

APPLICATION

OpenMEE: Intuitive, open-source software for meta-analysis in ecology and evolutionary biology

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Summary

1. Meta-analysis and meta-regression are statistical methods for synthesizing and modelling the results of different studies, and are critical research synthesis tools in ecology and evolutionary biology (E&E). However, many E&E researchers carry out meta-analyses using software that is limited in its statistical functionality and is not easily updatable. It is likely that these software limitations have slowed the uptake of new methods in E&E and limited the scope and quality of inferences from research syntheses.
2. We developed *OpenMEE: Open Meta-analyst for Ecology and Evolution* to address the need for advanced, easy-to-use software for meta-analysis and meta-regression. *OpenMEE* has a cross-platform, easy-to-use graphical user interface (GUI) that gives E&E researchers access to the diverse and advanced statistical functionalities offered in *R*, without requiring knowledge of *R* programming.
3. *OpenMEE* offers a suite of advanced meta-analysis and meta-regression methods for synthesizing continuous and categorical data, including meta-regression with multiple covariates and their interactions, phylogenetic analyses, and simple missing data imputation. *OpenMEE* also supports data importing and exporting, exploratory data analysis, graphing of data, and summary table generation.
4. As intuitive, open-source, free software for advanced methods in meta-analysis, *OpenMEE* meets the current and pressing needs of the E&E community for teaching meta-analysis and conducting high-quality syntheses. Because *OpenMEE*'s statistical components are written in *R*, new methods and packages can be rapidly incorporated into the software. To fully realize the potential of *OpenMEE*, we encourage community development with an aim to advance the capabilities of meta-analyses in E&E.

Key-words: effect sizes, meta-analysis, meta-regression, open-access, open-source, phylogenetic comparative analyses, research synthesis

Introduction

Meta-analysis provides a widely implemented, cross-disciplinary statistical framework for synthesizing different study outcomes on the same research question (Hedges & Olkin 1985; Cooper & Hedges 1994; Koricheva, Gurevitch & Mengersen 2013). It is difficult to overstate the impact of meta-analysis on science, as it has transformed standards for evidence in many disciplines, including medicine, epidemiology, management, education, psychology and other social sciences, as well as ecology and evolution (E&E) (e.g. Glass, McGaw & Smith 1981; Agrawal & Srikant 1994; Deeks *et al.* 2008; Hillebrand & Cardinale 2010; Koricheva, Gurevitch & Mengersen 2013;

McKenzie *et al.* 2013; Lortie 2014). As meta-analysis is increasingly applied to more complex data, practitioners can benefit from using state-of-the-science synthesis approaches that are based on advanced, theory-motivated modelling, such as the methods introduced by Normand (1999) and Van Houwelingen, Arends & Stijnen (2002), and reviewed in Koricheva, Gurevitch & Mengersen (2013). However, best practices in meta-analysis and many advanced synthesis approaches have remained unknown or inaccessible to many researchers in the E&E community.

We have developed *Open Meta-analyst for Ecology and Evolution (OpenMEE)*, the first open-access and open-source statistical software for carrying out and teaching meta-analysis in E&E. *OpenMEE* was developed to make advanced methods for statistical research synthesis, based on best practices, available without cost to the scientific community by providing an

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intuitive graphical user interface (GUI) to the diverse and growing statistical functionalities of the *R* ecosystem (R Core Team 2014). While other dedicated commercial software packages exist, such as *Comprehensive Meta-Analysis* (Borenstein *et al.* 2005), they are primarily designed for other disciplines. However, by tailoring *OpenMEE* to meet the needs of the E&E community, we hope to facilitate new scientific advances and insights from synthesizing E&E research, address common challenges unique to our discipline (e.g. phylogenetic analyses; Lajeunesse 2009), and offer an intuitive tool for teaching meta-analysis (since students do not have to master *R* while learning the statistics of meta-analysis). *OpenMEE*'s interface also guides users to build appropriate synthesis models that provide high-quality analyses for the most common and important ecological questions.

A BRIEF REVIEW OF EXISTING SOFTWARE

The first meta-analyses in E&E were published in the early 1990s (Järvinen 1991; Gurevitch *et al.* 1992), and the number of meta-analyses in these closely related fields increased greatly over the next two decades, reaching nearly 1000 publications today (web of science search on 12/11/2015). The first dedicated software for meta-analysis in E&E was *MetaWin* (Rosenberg, Adams & Gurevitch 1997) followed by *MetaWin* 2.0 (Rosenberg, Adams & Gurevitch 2000). This software has been widely cited (over 1000 times according to Google scholar), and was intended to be relatively inexpensive, widely distributed and user-friendly with a GUI. However, it has not been updated since 2000 and is currently no longer available from the publisher or supported by its developers (Lajeunesse 2016). Another serious limitation was its lack of flexibility: it could only perform the most basic meta-analyses that tested only one predictor at a time. This single-predictor limitation has largely defined the scope of syntheses typically performed in E&E.

Other disciplines in the medical and social sciences have their own dedicated GUI-based software, such as *Comprehensive Meta-Analysis* (Borenstein *et al.* 2005), *MetaAnalyst* (Wallace *et al.* 2009), *OpenMeta-analyst* (Wallace *et al.* 2012), and *RevMan* (Bero & Rennie 1995; Nordic Cochrane Centre 2014). However, they offer statistics and tools not widely used in E&E, and do not address the questions, data structures or experimental designs encountered in E&E (Schmid *et al.* 2013). For example, tools focus on point-estimation of grand means, rather than analyses asking how covariates systematically contribute to variation in outcomes (Lajeunesse 2010; Schmid *et al.* 2013) or phylogenetic analyses (Lajeunesse 2009, 2011). *OpenMEE* was developed from the medical software *Open Meta-Analyst* (Wallace *et al.* 2009, 2012) and takes its name from that program. (*OpenMEE* has no connection to the journal *Methods in Ecology and Evolution*, acronym MEE, nor does the name imply an endorsement of *OpenMEE* by this journal.)

Recently, statistical packages developed for *R* have emerged as powerful and flexible tools for meta-analysis; for example *metafor* (Viechtbauer 2010) and *mvmeta* (White

2011; Gasparrini 2012) are gaining traction in many disciplines. These packages allow for the inclusion of multiple covariates, multivariate analyses, and make use of the extensive linear modelling and optimization tools necessary for between-study variance estimation of random effects – a crucial component of modern meta-analysis not part of conventional statistical software (Mengerson & Schmid 2013). Other specialized *R* tools are also emerging, such as *metagear* (Lajeunesse 2016), which aims to provide end-to-end support for research synthesis by emphasizing systematic reviews and data extraction.

OpenMEE aims to combine the strengths of GUI-driven, easy-to-use programs like *MetaWin* with the statistical sophistication and flexibility afforded by *R*. In the following sections, we outline what functionalities *OpenMEE* offers and how they are tailored for the E&E community. For developers, we include Appendix S1, Supporting Information that describes the unique Python/*R* architecture of *OpenMEE* and how this design allows for the quick integration of new statistics as they emerge. This documentation also includes information on how stable builds are distributed and maintained with unit testing.

OpenMEE's interface

OpenMEE's GUI is built around a spreadsheet (see Fig. 1) where study data, such as means and sample sizes, may be entered manually, copied-and-pasted, or added using the 'data import tool' (see Table 1). Once these data have been entered, a column of study ID's needs to be specified, and data columns must also be designated as 'continuous' or 'count', or as containing standard or user-defined effect sizes and associated variances (if calculated prior to importation). Alternatively, *OpenMEE* can calculate these effect sizes (see Table 1). Effect sizes are then analysed via the desired drop-down menu options or quick-start buttons (see Fig. 1), where users are guided through a series of menus requesting model arguments, variables, and other options to perform analyses. Whenever possible, *OpenMEE* provides sensible defaults but allows user discretion in choosing options. Details on this workflow are found as follows: <http://www.cebm.brown.edu/openmee/help.html>.

Statistical and exploratory tools offered by *OpenMEE*

DATA PRE-PROCESSING, EXPLORATORY TOOLS, AND PUBLICATION BIAS DIAGNOSTICS

OpenMEE includes basic data-preprocessing (e.g. effect size calculations), exploratory analyses, and visualizations (Table 1). All conventional and less-familiar effect sizes are supported (Table 1) and can be calculated from means, standard deviations, proportions, or count data such as the number of individuals marked and recaptured (e.g. Beirincx *et al.* 2006). Exploratory tools include scatterplots, histograms and contingency tables useful for identifying research gaps, assessing collinearity of covariates, and detecting which groups have

	species (Study ID)	Family (cat)	type (cat)	mating_system (cat)	d (cont)	var_d (cont)	COII (cat)	H	I	J	K
1	Chilo_partellus	Crambidae	H	M	-0.041	0.052	AY320482				
2	Ostrinia_nubilalis	Crambidae	H	M	0.359	0.017	AF321880				
3	Trichoplusia_ni	Noctuidae	H	P	0.263	0.075	AB158623				
4	Busseola_fusca	Noctuidae	H	P	0.469	0.082	AY320474				
5	Helicoverpa_armigera	Noctuidae	H	P	0.304	0.128	DQ059302				
6	Jalmenus_evagoras	Lycaenidae	R	M	0.366	0.071	DQ456502				
7	Colias_eurytheme	Pieridae	R	P	1.013	0.205	AF044024				
8	Pieris_napi	Pieridae	R	P	1.169	0.255	AF170861				
9	Papilio_glaucus	Papilionidae	R	P	0.232	0.044	EF126474				
10	Papilio_machaon	Papilionidae	R	M	0.251	0.155	AY457593				
11	Zeiraphera_canadiensis	Tortricidae	H	M	0.016	0.067	DQ241506				
12	Choristoneura_fumiferana	Tortricidae	H	M	0.137	0.048	L19098				
13	Choristoneura_rosaceana	Tortricidae	H	P	1.028	0.037	L19099				
14											

Fig. 1. The *OpenMEE* graphical user interface (GUI) and spreadsheet. Columns are associated with data types: categorical (*cat*), counts (*count*) or continuous (*cont*). One column must be designated as containing the study labels, which must be unique per row. Collections of columns may be associated with outcomes (effects) and variances, in which case *OpenMEE* will automatically calculate and update the effect point estimate and variance when possible: the *d* and *var_d* columns here provide an illustrative example. The bottom of the GUI also includes helpful comments to facilitate data entry and workflow (not shown here).

Table 1. A summary of statistical functionalities provided by *OpenMEE*

Data pre-processing

- *Import and output* arbitrarily text delimited data (e.g. as exported from *R* and *Microsoft Excel*).
- *Automatic calculation of many standard effect sizes* for both continuous and dichotomous data from study-level parameters/data. These include:
 - (i) *Continuous outcome effect sizes*: raw mean differences, Hedges' *d*, log response ratios, bias-corrected log response ratios (Lajeunesse 2015).
 - (ii) *Dichotomous outcome effect sizes*: log odds ratio, rate difference, log relative risk, arcsine transformed risk, raw and log-, logit- or Arcsin-transformed proportions.
 - (iii) *Correlation coefficient* transformation to Fisher's-*Z* and back transformation.
 - (iv) *User-defined effect sizes* are allowed if users provide variances.
- *Simple missing data imputation methods* based on resampling approaches for filling gaps in the standard deviations used to estimate effect sizes (described in detail in Lajeunesse 2013a).
- *Sensitivity analyses* through quick elimination or inclusion of studies or study categories

Meta-analysis methods

- *Fixed-effects modelling* (simple inverse variance weighting).
- *Random-effects modelling* via any of the following τ^2 estimators: Maximum Likelihood, Hedges-Olkin, DerSimonian-Laird, Sidik-Jonkman, Restricted Maximum Likelihood, or Empirical Bayes.
- *Parametric estimation or non-parametric bootstrapping* for the variances and confidence intervals of pooled effect sizes.
- *Non-parametric randomization tests for heterogeneity statistics* (*Q*-test) in which observed effect sizes are resampled to assess the validity of main effect tests.
- *Phylogenetic meta-analysis* that account for shared evolutionary history among species (Lajeunesse 2009).
- *Automatic cumulative* (Lau *et al.* 1992), *leave-one-out* and *sub-group* meta-analyses.

Exploratory analyses and visualizations

- *Histograms and scatterplots* of effect sizes or column data, including weighted histograms (Oswald & Ercan 2013).
- *Contingency tables* of categorical variables.
- Standard tools for exploring publication bias, including 'fail-safe *N*' (Rosenthal 1979) and funnel plots (Egger *et al.* 1997).

Meta-regression methods

- *Basic univariate (fixed- or random-effects) meta-regression* for continuous and categorical covariates.
- *Multiple regression* including several predictors of mixed type (continuous and categorical) and their interaction effects.
- *Non-parametric bootstrap* (Efron 1979) estimation of coefficient variances.
- *Model building* tool to help assess which covariates (or combination of covariates) improve the predictions of effect.
- *Regression plots* for univariate models with a continuous covariate: see Fig. 3.

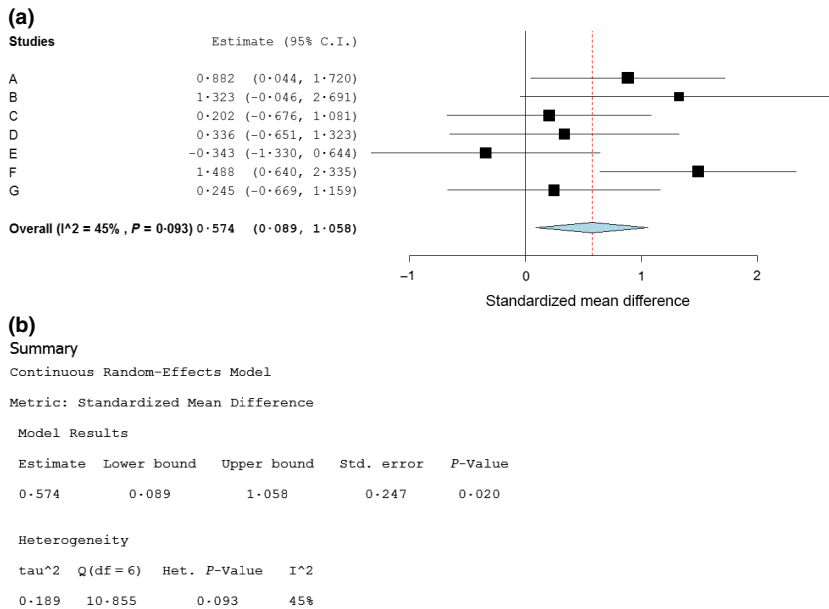


Fig. 2. Example output from *OpenMEE* for a simple random-effects meta-analysis on effect size data. Panel (a) displays a forest plot of the effect sizes (standardized mean difference) for each study and their 95% confidence intervals (CI). Symbol size indicates the inverse of the within-study sampling variance and thus the study weight (smaller symbols indicate higher variances and smaller weights), and the grand mean (pooled across studies) is indicated by the blue diamond at the bottom of the forest plot. Panel (b) shows the regression output of this estimated grand mean and its associated heterogeneity test (Q -test).

too few data for analyses. Publication bias can be assessed using funnel plots (Light & Pillemer 1984), forest plots (Fig. 2), Egger's regression-based test (Egger *et al.* 1997), and the 'fail-safe N ' method (Rosenthal 1979). However, we caution against mis- or over-interpretation of such diagnostics; see Becker (2005), Lau *et al.* (2006) and Sterne *et al.* (2011) for critical discussion on this issue.

META-ANALYSIS TOOLS INCLUDING META-REGRESSION

OpenMEE features full modelling capabilities to estimate summary effect sizes, conventional heterogeneity tests (Q -tests), as well as fixed- and random-effects models that rely on inverse-variance weighting to account for variation in precision (sampling error) within and between studies (Hedges & Olkin 1985). *OpenMEE* can also simultaneously estimate the effects of multiple explanatory variables (either continuous or categorical), and assess statistical interactions with the aid of a detailed 'model building tool'. This ability to select combinations of predictors and build more complete regression models resolves well-known problems associated with performing multiple and separate single-covariate analyses (as in *MetaWin*), affording more accurate evaluation of relationships between covariates (i.e. moderators) and effect sizes. Model building can also be leveraged for phylogenetic meta-analysis; which is a more powerful and flexible approach than compared to what was previously available in other phylogenetic software like *phyloMeta* (Lajeunesse 2011; Chamberlain *et al.* 2012). Further, a greater diversity of phenotypic evolution models can be explored (e.g. Ornstein-Uhlenbeck) and most phylogenetic tree file formats can be imported (e.g. Newick, CAIC). Finally, *OpenMEE* facilitates cumulative meta-analysis (Lau *et al.* 1992), in which effect sizes (and their variances) reported as studies are added in a particular order to a meta-analysis (e.g. by date of publication; Leimu & Koricheva 2004), and can also perform 'leave-one-out'

meta-analyses, which describe how overall estimates vary as a function of excluding individual studies from the analysis (see Table 1).

OpenMEE leverages most of these statistics 'under the hood' via *R* (see software architecture detailed in Appendix S1). Specifically, it primarily uses the stable and well-documented meta-analysis *R* package *metafor* (Viechtbauer 2010) and phylogenetic package *ape* (Paradis, Claude & Strimmer 2004). An advantage of using these packages is that their documentation, vignettes and testing also automatically provide support and robustness for *OpenMEE* (also see Appendix S1).

Output

OpenMEE substantially reformats the output of regression models to provide more readily interpretable results (these include 'conditional means' estimates of individual covariates; Table 1; Gurevitch & Nakagawa 2015). More conventional outputs include a point-estimate of the summary (pooled) grand-mean effect size, its confidence interval (CI), and a corresponding P -value testing whether this effect is non-zero (by default based on a Z -test). Also provided are estimates for the between-study random-effects variance (τ^2), the percentage of the variability that is due to heterogeneity rather than sampling variance (I^2), and conventional heterogeneity statistics (Q -statistics; Fig. 2) with between-group tests (Q_M but described in *MetaWin* as Q_b). Some of these are described in the *Worked Example* section below. Variance estimates and CI of pooled effects are obtained from the parametric model. However, nonparametric 'empirical' CI can also be calculated via bootstrapping (Efron 1979). When bootstrapped CIs are selected, a histogram of grand-mean effect sizes from the resampled data are generated to help visualize the data and to identify possible outliers. In addition, *OpenMEE* has extensive options for randomization (permutation) testing and confidence interval estimation

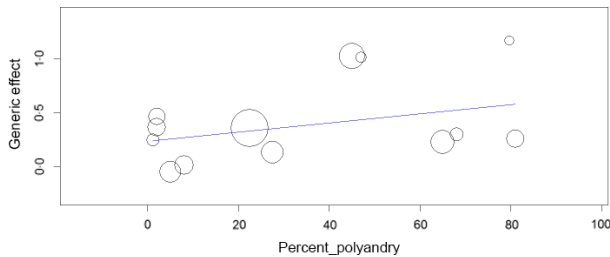


Fig. 3. A simple univariate meta-regression plot generated with *OpenMEE* (using a random-effects model based on a maximum likelihood estimator of the between-study variance). Each symbol is the effect size (generic effect size, here Hedges' d ; Y-axis) of the difference in reproductive outcomes for females mated to previously-mated males in comparison with virgin males, and the size of the symbol represents the inverse variance weight of the effect size. This type of figure is also known as a bubble plot (with size indicating relative weight of the effect). The relationship between the magnitude of the effect and the percent polyandry within a species is shown. The regression coefficients and summary output of this meta-regression are found as the Fig. S1.

(Table 1) that were available only in *MetaWin* and not in other standard software packages for meta-analysis (Adams, Gurevitch & Rosenberg 1997).

Meta-regression output is presented in terms of the relationship between each of the other categories (groups of studies) and the baseline group (as typically organized in *R* outputs of regression models), and *OpenMEE* will request a reference value from one of the categories as a baseline (to ensure model identifiability). The regression equation and parameters are also provided, and for more advanced users, variance-covariance matrix and other regression nuts-and-bolts outputs are reported. As *metafor* only outputs estimates of regression parameters and does not include an effects table (or ANOVA-like table summarizing all main-effect estimates and tests; see Hedges & Olkin 1985), we have added this output where possible.

Users have a choice for regression output in the form of tabular and graphical format; tables and graphs can be saved or copied-and-pasted into other programs. Figure 2 depicts a forest plot generated in *OpenMEE* showing the mean effect sizes and their confidence intervals for each study as well as the grand mean across studies, using a random-effects meta-regression; Fig. 3 depicts a meta-regression with a continuous predictor. These figures can be saved as vector graphics (e.g. PDF format) and are publication-ready, or may be exported into vector graphics editing software if additional changes are desired. Finally, *OpenMEE* provides basic editing options to change default forest plot settings, as well as weighted histograms which are unique to the meta-analysis framework (Oswald & Ercan 2013).

A worked example

We showcase some of *OpenMEE*'s capabilities by re-working a meta-analysis that addressed whether female moths and butterflies had greater fecundity when mated with virgin males (Torres-Vila & Jennions 2005). The outcome of each study was

quantified as the standardized mean difference (Hedges' d) between the fecundity of females mated with either virgins or males with a prior mating history. These data were originally analysed in *MetaWin* 2.0, but have since been re-analysed several times (see examples in Koricheva, Gurevitch & Mengersen 2013), including with a phylogenetic meta-analysis (Lajeunesse 2009). We begin with a two-way ANOVA-like meta-analysis testing for an interaction effect among mating system and taxonomy, and then end with a model comparison between a conventional and phylogenetic meta-analysis. Our analyses use a subset of the original data and therefore all inferences serve only to illustrate *OpenMEE*'s capabilities (Table S1, Appendix S1). Further, to ease model comparisons, all analyses model random-effects with τ^2 estimated via maximum likelihood.

Torres-Vila & Jennions (2005) were interested in comparing mating types (monandrous and polyandrous) while controlling for effects due to the two major taxonomic divisions in the data: moths (Heterocera) and butterflies/skippers (Rhopalocera). *MetaWin* could not perform this test with its limited single-predictor analyses, and therefore conventional statistical software was used to perform a weighted (inverse variance) two-way ANOVA (following recommendations by Cooper & Hedges 1994). However, this analysis was a significant compromise because the conventional software could not estimate the τ^2 crucial for random-effects modelling, and therefore inferences were limited to a fixed-effect model. Fixed-effect models (or more accurately an equal-effects model; Laird & Mosteller 1990) are rarely used now in ecology because one generally expects that there is true variation in effects among studies in addition to random sampling variation (Lajeunesse 2013b).

Under the 'meta-regression' tools of *OpenMEE*, we can perform the more appropriate random-effects meta-analysis with a two-way ANOVA-like design by building a regression model that includes two categorical predictors (mating type and taxonomic division) and their interaction term. Under this model, *OpenMEE* will generate both an effect test table and a regression coefficient table (see Figs S2 and S3). Beginning with the effects table, the meta-regression found no significant interaction between mating type and taxonomic division (mating type: $Q = 5.83$, d.f. = 1, $P = 0.0158$; taxonomic division: $Q = 0.004$, d.f. = 1, $P = 0.9488$; mating type \times taxonomic division: $Q = 0.525$, d.f. = 1, $P = 0.4689$). Excluding the non-significant interaction term from this model, and controlling for the non-significant effects of taxonomic division ($Q = 0.022$, d.f. = 1, $P = 0.8822$), there was a significant effect of mating type ($Q = 5.385$, d.f. = 1, $P = 0.0203$). This reduced model explained 54.7% of the heterogeneity among effect sizes ($I^2 = 54.7\%$), and based on the regression coefficients, the mean difference in effect size between monandrous and polyandrous groups controlling for taxonomic division was non-zero (slope = 0.38, lower-95% CI = 0.051, upper-95% CI = 0.708; Z -test = 2.265, $P = 0.023$, $k = 13$).

An alternative way to control for effects due to the shared evolutionary history of taxa (broadly reviewed in Lajeunesse & Fox 2015; Lajeunesse, Rosenberg & Jennions 2013) is to

perform analyses, using the ‘phylogenetic meta-analysis’ tool in *OpenMEE*. To achieve this, we will use a phylogenetic tree (see Fig. S6) to model dependencies among effect sizes that can arise due to the shared evolutionary history of moths and butterflies. Here, the phylogenetic correlations derived from this tree are treated as unstructured random effects, and *OpenMEE* will use these correlations to estimate a phylogenetic random-effects component (or phylogenetic variance, τ_λ^2) along with the traditional between-study variance component (τ^2). Let’s begin with a conventional random-effects meta-analysis to estimate the grand mean effect size ($\bar{\delta}$) across all moths and butterflies. Under the ‘meta-analysis’ tool in *OpenMEE*, which performs analyses without predictors, we get the following grand mean effect size ($\bar{\delta} = 0.375$, lower-95% CI = 0.1869, upper-95% CI = 0.5629; $k = 13$; $\tau^2 = 0.049$; Fig. S4). Now under the ‘phylogenetic meta-analysis’ tool, we repeat this analysis with the phylogeny while assuming a Brownian motion model of evolution (lambda fitted with $\lambda = 1.0$). Under this model, the grand-mean effect size remained the same ($\bar{\delta}^\lambda = 0.375$, lower-95% CI = 0.187, upper-95% CI = 0.563; $k = 13$; Fig. S5). There was no added benefit of including phylogenetic correlations, as there was no phylogenetic heterogeneity modelled among effect sizes ($\tau_{\lambda=1}^2 = 0.0$); however, the large amount of between-study variance remained ($\tau^2 = 0.049$). Finally, *OpenMEE* also outputs the log likelihood scores (\bar{L}) for both the conventional ($\bar{\delta} = -0.049$) and phylogenetic meta-analysis models ($\bar{\delta} = -4.992$). These can be used to calculate the overall variance explained by the phylogeny when included in the random-effects meta-analysis. Here, we will use McFadden’s pseudo- R^2 (Veall & Zimmermann 1996) to estimate this variance explained by phylogenetic history: pseudo- $R^2 = 1 - (-4.992/-4.992) = 0$. Under a full Brownian motion model of evolution ($\lambda = 1.0$), 0% of the heterogeneity was explained by the phylogenetic history of moths and butterflies.

Conclusions

Going forward, we encourage developers to contribute to the project, and we hope that *OpenMEE* will become a platform for quickly disseminating and teaching new methods for meta-analysis, as well as an important tool for improving the quality and scope of research syntheses in E&E. We also frequently update *OpenMEE*, and encourage users to provide feedback on the software, as well as suggest new statistics and functionalities to be integrated into future builds. The statistics of meta-analysis is an ever-growing discipline, and we hope that by facilitating access to these emerging tools, we can help propel hypothesis testing and improve inferences with these rigorous research synthesis practices.

Author’s contributions

B.C.W., M.J.L. and J.G. conceived the project; B.C.W., G.D. and M.J.L. coded the software; M.J.L., J.G. and B.C.W. lead the writing of the manuscript; I.J.D., T.A.K. and C.H.S. provided statistical consultation. All authors contributed to drafts, tested and verified the software, and gave final approval for publication.

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Data accessibility

The website for *OpenMEE* is at <http://www.cebm.brown.edu/openmee/>. Builds for Mac OS X and Windows operating systems are freely available and updated at <http://www.cebm.brown.edu/openmee/download>. Documentation is available at <http://www.cebm.brown.edu/openmee/help> and a discussion forum (hosted as a Google group) at <http://www.cebm.brown.edu/openmee/forum>. The source code is publicly available and distributed under the GNU General Public License at <https://github.com/gdietz/OpenMEE>, and details on unit testing are found at <https://github.com/gdietz/OpenMEE/wiki/Unit-Testing>. The DOI of the software is: <https://doi.org/10.5281/zenodo.166415>. The statistical background for *OpenMEE* is largely documented by Koricheva, Gurevitch & Mengersen (2013).

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Supporting Information

Details of electronic Supporting Information are provided below.

Appendix S1. *OpenMEE* software architecture, builds, unit testing, and full data/results of worked meta-analysis example.

Supplemental Material

OpenMEE: Intuitive, open-source software for meta-analysis in ecology and evolutionary biology

Software architecture, builds, and unit testing

OpenMEE is cross-platform and open-source, and the source code may be run on *Windows*, *Mac OS X* and *Linux* operating systems, but for convenience we release ready-to-use “builds” for *Windows* (7 and 8) and *Mac OS X* (10.10/10.11) users (see: <http://www.cebm.brown.edu/openmee/download>). Other users may consult our instructions for compiling and running the program from source (see: <https://github.com/gdietz/OpenMEE/blob/master/README.md>; and for the source DOI: <https://doi.org/10.5281/zenodo.166415>). *OpenMEE* was designed to enable the inclusion of existing and new meta-analytic methods; its underlying architecture relies on the *R* programming language (R Core Team 2014) and environment as a statistical back-end, while the GUI is rendered in *Python* (<http://www.python.org>). *OpenMEE* has the same underlying structure as the package *Open Meta-analyst* (http://www.cebm.brown.edu/open_meta), and we have adopted its development strategy which was described at length previously (Wallace *et al.* 2012).

The *Python* GUI is responsible for gathering required parameters from the user and passing these, along with the data to be analyzed, to the relevant routines in *R*, which then returns the results to *Python* for rendering. The program can thus be adapted to fit any functionality available in *R*, with minimal programming knowledge or effort required on the part of users. Adding new methods written in *R* requires implementing in *Python*: (1) a suitable graphical interface that gathers parameters selected by the user and passes these off for analysis in *R*, and, (2) code to gather and display the outputs (graphics and tables) of the *R* routine. These two steps require much less effort compared to porting entire statistical methods from *R* to *Python* (which would further require that the ‘ported’ version be

kept up to date with the *R* implementation, and which is not required in *OpenMEE*; see Wallace *et al.* 2012). In addition, although *OpenMEE* is dependent on *R* and many *R* packages, as well as specific versions of these tools, it is important to emphasize that *OpenMEE* builds are distributed with built-in versions of *R* and *R* packages. In other words, users do not need to install *R* or have *R* installed prior to using *OpenMEE* and everything needed by *OpenMEE* is prepackaged with the software. This avoids the common trappings of having to continuously update *R* libraries since *OpenMEE* users are fully detached from this process. *R* package dependencies of *OpenMEE* include *metafor* (Viechtbauer 2010) and *ape* (Paradis *et al.* 2004).

When new versions of libraries are available, we perform unit testing of both the relevant *Python* and *R* components of *OpenMEE* prior to their inclusion in builds, thus ensuring that only functioning and stable versions of these tools are shipped with our software. We currently have unit tests in place for all analyses performed by *OpenMEE*, and are actively adding additional tests. We emphasize that these are meant to ensure that our *R* routines—which wrap the functionality of external packages—are functioning and returning results in the expected format. However, we do not aim to fully test established, externally maintained packages on which *OpenMEE* relies; for example, *metafor* maintains its own suite of unit testing that we do not aim to reproduce. For details on running the unit tests for *OpenMEE*, see: <https://github.com/gdietz/OpenMEE/wiki/Unit-Testing>.

Because all analyses are carried out in *R*, *OpenMEE* makes the *R* session record (i.e., log of commands) optionally available to the user. This means they can see exactly the code that produced the output, as well as interact with the command line interface of the *R* session running in the back-end of *OpenMEE*. We call this functionality: “through the looking glass”. This may serve as a teaching tool, and may also facilitate the reproducibility of analyses, as the command logs provide explicit record of the analyses performed and the *R* functions used.

Finally, to facilitate interaction among users and developers, we rely on *GitHub* to track modifications of our source code (<https://github.com/gdietz/OpenMEE>). We note that *GitHub* facilitates community contributions by allowing us to maintain a ‘master’ repository in which we can accept codebase changes and additions at our discretion. It also allows contributors to create their own copies of the repository, which may then evolve independently. We maintain a Wiki and track issues via *GitHub*, as well.

Data and Detailed Output of Worked Example of Meta-analysis with *OpenMEE*

Suppl. Table 1. Data used the worked example of Torres-Vila & Jennions (2005) meta-analysis. The d is the effect size Hedges’ d and var_d is it’s variance used for weighted analyses.

ID	species	COII accession number	Percent polyandry	Taxonomy division	Mating type	d	var_d
1	<i>Chilo_partellus</i>	AY320482	5	Heterocera	monandrous	-0.041	0.052
2	<i>Ostrinia_nubilalis</i>	AF321880	22.5	Heterocera	monandrous	0.359	0.017
3	<i>Trichoplusia_ni</i>	AB158623	81	Heterocera	polyandrous	0.263	0.075
4	<i>Busseola_fusca</i>	AY320474	2	Heterocera	polyandrous	0.469	0.082
5	<i>Helicoverpa_armigera</i>	DQ059302	68	Heterocera	polyandrous	0.304	0.128
6	<i>Jalmenus_evagoras</i>	DQ456502	2	Rhopalocera	monandrous	0.366	0.071
7	<i>Colias_eurytheme</i>	AF044024	47	Rhopalocera	polyandrous	1.013	0.205
8	<i>Pieris_napi</i>	AF170861	79.7	Rhopalocera	polyandrous	1.169	0.255
9	<i>Papilio_glaucus</i>	EF126474	65	Rhopalocera	polyandrous	0.232	0.044
10	<i>Papilio_machaon</i>	AY457593	1.16	Rhopalocera	monandrous	0.251	0.155
11	<i>Zeiraphera_canadiensis</i>	DQ241506	8	Heterocera	monandrous	0.016	0.067
12	<i>Choristoneura_fumiferana</i>	L19098	27.5	Heterocera	monandrous	0.137	0.048
13	<i>Choristoneura_rosaceana</i>	L19099	45	Heterocera	polyandrous	1.028	0.037

Suppl. Figure 1. Results of a simple meta-regression of d (generic effect size) versus percent polyandry from Torres-Vila & Jennions (2005) data presented in Suppl. Table 1.

OpenMEE build date: 2015-11-15

Summary

Model Summary:

```
-----
SOURCE      Q DF      P
model      1.6  1 0.205
residual error 12.0 11 0.360
total     13.7 12 0.323
```

Effect Tests Summary:

```
-----
SOURCE      Q DF      P
percent_polyandry 1.6  1 0.205
```

Mixed-Effects Model (k = 13; tau² estimator: ML)

```
tau^2 (estimated amount of residual heterogeneity):    0.040 (SE = 0.040)
tau (square root of estimated tau^2 value):           0.199
I^2 (residual heterogeneity / unaccounted variability): 39.56%
H^2 (unaccounted variability / sampling variability):  1.65
R^2 (amount of heterogeneity accounted for):          18.33%
```

Test for Residual Heterogeneity:
QE(df = 11) = 20.779, p-val = 0.036

Test of Moderators (coefficient(s) 2):
QM(df = 1) = 1.605, p-val = 0.205

Model Results:

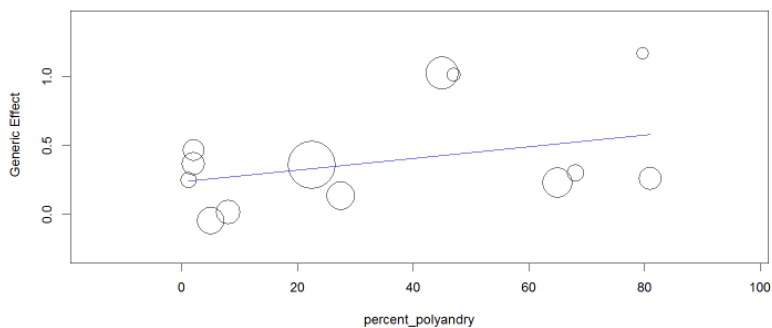
```

              estimate      se    zval    pval    ci.lb    ci.ub
intrcpt          0.237    0.142    1.670    0.095   -0.041    0.515
percent_polyandry  0.004    0.003    1.267    0.205   -0.002    0.011
.
```

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

Regression model formula: yi ~ percent_polyandry
Regression model equation: 0.237 + 0.004*percent_polyandry

Regression Plot



k: number of outcomes included in the model fitting.

Suppl. Figure 2. Results of two-way ANOVA-style random-effects meta-regression with interaction term of Torres-Vila & Jennions (2005) data presented in Suppl. Table 1.

OpenMEE build date: 2015-11-15

Summary

Model Summary:

```
-----
SOURCE      Q DF      P
model      6.35  3 0.0956
residual error 11.68  9 0.2317
total     18.04 12 0.1146
```

Effect Tests Summary:

```
-----
SOURCE      Q DF      P
mating_type 5.82505  1 0.0158
taxonomy_division 0.00413  1 0.9488
mating_type:taxonomy_division 0.52466  1 0.4689
```

Mixed-Effects Model (k = 13; tau² estimator: ML)

```
tau^2 (estimated amount of residual heterogeneity):    0.015 (SE = 0.027)
tau (square root of estimated tau^2 value):           0.124
I^2 (residual heterogeneity / unaccounted variability): 19.25%
H^2 (unaccounted variability / sampling variability):  1.24
R^2 (amount of heterogeneity accounted for):           68.18%
```

Test for Residual Heterogeneity:
QE(df = 9) = 15.082, p-val = 0.089

Test of Moderators (coefficient(s) 2,3,4):
QM(df = 3) = 6.354, p-val = 0.096

Model Results:

	estimate	se	zval
intrcpt	0.174	0.117	1.494
mating_typepolyandrous	0.447	0.186	2.402
taxonomy_divisionRhopalocera	0.153	0.266	0.575
mating_typepolyandrous:taxonomy_divisionRhopalocera	-0.263	0.363	-0.724
	pval	ci.lb	ci.ub
intrcpt	0.135	-0.054	0.403
mating_typepolyandrous	0.016	0.082	0.813 *
taxonomy_divisionRhopalocera	0.565	-0.369	0.675
mating_typepolyandrous:taxonomy_divisionRhopalocera	0.469	-0.975	0.449

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

Regression model formula: yi ~ mating_type + taxonomy_division + mating_type:taxonomy_division
Regression model equation: 0.174 + 0.447*mating_typepolyandrous + 0.153*taxonomy_divisionRhopalocera

k: number of outcomes included in the model fitting.

Suppl. Figure 3. Results of two-way ANOVA-style random-effects meta-regression excluding the non-significant interaction term of Torres-Vila & Jennions (2005) data presented in Suppl. Table 1.

OpenMEE build date: 2015-11-15

Summary

Model Summary:

SOURCE	Q	DF	P
model	5.41	2	0.067
residual error	11.14	10	0.347
total	16.54	12	0.168

Effect Tests Summary:

SOURCE	Q	DF	P
mating_type	5.3854	1	0.0203
taxonomy_division	0.0219	1	0.8822

Mixed-Effects Model (k = 13; tau² estimator: ML)

tau² (estimated amount of residual heterogeneity): 0.022 (SE = 0.031)
tau (square root of estimated tau² value): 0.148
I² (residual heterogeneity / unaccounted variability): 25.53%
H² (unaccounted variability / sampling variability): 1.34
R² (amount of heterogeneity accounted for): 54.67%

Test for Residual Heterogeneity:
QE(df = 10) = 15.973, p-val = 0.100

Test of Moderators (coefficient(s) 2,3):
QM(df = 2) = 5.407, p-val = 0.067

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub	
intrcpt	0.193	0.117	1.648	0.099	-0.037	0.424	.
mating_typepolyandrous	0.380	0.168	2.265	0.023	0.051	0.708	*
taxonomy_divisionRhopalocera	0.028	0.188	0.148	0.882	-0.341	0.397	

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

Regression model formula: yi ~ mating_type + taxonomy_division
Regression model equation: 0.193 + 0.38*mating_typepolyandrous + 0.028*taxonomy_divisionRhopalocera

k: number of outcomes included in the model fitting.

Suppl. Figure 4. Results of conventional random-effects meta-analysis of the grand-mean effect of Torres-Vila & Jennions (2005) data presented in Suppl. Table 1.

OpenMEE build date: 2015-11-15

weights

```
study names  weights
1 : 9.154%
2 : 14.045%
3 : 7.450%
4 : 7.050%
5 : 5.213%
6 : 7.699%
7 : 3.630%
8 : 3.032%
9 : 9.946%
10: 4.521%
11: 7.966%
12: 9.534%
13: 10.760%
```

Summary

Continuous Random-Effects Model

Metric: Generic Effect

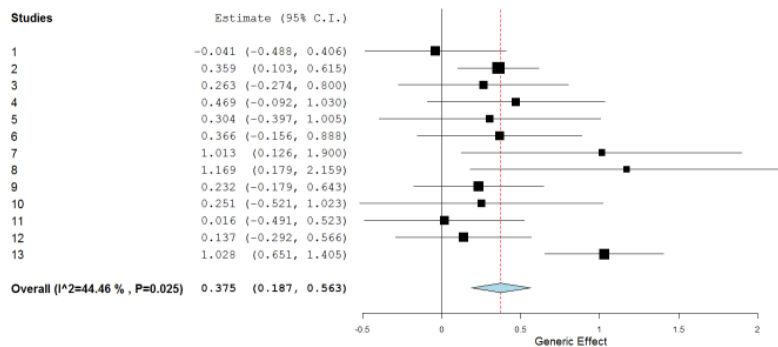
Model Results

Estimate	Lower bound	Upper bound	Std. error	p-Value
0.375	0.187	0.563	0.096	< 0.001

Heterogeneity

tau^2	Q(df=12)	Het. p-Value	I^2
0.049	23.308	0.025	44.456

Forest Plot



References

1. metafor: Viechtbauer, Wolfgang. "Conducting meta-analyses in R with the
2. OpenMetaAnalyst: Wallace, Byron C., Issa J. Dahabreh, Thomas A. Trikalini
3. this is a placeholder for continuous random reference

k: number of outcomes included in the model fitting.

Suppl. Figure 5. Results of phylogenetic random-effects meta-analysis of the grand-mean effect of Torres-Vila & Jennions (2005) data presented in Suppl. Table 1.

OpenMEE build date: 2015-11-15

Summary

Multivariate Meta-Analysis Model (k = 13; method: ML)

Variance Components:

	estim	sqrt	nlvls	fixed	factor	R
sigma^2.1	0.0485	0.2203	13	no	betweenStudyVariance	no
sigma^2.2	0.0000	0.0000	13	no	phylogenyVariance	yes

Test for Heterogeneity:

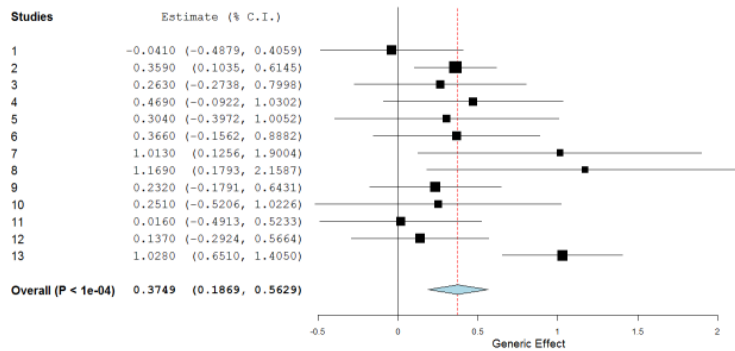
Q(df = 12) = 23.3077, p-val = 0.0252

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub	***
0.3749	0.0959	3.9086	<.0001	0.1869	0.5629	***

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

Forest Plot

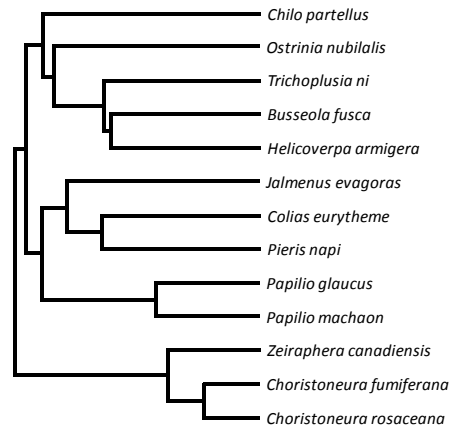


k: number of studies included in the model.

13

Suppl. Figure 6. The tree used in the phylogenetic meta-analysis on differences in lifetime fecundity between female moth and butterflies mated with virgin and non-virgin males (Torres-Vila & Jennions 2005). Details on how this tree was constructed was described in Lajeunesse (2009). The Newick version of this tree is:

```
((Chilo_partellus:0.145039,(Ostrinia_nubilalis:0.137127,(Trichoplusia_ni:0.104551,(Busseola_fusca:0.098911,Helicoverpa_armigera:0.098911):0.00564):0.032576):0.007912):0.010818,((Jalmenus_evagoras:0.128362,(Colias_eurytheme:0.105397,Pieris_napi:0.105397):0.022966):0.017653,(Papilio_glaucus:0.069342,Papilio_machaon:0.069342):0.076673):0.009841):0.007589,(Zeiraphera_canadiensis:0.061651,(Choristoneura_fumiferana:0.036413,Choristoneura_rosaceana:0.036413):0.025238):0.101795);
```



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