Citation:

Schlattmann, P., Malzahn, U. & Böhning, D. (2003). META – A software package for meta-analysis in medicine, social sciences and the pharmaceutical industry. In R. Schulze, H. Holling & D. Böhning (Eds.), *Meta-analysis: New developments and applications in medical and social sciences* (pp. 251-261). Hogrefe & Huber.

16

META – A Software Package for Meta-Analysis in Medicine, Social Sciences, and the Pharmaceutical Industry

Peter Schlattmann
Uwe Malzahn
Dankmar Böhning

Working Group: Biometry and Epidemiology
Institute for International Health, Joint Center for Humanities and Health Sciences
Humboldt-University in Berlin / Free University Berlin

Summary

The software META provides statistical methods for the performance of meta-analyses in medicine, psychology, and quality assurance in the pharmaceutical industry. META makes a variety of effect measures available, like the relative risk, the standardized difference, and quality indices. For these effect measures, classical pooled estimators as well as "modern" random effect models can be calculated, for example, the approach of DerSimonian and Laird (1986) or the mixture distribution approach (Böhning, 2000a; Böhning et al., 1998). The latter approach allows the semiparametric estimation of the heterogeneity structure and classification of individual studies or batches. In addition to statistical methods there are graphical facilities, such as funnel plots for the identification of a publication bias or plots of confidence intervals for an illustration of individual studies and the pooled effect measure. META is a public domain program. It comes with a graphical interface and is available for Windows 9x/NT and Unix (Linux).

16.1 INTRODUCTION

In the past few years, meta-analysis has become increasingly popular in many areas of science such as medicine, psychology, and other social sciences. In these areas of application meta-analyses have been performed in order to obtain a pooled estimate of various single studies. Obtaining a single summary measure implicitly assumes *homogeneity* of these studies, that is, the results of individual studies differ only by chance. In this case a combined estimate of the individual studies provides a powerful and important result. However, this pooled estimate may be seriously misleading if study conditions are *heterogenous*.

Thus, an approach which considers meta-analysis as a study over studies has increasingly been advocated. This approach seeks to investigate heterogeneity between studies. An important feature of this type of meta-analysis lies in the fact that it tries to identify factors which cause heterogeneity.

This approach may easily be extended to the area of quality control, where batches of the produced goods replace the role of studies in medicine or the social sciences. Clearly, in this setting an investigation of heterogeneity is equally attractive, since identification and modeling of heterogeneity helps to improve the production process. An introduction how to use the methodology of meta-analysis in quality control is given by Böhning and Dammann in Chapter 10 of this volume.

16.2 THE PROGRAM META

The software META has been developed to provide a tool which allows to perform meta-analyses within the areas of application described above. The focus of META is on the analysis of heterogeneity, which may be considered here the unifying concept for several fields of application.

For different areas of application, different measures of effects are important and necessary. Thus, META enables the meta-analyst to choose out of a variety of measures of effects, such as the relative risk in medicine, the standardized difference in psychology and proportions in quality control, just to mention a few.

META provides various statistical methods to perform meta-analyses such as simple pooled estimates, random effects models, and graphical procedures such has confidence interval plots, funnel plots, and so forth. We will illustrate the possible use of META using a data set from psychiatric epidemiology.

16.3 A WORKED EXAMPLE

The following meta-analysis investigates the prevalence of agoraphobia based on seven studies (Eaton, 1995) in several countries all over the world. Agoraphobia may be defined as space anxiety, as a fear of being in public places.

This psychiatric disorder may even lead to total avoidance of public places and thus may cause severe disability.

An initial step in any meta-analysis might be to plot the effect measure together with a 95% confidence interval. This may be done using META and its graphics facilities. Figure 16.1 shows a screen dump of META and its data window. The data window shows the prevalent cases of agoraphobia together with the population at risk of the respective study.

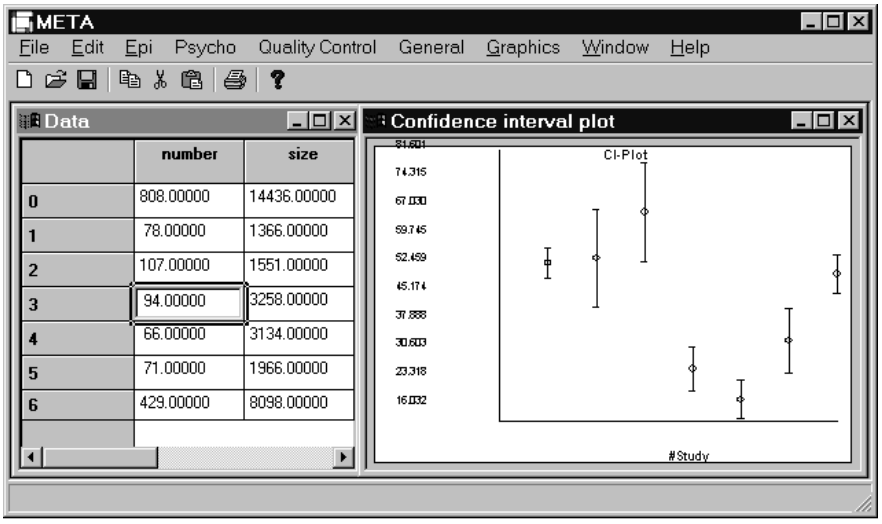

Figure 16.1 Data window and confidence interval plot.

The simplest model possible assumes parametric density $f(x, \theta, \sigma^2)$ for some random quantity X where θ is a parameter of interest and σ^2 is a nuisance parameter which might or might not be present in the model. In the example at hand, $f(x, \theta) = \binom{n}{x}\theta^x(1-\theta)^{n-x}$. In this case all studies are assumed to measure the same overall effect θ, and they only differ in variability. Thus, the summary measure needs to assign weights according to the inverse of the variance of the individual study in order to obtain the summary measure.

Looking at the confidence interval plot, there seems to be a large degree of variability to be present. However, frequently one is interested in obtaining a summary measure for all studies. Using META we obtain the following results:

```
POOLED ESTIMATOR FOR PROPORTIONS

RESULTS
Pooled estimate:      0.048892
Common variance:    0.00000145

95 percent confidence interval (0.04654, 0.05125)

Chi-Square test for homogeneity of proportions:
     115.23539 df = 6  p-value:       0.00000
```

Clearly, looking at the value of the χ^2 test of homogeneity, we reject the null-hypothesis and conclude that there is substantial heterogeneity in terms of the prevalence of agoraphobia in the countries studied. As a result, the computation of an overall rate is not very meaningful, since we would ignore the underlying heterogeneity.

In order to deal with heterogeneity, a two-level model is implemented in META. As before, $f(x, \theta, \sigma^2)$ denotes a parametric density for some random quantity X. But now it is assumed that θ is not constant but is varying itself according to some further distribution P for which the moments $E_P(\theta) = \mu$ and $Var_P(\theta) = \tau^2$ are assumed to exist. Consequently, we are lead to a *marginal* or *unconditional* distribution $f(x, P) = \int f(x, \theta) P(d\theta)$.

Frequently, τ^2 is called the *heterogeneity variance*. META offers modeling according to two different distributions in order to deal with heterogeneity: one is the moment approach which is based on equating the expected value of the χ^2-statistic to the observed one and then solving for τ^2. Actually, this is the approach by DerSimonian and Laird (1986). The other approach does not specify P any further and leads to the marginal density, a mixture model. Here, $f(x, P) = \sum_{j=1}^{k} p_j f(x_i, \theta_j, \sigma_i^2)$. According to this model, we assume the existence of k subpopulations with parameters θ_j receiving weight p_j for the j^{th} subpopulation. A detailed description of the use of this approach in meta analysis may be found in Böhning et al. (1998), or in Böhning (2000a).

We proceed in our analysis with the estimation of the DerSimonian-Laird estimator:

```
RESULTS
Pooled DerSimonian-Laird estimate:       0.0455

Heterogeneity variance:       0.0003

Variance of pooled estimator: 0.0000465

0.04545 95 percent CI: (0.0321,   0.0588)
```

Please note that we find a substantial value for the heterogeneity variance τ^2 in this data set. As expected, incorporating heterogeneity leads to a larger variance for the DerSimonian-Laird estimator. As a result, we obtain a much wider confidence interval compared to the pooled estimator where we assume a constant value for θ.

Frequently, there is a debate whether one should use a summary measure in the presence of heterogeneity. One might argue that this may be done, but one has to be careful how to interpret the results. Under the presence of heterogeneity a summary measure will reflect the overall mean in the population well, knowing that this effect might be different in subparts of the population.

If the presence of heterogeneity has been identified, one might wish to model the *structure* of this heterogeneity and, for example, find the levels of effect in subparts of the population. This can be accomplished using the finite mix-

ture model approach outlined above. A convenient computational strategy uses a fixed grid of potential support points (subpopulation means θ_j) which may or may not receive weights p_j.

Figure 16.2 shows the dialog box which allows the user to define a grid of potential support points.

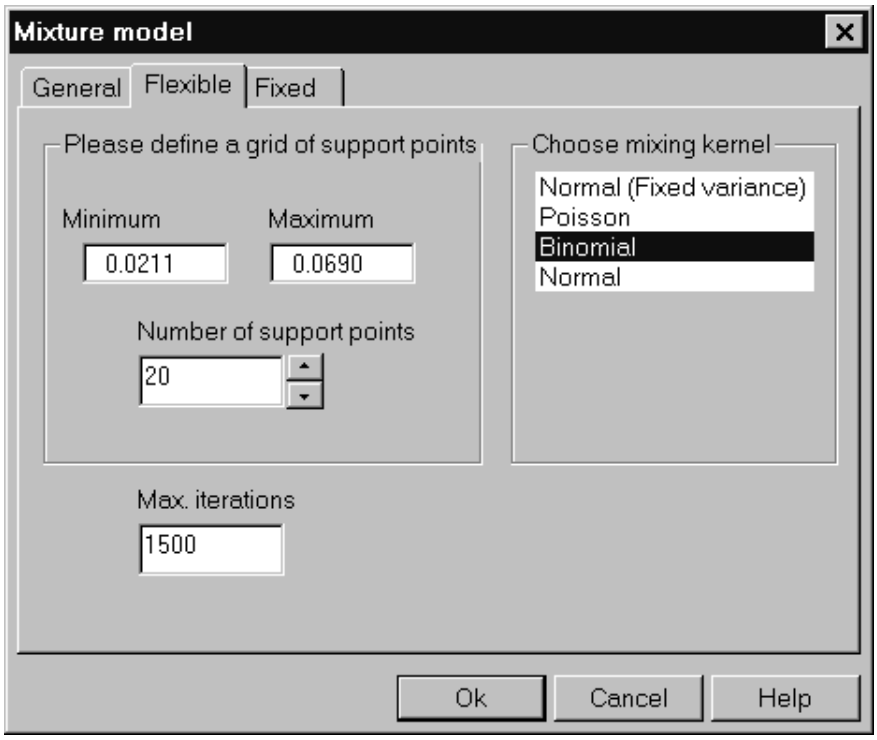

Figure 16.2 Dialog box for the definition of a grid of potential support points in the mixture model.

Depending on the current measure of effect an appropriate mixing kernel may be chosen by the user. In this case – since we are dealing with rates – the binomial distribution is the natural choice.

```
Initial number of components: 5
Parameter:   0.0211, Weight:   0.1441
Parameter:   0.0317, Weight:   0.2840
Parameter:   0.0530, Weight:   0.3073
Parameter:   0.0584, Weight:   0.1533
Parameter:   0.0690, Weight:   0.1113

Log-likelihood at iterate: -34.8009
```

Based on this grid META identifies five potential subpopulations. Now these grid points with positive support may be used to find a refined solution using the EM-algorithm (Dempster et al., 1977). Here, we keep the number of components fixed and update mixing weights and subpopulation means. Fre-

quently, some population means coincide and thus the number of components decreases. For our data at hand, after applying the EM-algorithm, we find four remaining components (results not shown here).

Now a backward elimination approach may be used in order to reduce the number of mixing components. This would imply that we test $k = 4$ vs. $k = 3$ using a Likelihood Ratio test approach (see Figure 16.3).

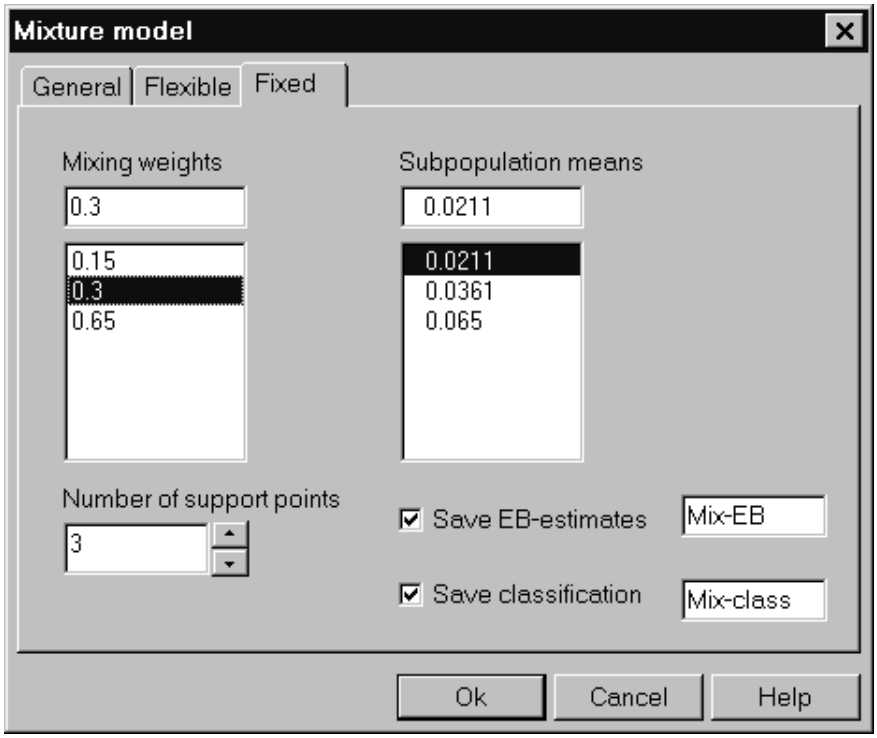

Figure 16.3 Dialog box for fixed effect mixture model.

```
NPMLE for Fixed support size

Number of components after combining equal parameter estimates: 3

Parameter:   0.0212, Weight:   0.1440
Parameter:   0.0316, Weight:   0.2844
Parameter:   0.0559, Weight:   0.5716

Log-likelihood at iterate: -34.3889
```

Clearly, the log-likelihood is only slightly smaller for this three component mixture model and we would conclude that a three component solution is appropriate. Once a mixture model has been chosen, one might be interested in classifying the individual study. Due to their discrete structure, mixture models provide a natural way of classifying the individual study. This is achieved by applying Bayes theorem and using the estimated mixing distribution as a

prior distribution. Thus, we are able to compute the posterior probability for each study to belong to a certain component:

$$Pr(Z_{ij} = 1|x_i, \hat{P}) = \frac{\hat{p}_j f(x_i, \hat{\theta}_j)}{\sum_{l=1}^{k} \hat{p}_l f(x_i, \hat{\theta}_l)}.$$

The ith study is then assigned to that subpopulation j for which it has the highest posterior probability of belonging. META offers the option to classify the studies and to store the results of this classification in the data spreadsheet (see Figure 16.3).

META also computes the posterior expectation for the measure of effect for the individual study based on the assumed distribution. Likewise, the posterior expectations may also be stored within the data frame as may be seen in Figure 16.4.

META - [Data]

File Edit Epi Psycho Quality Control General Graphics Window Help

	number	size	prev	DerL-EB	Mix-class	Mix-EB
0	808.00000	14400.00000	0.05597	0.05603	3.00000	0.05594
1	78.00000	1370.00000	0.05710	0.05604	3.00000	0.05594
2	107.00000	1550.00000	0.06899	0.06666	3.00000	0.05594
3	94.00000	3260.00000	0.02885	0.02938	2.00000	0.03142
4	66.00000	3130.00000	0.02106	0.02167	1.00000	0.02122
5	71.00000	1970.00000	0.03611	0.03674	2.00000	0.03156
6	429.00000	8100.00000	0.05298	0.05288	3.00000	0.05594

Figure 16.4 Spreadsheet with original data and empirical Bayes estimates.

16.4 AVAILABILITY

META is designed to be platform independent and uses the wxWindows 2.0 class library (Smart, 2000). META may be obtained for Microsoft Windows 9x/NT and for Unix(Linux) operating systems. META is available from the authors on request.

REFERENCES

Böhning, D. (2000). *Computer-assisted analysis of mixtures and applications: Meta-analysis, disease mapping, and others.* Boca Raton, FL: Chapman & Hall/CRC.

Böhning, D., Dietz, E., & Schlattmann, P. (1998). Recent developments in computer-assisted analysis of mixtures. *Biometrics*, *54*, 525–536.

Dempster, A. P., Laird, N. M., & Rubin, D. B. (1977). Maximum likelihood from incomplete data via the EM algorithm (with discussion). *Journal of the Royal Statistical Society, Series B*, *39*, 1–38.

DerSimonian, R., & Laird, N. M. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials*, *7*, 177–188.

Eaton, W. W. (1995). Progress in the epidemiology of anxiety disorders. *Epidemiologic Reviews*, *17*, 32–38.

Smart, J. (2000). wxwindows – a cross-platform GUI-solution. Available via WWW: http://www.wxwindows.org.

Contributors

DR. DOROTHEE ABRAHAM-RUDOLF, Psychiatrische Klinik der Technischen Universität München, Ismaninger Str. 22, D-81675 München

DR. GERD ANTES, Deutsches Cochrane Zentrum, Universitätsklinikum der Albert-Ludwigs-Universität Freiburg, Institut für Medizinische Biometrie und Medizinische Informatik, Stefan-Meier-Str. 26, D-79104 Freiburg; antes@cochrane.de

DR. DOGAN ARGAC, Fachbereich Statistik, Universität Dortmund, Vogelpothsweg 87, D-44221 Dortmund; argac@statistik.uni-dortmund.de

PROF. DR. MARIA BLETTNER, Epidemiologie und Medizinische Statistik, Fakultät für Gesundheitswissenschaften, Universität Bielefeld, Postfach 10 01 31, D-33501 Bielefeld; blettner@uni-bielfeld.de

PROF. DR. DANKMAR BOEHNING, AG Biometrie und Epidemiologie, Institut für Soziale Medizin, Zentrum für Human- und Gesundheitswissenschaften, Freie Universität Berlin / Humboldt-Universität zu Berlin, Fabeckstr. 60-62, D-14195 Berlin; boehning@zedat.fu-berlin.de

MICHAELA BROCKE, Psychologisches Institut IV, Westfälische Wilhelms-Universität, Fliednerstr. 21, D-48149 Münster; brockem@psy.uni-muenster.de

DR. UWE CZIENSKOWSKI, Max Planck Institute for Human Development, ABC Research Group, Lentzealle 94, D-14195 Berlin; sciencec@zedat.fu-berlin.de

DR. SUSANNE DAHMS, Institut für Biometrie und Informationsverarbeitung, Freie Universität Berlin, Oertzenweg 19b, D-14163 Berlin; sdahms@zedat.fu-berlin.de

UWE-PETER DAMMANN, Asta Medica AG, Kantstr. 2, D-33790 Halle / Westfalen; Uwe-Peter.Dammann@astamedica.de

DR. EKKEHART DIETZ, AG Biometrie und Epidemiologie, Institut für Soziale Medizin, Zentrum für Human- und Gesundheitswissenschaften, Freie Universität Berlin, Fabeckstr. 60-62, D-14195 Berlin; lungtung@zedat.fu-berlin.de

PROF. DR. ROLF R. ENGEL, Abteilung für Klinische Psychologie und Psychophysiologie, Klinik für Psychiatrie und Psychotherapie der LMU München, Nussbaumstr. 7, D-80336 München; re@psy.med.uni-muenchen.de

JEREMY FRANKLIN, Biometrie, Klinik I für Innere Medizin, Universität Köln, Herder Str. 52-54, D-50931 Köln; jeremy.franklin@Biometrie.uni-koeln.de

DR. MATTHIAS GREINER, International EpiLab, Danish Veterinary Institute, Bülowsvej 27, DK-1790 Copenhagen V; mgreiner@gmx.net

DR. HEIKO GROSSMANN, Psychologisches Institut IV, Westfälische Wilhelms-Universität, Fliednerstr. 21, D-48149 Münster; grossman@psy.uni-muenster.de

PROF. DR. JOACHIM HARTUNG, Fachbereich Statistik, Universität Dortmund, Vogelpothsweg 87, D-44221 Dortmund; hartung@statistik.uni-dortmund.de

PROF. DR. HEINZ HOLLING, Psychologisches Institut IV, Westfälische Wilhelms-Universität, Fliednerstr. 21, D-48149 Münster; holling@psy.uni-muenster.de

DR. ANDREAS JUETTING, Psychologisches Institut IV, Westfälische Wilhelms-Universität, Fliednerstr. 21, D-48149 Münster; juetting@psy.uni-muenster.de

DR. JÜRGEN KLEIN, Institut für Arbeits- und Sozialmedizin der Universität zu Köln, Joseph-Stelzmann-Str. 9, D-50924 Köln; juergen.klein@uni-koeln.de

DR. GUIDO KNAPP, Fachbereich Statistik, Universität Dortmund, Vogelpothsweg 87, D-44221 Dortmund; Knapp@statistik.uni-dortmund.de

DR. ARMIN KOCH, Bundesinstitut für Arzneimittel und Medizinprodukte, Seestr. 10, D-13353 Berlin; a.koch@bfarm.de

DR. KEPHER HENRY MAKAMBI, Fachbereich Statistik, Universität Dortmund, Vogelpothsweg 87, D-44221 Dortmund; makambi@amadeus.statistik.uni-dortmund.de

DR. UWE MALZAHN, AG Biometrie und Epidemiologie, Institut für Soziale Medizin, Zentrum für Human- und Gesundheitswissenschaften, Freie Universität Berlin, Fabeckstr. 60-62, D-14195 Berlin; malzahn@zedat.fu-berlin.de

PROF. DR. GEORG MATT, Department of Psychology, San Diego State University, San Diego, CA 92182-4611; gmatt@sciences.sdsu.edu

PROF. DR. JOACHIM ROEHMEL, Bundesinstitut für Arzneimittel und Medizinprodukte, Seestr. 10, D-13353 Berlin; j.roehmel@bfarm.de

DR. WILHELM SAUERBREI, Universitätsklinikum der Albert-Ludwigs-Universität Freiburg, Institut für Medizinische Biometrie und Medizinische Informatik, Stefan-Meier-Str. 26, D-79104 Freiburg; wfs@imbi.uni-freiburg.de

DR. PETER SCHLATTMANN, AG Biometrie und Epidemiologie, Institut für Soziale Medizin, Zentrum für Human- und Gesundheitswissenschaften, Freie Universität Berlin, Fabeckstr. 60-62, D-14195 Berlin; schlattmann@medizin.fu-berlin.de

DR. CLAUDIA SCHOECHLIN, Abteilung für Klinische Psychologie und Psychophysiologie, Klinik für Psychiatrie und Psychotherapie der LMU München, Nussbaumstr. 7, D-80336 München;
claudia.schoechlin@psy.med.uni-muenchen.de

DR. RALF SCHULZE, Psychologisches Institut IV, Westfälische Wilhelms-Universität, Fliednerstr. 21, D-48149 Münster; rs@psy.uni-muenster.de

PROF. DR. MARTIN SCHUMACHER, Universitätsklinikum der Albert-Ludwigs-Universität Freiburg, Institut für Medizinische Biometrie und Medizinische Informatik, Stefan-Meier-Str. 26, D-79104 Freiburg;
ms@imbi.uni-freiburg.de

GUIDO SCHWARZER, Universitätsklinikum der Albert-Ludwigs-Universität Freiburg, Institut für Medizinische Biometrie und Medizinische Informatik, Stefan-Meier-Str. 26, D-79104 Freiburg; sc@imbi.uni-freiburg.de

PROF. DR. KARL WEGSCHEIDER, Institut für Statistik und Ökonometrie, Universität Hamburg, Von-Melle-Park 5, D-20146 Hamburg;
wegsch@econ.uni-hamburg.de

DR. KLAUS WEIST, Institut für Hygiene und Umweltmedizin, Freie Universität Berlin, Hindenburgdamm 30, D-12203 Berlin; weist@ukbf.fu-berlin.de

PROF. DR. WERNER W. WITTMANN, Lehrstuhl Psychologie II, Universität Mannheim, Schloss, D-68131 Mannheim;
wittmann@tnt.psychologie.uni-mannheim.de