomization trials, four[12–15] of which overlapped with trials of a former meta-analysis.[10] Four of these five cluster randomization trials used a completely randomized design and one used a matched-pair design. Three of the five trials reported analyses performed at an individual level, two of them adjusted for clustering effect. The remaining two trials reported analyses carried out at cluster level. The meta-analysis reported the fixed effect model of the Mantel–Haenszel method used to pool the results. Individual pooled results were adjusted for clustering effect by increasing the variances of their odds ratios with different degrees. The estimates of the adjusted effects were obtained from the meta-analysis studied by Beaton *et al.*,[17] which was carried out in a related topic to this meta-analysis. We did not review the Beaton *et al.* study,[17] because it could not be accessed from any electronic database searched by our study. However, Donner *et al.*[1] mentioned that Beaton *et al.*[17] used the method of Rao and Scott[9] in their meta-analysis

with satisfaction regarding the method assumption. The adjustment for different degrees of clustering effects seemed to be a reasonable procedure because the unit of randomization for each cluster randomization trial was quite different. However, there were two trials[15,18] that had the results analysed at cluster level and for whether they needed to be adjusted for clustering effects. Therefore, the two trials are excluded, the adjustment approach shown in this meta-analysis seemed to be justified. Q3

4 Discussion

In principle, when doing a meta-analysis including individual randomization trial results, an overall treatment effect could be estimated in a straightforward way if the valid estimated treatment effects and their variances were provided. This concept could also be further applied to the meta-analyses that included results from cluster randomization trials with the same randomized designs and analysed at individual level adjusted for clustering effect or at cluster level. Furthermore, even if the cluster randomization trial results were analysed at individual level not adjusted for clustering effect, if all information on appropriate clustering effects was available, the results could be pooled. In practice this was unlikely to happen, as seen in this review.

One simple approach for adjustment of clustering effect in binary outcome was that of Mantel–Haenszel, proposed for clustered data by Rao and Scott.[9] This approach could be applied to the meta-analysis of cluster randomization trials comparing two treatment groups with a completely randomized design.[2] Requirements of the approach that relate to the results of cluster randomization trials were the results analysed at individual level. In addition, total sample size, count number of treatment outcome and clustering effect of each treatment group were needed. Furthermore, the method required a large number of clusters for each treatment group of each individual cluster randomization trial. It might be impossible, however, to use this approach in real situations, because all the data required to estimate an overall odds ratio by this approach are unlikely to be available.

The results show that 44% (11/25) of the meta-analyses reported the methods considering the clustering effect in the synthesis. This figure was quite low. In addition, the meta-analyses that reported estimation approaches adjusted for clustering effect might provide imprecise estimates of overall treatment effects. Various issues need to be considered. Q4

It was found that 15 meta-analyses included more than one cluster randomization trial. The trials included in each of the meta-analyses had various randomized designs, as shown in Table 3. This was an additional source of heterogeneity and might raise more difficulties in methodologic issues beyond those already existing in meta-analyses including only individual randomization trials. Conventional approaches might be inappropriately used for estimating overall treatment effects from these trial results. However, this issue was not considered properly in any meta-analysis reviewed and might lead to inappropriate use of synthesis procedures. This difficulty could possibly produce imprecise results for the overall treatment effect.

Invalid results obtained from cluster randomization trials, that is, the results without adjusting for clustering effect, were crucial and led to a difficulty in estimating the

effects in the meta-analysis including the trial results, especially when the trials did not report clustering effect information.

The figure of 56.8% (42/74) for the cluster randomization trial results that adjusted for clustering effect was found in this review. It was interesting that the results reflected this persistant figure on analysis of cluster randomization trials, when compared with the reviews by Donner *et al.*[19] in 1990 on cluster randomized nontherapeutic intervention trials from 1979–1989, and later by Simpson *et al.*[20] in 1995 on cluster randomized primary prevention trials from 1990–1993. They found that 50% (8/16) and 57.1% (12/21), respectively, took account of clustering effect in the analyses. One reason might be that the cluster randomization trials reviewed in this study were performed around the same period as those of the previous reviews. In addition, three cluster randomization trials[8,12,21] in the previous reviews were included in this study. Q4

Recently, some authors[22–24] have proposed reporting design effects and intra-cluster correlation when publishing cluster randomization trials. Thus, hopefully, the difficult situation mentioned above will be corrected in the near future.

In total, 52% (13/25) of the meta-analyses used inappropriate methods that ignored clustering effect to combine invalid results of cluster randomization trials. Here, we can speculate about the reasons. In the first place, 9 out of 13 meta-analyses were obtained from the Cochrane library and the Cochrane collaboration lacked the appropriate software to analyse the cluster randomization trial results during the study period. Some authors were aware of this constraint and warned readers that the confidence intervals provided might be too narrow. Secondly, generally there were neither guideline nor proposal methods to combine cluster randomization trial results. Finally, some meta-analysts might not know that variation of the estimated outcome obtained from the cluster randomization trials differed from that of the individually randomization trials and that this would have an impact on the combined results. However, some approaches involving binary outcome variables have recently been proposed by Donner *et al.*[1,2]

The results show three meta-analyses[6,10,16] involving binary endpoints attempting to take clustering effect into account in the analysis in order to solve the problem of invalid results. The invalid results were due to not adjusting for the clustering effect in analysis at the individual level. The synthesis attempted to estimate the clustering effects; some from internal available clustering effect information and some from external clustering effects. Some unclear issues were still noted. First, no rationale for the methods used to estimate clustering effects was seen. Secondly, some cluster randomization trials providing results with appropriate analysis seemed to be forced to adjust for clustering effect. Thirdly, complex situations, different randomized designs, heterogeneity in units of randomization and variation of the randomization units, and different levels of units of analysis among the cluster randomization trials included were found, but not taken into account in the three meta-analyses.

Some limitations of this review are considered. One meta-analysis[17] satisfied inclusion criteria but was not reviewed because we could not retrieve it from the searched electronic database. It is, however, mentioned in Donner *et al.*[1] that Rao and Scott's method was used in the meta-analysis. The method is not different from what we found in the review. In addition, four incorrect references of cluster randomization trials could not be accessed. With these limitations we believe the findings of this review could reflect the recent practice of meta-analyses involving cluster randomization.

From the difficulties found in the reviewed meta-analysis involving cluster randomization trials, some suggestions are introduced. The first suggestion focuses on some specific issues in reporting cluster randomization trials that relate to the information needed in meta-analysis. The number of clusters assigned to each treatment group is required in the report. This is because when the trial has only one cluster for each treatment arm, variation between clusters is confounded by the treatment effect and cannot be measured from the trial.[24] Consequently, when including this trial in a meta-analysis, there is a need to adjust for clustering effect from a similar available source. Unit of analysis must be clearly stated whether at cluster or individual level. If analysis is performed at individual level, the degree of clustering effects for each treatment group that is adjusted for in the analysis must be reported. This information is of benefit not only to the meta-analysis where the trial is included, but also to any future plan for performing a cluster randomization trial in a related field. There have been, however, more complete suggestions for reporting trials, provided by Donner and Klar,[25] and Elbourne and Campbell.[23]

The second suggestion focuses on the synthesis approach. If the number of cluster randomization trials included is relatively small and diverse in randomized designs and units, it might be reasonable to do qualitative synthesis, that is, explaining individual cluster randomization trials separately as was done in some reviewed meta-analyses.[3,26–30] Alternatively, if the number of trials is large, subgroup analyses, which are meta-analyses on subgroups of the studies, might be sensible when the categories of interest factors are quite small, for example, three types of randomized designs: completely randomized, matched-pair and stratified randomized. Some approaches involving binary outcome variable have been proposed by Donner *et al.*[1,2] They are recommended to be used for the included trials involving a completely randomized design. Advantages and disadvantages of each approach are also provided. In addition, recommendations of application of the approaches to combine results from different designs under limitation issues have also been discussed in the literature.[1] Furthermore, an alternative approach of the generalized linear mixed models under the nonparametric maximum likelihood estimator has been proposed and the models will be much more efficient when they are applied to large meta-analyses.[31]

In conclusion, attempts to work on some difficulties due to involving cluster randomization trials in meta-analyses were seen. Some suggestions on the methods for meta-analyses of cluster randomization trials measured in a binary outcome have been proposed.[1,2,31] The problem of heterogeneity results from complex situations on various randomized designs and units, different eligibility criteria at cluster and individual level, and unit of analysis that might be beyond the heterogeneity results obtained from individual randomization trials have been found and still needed further methodologic investigation.

Acknowledgements

This study was supported by a grant from the Thailand Research Fund. The author is most grateful to Professor Allan Donner, Professor Pisake Lumbiganon and the referee for their valuable comments on the manuscript.

Part of this study was carried out while I was spending several research visits at the Institute of International Health, Unit of Epidemiology and Biometery of the Joint Center of Health Sciences and Humanities at the Free University Berlin. I would like to thank Professor Dankmar Böhning, Professor Frank-Peter Schelp, Dr Ekkehart Dietz, Dr Martina Stallmann and Ms Yoong Moy Chew for their help, discussion and encouragement during this time in Berlin.

References

1 Donner A, Piaggio G, Villar J. Statistical methods for the meta-analysis of cluster randomization trials. *Statistical Methods in Medical Research* 2001; 10 (5): 325–38.

2 Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Statistics in Medicine* 2002; 21: 2971–80.

3 Sowden A, Arblaster L. Mass media interventions for preventing smoking among young people. *The Cochrane Library* 1999; Issue 1.

4 Hendrick R, Smith R, Rutledge IJ, Smart C. Benefit of screening mammography in women aged 40–49: a new meta-analysis of randomized controlled trials. *Journal of the National Cancer Institute Monographs* 1997; 22: 87–92.

5 Kramer M. Balanced protein/energy supplementation in pregnancy. *The Cochrane Library* 1999; Issue 1.

6 Glasziou PP, Woodward AJ, Mahon CM. Mammographic screening trials for women aged under 50: a quality assessment and meta-analysis. *The Medical Journal of Australia* 1995; 162: 625–629.

7 Roberts M, Alexander F, Anderson T, Chetty U, Donnan P, Forrest P *et al.* Edinburgh trial of screening for breast cancer: mortality at seven years. *The Lancet* 1989; 335: 241–46.

8 Tabar L, Fagerberg CG, Gad A, Holmberg L, Grontoft O, Ljungquist U *et al.* Reduction in mortality from breast cancer after mass screening with mammography. *The Lancet* 1985; 829–32.

9 Rao J, Scott AJ. A simple method for the analysis of clustered binary data. *Biometrics* 1992; 48: 577–85.

10 Fawzi WW, Chalmers T, Herrera MG, Mosteller F. Vitamin A supplementation and child mortality: a meta-analysis. *The Journal of the American Medical Association* 1993; 269 (7): 898–903.

11 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986; 7: 177–88.

12 Sommer A, Djunaedi E, Loeden A, Tarwotjo I, West KP, Tilden R. Impact of vitamin A supplementation on childhood mortality: A randomised controlled community trial. Lancet 1986: 1169–73.

13 Rahmathullah L. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *New England Journal of Medicine* 1990; 323: 929–35.

14 West KP, Jr, Pokhrel RP, Katz J, LeClerq SC, Khatry SK, Shrestha SR *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; 338 (8759): 67–71.

15 Daulaire NM, Starbuck ES, Houston RM, Church MS, Stukel TA, Pandey MR. Childhood mortality after a high dose of vitamin A in a high risk population. *British Medical Journal* 1992; 304 (6821): 207–10.

16 The Vitamin A and Pneumonia Working Group. Potential interventions for the prevention of childhood pneumonia in developing countries: a meta-analysis of data from field trials to assess the impact of vitamin A supplementation on pneumonia morbidity and mortality. *Bulletin of the World Health Organization* 1995; 73 (5): 609–19.

17 Beaton GH, Martorell R, Aronson KJ, Edmonston B, McCabe G, Ross AC *et al.* Effectiveness of Vitamin A supplementation in the control of young child morbidity and

mortality in developing countries. The ACC/SCN State-of-the-Art Series Nutrition Policy Discussion Paper No. 13, December 1993.

18 Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effect on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; 342: 7–12.

19 Donner A, Brown K, Brasher P. A methodological review of non-therapeutic intervention trials employing cluster randomization, 1979–1989. *International Journal of Epidemiology* 1990; 19 (4): 795–800.

20 Simpson J, Klar N, Donnor A. Accounting for cluster randomization: a review of primary prevention trials, 1990 through 1993. *American Journal of Public Health* 1995; 85 (10): 1378–83.

21 Bauman KE, LaPrelle J, Brown JD, Koch GG, Padgett CA. The influence of three mass media campaigns on variables related to adolescent cigarette smoking: results of a field experiment. *American Journal of Public Health* 1991; 81 (5): 597–604.

22 Campbell M, Grimshaw J. Cluster randomised trials: time for improvement. The implications of adopting a cluster design are still largely being ignored. *British Medical Journal* 1998; 317: 1171–72.

23 Elbourne D, Campbell M. Extending the CONSORT statement to cluster randomized trials: for discussion. *Statistics in Medicine* 2001; 20 (3): 489–96.

24 Klar N, Donner A. Current and future challenges in the design and analysis of cluster randomization trials. *Statistics in Medicine* 2001; 20 (24): 3729–40.

25 Donner A, Klar N. Design and analysis of cluster randomization trials in health research. London: Arnold, 2000.

26 Panpanich R, Garner P. Growth monitoring in children. *The Cochrane Library* 1999; Issue 1.

27 Garner P, Gulmezoglu A. Prevention versus treatment for malaria in pregnancy women. *The Cochrane Library* 1999; Issue 1.

28 Lumley J, Oliver S, Waters E. Intervention for promoting smoking cessation during pregnancy. *The Cochrane Library* 1999; Issue 1.

29 Thomson M, Oxman A, Davis D, Haynes R, Freemantle NEH. Audit and feedback: effects on professional practice and health care outcomes. *The Cochrane Library* 1999; Issue 1.

30 Thomson M, Oxman A, Haynes R, Davis D, Freemantle N, Harvey E. Local opinion leaders: effects on professional practice and health care outcomes. *The Cochrane Library* 1999.

31 Laopaiboon M, Böhning D, eds. Describing heterogeneity in meta-analysis involving cluster randomized trials: normality versus nonparametric approaches of random effects models. In *The 10th Cochrane Colloqium*, 2002, 31 July–3 August 2002; Stavanger, Norway, 2002.

32 Jefferson T, Demicheli V, Deeks J, Graves P, Pratt M, Rivetti D. Vaccines for preventing anthrax. *The Cochrane Library* 1999; Issue 1.

33 Villar JDK-N. Patterns of routine antenatal care for low-risk pregnancy. *The Cochrane Library* 1999; Issue 1.

34 Howe R. Circumcision and HIV infection: a review of the literature and meta-analysis. *International Journal of STD&Aids* 1999; 10: 8–16.

35 Brunner E, White I, Thorogood M, Bristow A, Curle D, Marmot M. Can dietary interventions change diet and cardiovascular risk factors? A meta-analysis of randomized controlled trials. *American Journal of Public Health* 1997; 87 (9): 1415–22.

36 Mahomed K. Iron supplementation in pregnancy. *The Cochrane Library* 1999; Issue 1.

37 Silagy C, Ketteridge S. Physician advice for smoking cessation. *The Cochrane Library* 1999; Issue 1.

38 Lancaster T, Stead L. Self-help interventions for smoking cessation. *The Cochrane Library* 1999; Issue 1.

39 Ebrahim S, Smith GD. Systematic review of randomised controlled trials of multiple risk factor interventions for preventing coronary heart disease. *British Medical Journal* 1997; 314: 1666–74.

40 Stead L, Lancaster T. Group behaviour therapy programmes for smoking cessation. *The Cochrane Library* 1999; Issue 1.

41 Dickson R, Awasthi S, Demellweek C, Williamson P. Anthelminthic drug for treating worms in children: effects on growth and cognitive performance. *The Cochrane Library* 1999; Issue 1.

42 Glasziou P, Mackerras D. Vitamin A supplementation in infectious diseases: a meta-analysis. *British Medical Journal* 1993; 306: 366–70.

43 Gillespie L, Gillespie W, Robertson M, Cumming R, Lamb S, Rowe B. Interventions for preventing falls in elderly people. *The Cochrane Library* 2000; Issue 3.
44 Choi H, Breman J, Teutsch S, Liu S, Hightowe W, Sexton J. The effectiveness of insecticide-impregnated bed nets in reducing cases of maralia infection: a meta-analysis of published results. *American Journal of Tropical Medicine and Hygiene* 1995; 52: 377–82.
45 Lengeler C. Insecticide treated bednets and curtains for preventing malaria. *The Cochrane Libary* 1999; Issue 3.

Appendix: references of trials reviewed (see Table 2)

1 George SM, Latham MC, Abel R, Ethirajan N, Frongillo EA, Jr. Evaluation of effectiveness of good growth monitoring in south Indian villages. *Lancet* 1993; 342(8867): 348–52.
2 Munjanja S, Lindmark G, Nystrom L. Randomised controlled trial of a reduced-visits programme of antenatal care in Harare, Zimbabwe. *Lancet* 1996; 348: 364–369.
3 Grosskurth H, Mosha F, Todd J, Mwijarubi E, Klokke A, Senkoro K *et al.* Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995; 346(8974): 530–36.
4 Roberts MM, Alexander FE, Anderson TJ, Chetty U, Donnan PT, Forrest P *et al.* Edinburgh trial of screening for breast cancer: mortality at seven years. *Lancet* 1990; 335(8684): 241–46.
5 Ceesay SM, Prentice AM, Cole TJ, Foord F, Weaver LT, Poskitt EM *et al.* Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. *British Medical Journal* 1997; 315(7111): 786–90.
6 Shulman CE, Dorman EK, Talisuna AO, Lowe BS, Nevill C, Snow RW *et al.* A community randomized controlled trial of insecticide-treated bednets for the prevention of malaria and anaemia among primigravid women on the Kenyan coast. *Tropical Medicine and Internal Health* 1998; 3(3): 197–204.
7 Sorenson G, Morris DM, Hunt MK. Work-site nutrition intervention and employee's dietary habit: the Treatwell program. *American Journal of Public Health* 1992; 82: 877–80.
8 Menendez C, Todd J, Alonso PL, Francis N, Lulat S, Ceesay S *et al.* The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994; 88(5): 590–93.
9 Kendrick JS, Zahniser SC, Miller N, Salas N, Stine J, Gargiullo PM *et al.* Integrating smoking cessation into routine public prenatal care: the Smoking Cessation in Pregnancy project. *American Journal of Public Health* 1995; 85(2): 217–22.
10 Tabar L, Fagerberg CJ, Gad A, Baldetorp L, Holmberg LH, Grontoft O *et al.* Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *Lancet* 1985; 1(8433): 829–32. Q6
11 Bauman KE, LaPrelle J, Brown JD, Koch GG, Padgett CA. The influence of three mass media campaigns on variables related to adolescent cigarette smoking: results of a field experiment. *American Journal of Public Health* 1991; 81(5): 597–604.
12 Flay BR, Miller TQ, Hedeker D, Siddiqui O, Britton CF, Brannon BR *et al.* The television, school, and family smoking prevention and cessation project. VIII. Student outcomes and mediating variables. *Preventive Medicine* 1995; 24(1): 29–40.
13 Flynn BS, Worden J, Secker-Walker RH, Badger GJ, Geller BM. Cigarette smoking prevention effects of mass media and school interventions targeted to gender and age groups. *Journal of Health Education* 1995; 26(2): S45–S51.
14 Haug K, Fugelli P, Aaro LE, Foss OP. Is smoking intervention in general practice more successful among pregnant than non-pregnant women? *Family Practice* 1994; 11: 111–16.

15 Wilson DH, Wakefield MA, Steven ID, Rohrsheim RA, Esterman AJ, Graham NM. 'Sick of Smoking': evaluation of a targeted minimal smoking cessation intervention in general practice. *The Medical Journal of Australia* 1990; 152(10): 518–21.
16 Janz NK, Becker MH, Kirscht JP, Eraker SA, Billi JE, Woolliscroft JO. Evaluation of a minimal-contact smoking cessation intervention in an outpatient setting. *American Journal of Public Health* 1987; 77(7): 805–809.
17 Lomas J, Enkin M, Anderson GM, Hannah WJ, Vayda E, Singer J. Opinion leaders vs audit and feedback to implement practice guidelines. Delivery after previous cesarean section. *Journal of the American Medical Association* 1991; 265(17): 2202–207.
18 Brown LF, Keily PA, Spencer AJ. Evaluation of a continuing education intervention 'Periodontics in General Practice'. *Community Dental Oral Epidermiology* 1994; 22: 441–47.
19 Howe A. Detecting psychological distress: can general practitioners improve their performance? *British Journal of General Practice* 1996; 46: 407–10.
20 Lando HA, McGovern PG. The influence of group cohesion on the behavioral treatment of smoking: a failure to replicate. *Addictive Behavior* 1991; 16(3–4): 111–21.
21 Resnicow K, Vaughan R, Futterman R. A self-help smoking cessation program for inner-city African Americans: results from the Harlem Health Connection Project. *Health Education & Behavior* 1997; 24(2): 201–17.
22 Group W. Multifactorial trial in the prevention of coronary heart disease. II Risk factor changes at two and four years. *European Heart Journal* 1982; 3: 184–90.
23 Group I C R F Ë S. Effectiveness of health checks conducted by nurses in primary care: results of the OXCHECK study after one year. *British Medical Journal* 1994; 308: 308–12.
24 Group FHS. Randomised controlled trial evaluating cardiovascular screening and intervention in general practice: principal results of the British family heart study. *British Medical Journal* 1994; 308: 313–20.
25 Glasgow RE, Terborg JR, Hollis JF, Severson HH, Boles SM. Take heart: results from the initial phase of a work-site wellness program. *American Journal of Public Health* 1995; 85(2): 209–16.
26 Hill R, Rigdon M, Johnson S. Behavioral smoking cessation treatment for older chronic smokers. *Behavior Therapy* 1993; 24: 321–29.
27 Jason LA, Lesowitz T, Michaels M, Blitz C, Victors L, Dean L et al. A worksite smoking cessation intervention involving the media and incentives. *American Journal of Community Psychology* 1989; 17(6): 785–99.
28 Jason LA, McMahon SD, Salina D, Hedeker D, Stockton M, Dunson, K *et al.* Assessing a smoking cessation intervention involving groups, incentives, and self-help manuals. *Behavior Therapy* 1995; 26: 393–408.
29 Thein-Hlaing, Thane-Toe, Than-Saw. A controlled chemotherapeutic intervention trial on the relationship between Ascaris lumbricoides infection and mulnutrition in children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1991; 85: 523–28.
30 Rousham E, Mascie-Taylor C. An 18-month study of the effect of periodic anthelminthic treatment on the growth and nutritional status of pre-school children in Bangladesh. *Annals of Human Biology* 1994; 21: 315–24.
31 Stoltzfus RJ, Albonico M, Tielsch JM, Chwaya HM, Savioli L. School-based deworming program yields small improvement in growth of Zanzibari school children after one year. *Journal of Nutrition* 1997; 127(11): 2187–93.
32 Hodnett ED, Kaufman K, O'Brien-Pallas L, Chipman M, Watson-MacDonell J, Hunsburger W. A strategy to promote research-based nursing care: effects on childbirth outcomes. *Research in Nursing & Health* 1996; 19(1): 13–20.
33 Sommer A, Tarwotjo I, Djunaedi E, West KP, Jr., Loeden AA, Tilden R *et al.* Impact of vitamin A supplementation on childhood mortality. A randomised controlled community trial. *Lancet* 1986; 1(8491): 1169–73.
34 Rahmathullah L. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *New England Journal of Medicine* 1990; 323: 929–35.
35 West KP, Jr, Pokhrel RP, Katz J, LeClerq SC, Khatry SK, Shrestha SR *et al.* Efficacy of vitamin A in reducing preschool child mortality in Nepal. *Lancet* 1991; 338(8759): 67–71.
36 Daulaire NM, Starbuck ES, Houston RM, Church MS, Stukel TA, Pandey MR. Childhood mortality after a high dose of vitamin A in a high risk population. *British Medical Journal* 1992; 304(6821): 207–10.

37 Muhilal, Murdiana A, Azis I, Saidin S, Jahari AB, Karyadi D. Vitamin A-fortified monosodium glutamate and vitamin A status: a controlled field trial. *American Journal of Clinical Nutrition* 1988; 48(5): 1265–70.

38 Herrera MG, Nestel P, el Amin A, Fawzi WW, Mohamed KA, Weld L. Vitamin A supplementation and child survival. *Lancet* 1992; 340(8814): 267–71.

39 Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effect on clinic attendances, hospital admissions, and child mortality. *Lancet* 1993; 342: 7–12.

40 Tinetti ME, Baker DI, McAvay G, Claus EB, Garrett P, Gottschalk M *et al.* A multifactorial intervention to reduce the risk of falling among elderly people living in the community. *New England Journal of Medicine* 1994; 331(13): 821–27.

41 Tinetti M, McAvay G, Claus E. Does multiple risk factor reduction explain the reduction in fall rate in the Yale FICSIT trial? *American Journal of Epidemiology* 1996; 144: 389–99.

42 Vetter N, Lewis P, Ford D. Can health visitors prevent fractures in elderly people? *British Medical Journal* 1992; 304: 888–90.

43 Hornbrook MC, Stevens VJ, Wingfield DJ, Hollis JF, Greenlick MR, Ory MG. Preventing falls among community-dwelling older persons: results from a randomized trial. *Gerontologist* 1994; 34(1): 16–23.

44 Reinsch S, MacRae P, Lachenbruch PA, Tobis JS. Attempts to prevent falls and injury: a prospective community study. *Gerontologist* 1992; 32: 450–56.

45 Stross JK, Bole GG. Evaluation of a continuing education program in rheumatoid arthritis. *Arthritis and Rheumatism* 1980; 23: 846–49.

46 Stross JK, Hiss RG, Watts CM, Davis WK, Macdonald R. Continuing education in pulmonary disease for primary-care physicians. *American Review in Respiratory Disease* 1983; 127(6): 739–46.

47 Stross J, Bole G. Evaluation of an educational program for primary care practitioners, on the management of osteoarthritis. *Arthritis and Rheumatism* 1985; 28: 108–11.

48 Elliott TE, Murray DM, Oken MM, Johnson KM, Braun BL, Elliott BA *et al.* Improving cancer pain management in communities: main results from a randomized controlled trial. *Journal of Pain and Symptom Management* 1997; 13(4): 191–203.

49 Snow R, Rowan K, Greenwood B. A trial of permetrin-treated bed nets in the prevention of malaria in Gambian children. *Transactions of The Royal Society of Tropical Medicine and Hygiene* 1987; 81: 563–67.

50 Snow R, Rowan K, Lindsay S, Greenwood B. A trial of bed nets (mosquito nets) as a malaria control strategy in a rural area of the Gambia, West Africa. *Transactions of The Royal Society of Tropical Medicine and Hygiene* 1988; 82: 212–15.

51 Sexton JD, Ruebush TK, Brandling-Benett AD. Permethrin-impregnated curtains and bed-nets prevent malaria in western Kenya. *American Journal of Tropical Medicine and Hygiene* 1990; 43: 11–18.

52 Kamol-Ratanakul P, Prasittisuk C. The effectiveness of permethrin-impregnated bed nets against malaria for migrant workers in Eastern Thailand. *American Journal of Tropical Medicine and Hygiene* 1992; 47: 305–309.

53 Beach RF, Ruebush TK, 2nd, Sexton JD, Bright PL, Hightower AW, Breman JG *et al.* Effectiveness of permethrin-impregnated bed nets and curtains for malaria control in a holoendemic area of western Kenya. *American Journal of Tropical Medicine and Hygiene* 1993; 49(3): 290–300.

54 Graves PM, Brabin BJ, Charlwood JD, Burkot TR, Cattani JA, Ginny M *et al.* Reduction in incidence and prevalence of Plasmodium falciparum in under-5-year-old children by permethrin impregnation of mosquito nets. *Bulletin of the World Health Organization* 1987; 65(6): 869–77.

55 Kothari G. The effect of vitamin A prophylaxis on morbidity and mortality among children in urban slums in Bombay. *Journal of Tropical Pediatrics* 1991; 37: 141.

56 D'Alessandro U, Olaleye BO, McGuire W, Langerock P, Bennett S, Aikins MK *et al.* Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. *Lancet* 1995; 345(8948): 479–83.

57 Habluetzel A, Diallo DA, Esposito F, Lamizana L, Pagnoni F, Lengeler C *et al.* Do insecticide-treated curtains reduce all-cause child mortality in Burkina Faso? *Tropical Medicine and International Health* 1997; 2(9): 855–62.

58 Kroeger A, Manchcheno M, Alarcon J, Pesse K. Insecticide-impregnated bed nets for malaria control: varying experiences from Ecuador, Colombia, and Peru concerning

acceptability and effectiveness. *American Journal of Tropical Medicine and Hygiene* 1995; 53: 313–23.

59 Moyou-Somo R, Lehman LG, Awahmukalah S, Ayuk Enyong P. Deltamethrin impregnated bednets for the control of urban malaria in Kumba Town, South-West Province of Cameroon. *Journal of Tropical Medicine and Hygiene* 1995; 98(5): 319–24.

60 Rowland M, Bouma M, Ducornez D, Durrani N, Rozendaal J, Schapira A *et al.* Pyrethroid-impregnated bed nets for personal protection against malaria for Afghan refugees. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996; 90(4): 357–61.

61 Nevill CG, Some ES, Mung'ala VO, Mutemi W, New L, Marsh K *et al.* Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. *Tropical Medicine and International Health* 1996; 1(2): 139–46.

62 Binka FN, Kubaje A, Adjuik M, Williams LA, Lengeler C, Maude GH *et al.* Impact of permethrin impregnated bednets on child mortality in Kassena–Nankana district, Ghana: a randomized controlled trial. *Tropical Medicine and International Health* 1996; 1(2): 147–54.