REVEIW ARTICLE

Evidence-based nutrition — using a meta-analysis to review the literature

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A meta-analysis is the structured result of a literature review in which results from several independent but related or comparable studies are systematically and statistically combined or integrated in order to increase power and precision. In this paper the advantages and limitations of a meta-analysis and the different steps (process) to conduct one are briefly outlined. These steps include formulation of the objectives of the meta-analysis (the research questions); selection of appropriate studies (literature search); defining and applying inclusion and exclusion criteria for studies; coding (stratifying, scoring) of studies combined with a qualitative assessment; and quantitative assessment and statistical analysis. In the analysis the heterogeneity of studies is tested, study results are pooled, combined level of effect calculated, and interactive effects and effects of confounders and moderators determined. This is followed by interpretation of the combined results, drawing of conclusions and writing of the review.

The meta-analysis method can be used by nutrition researchers and practitioners to structurally evaluate and integrate large amounts of often conflicting information. When possible limitations and problems are recognised and handled, a meta-analysis can be used to minimise bias in results, to formulate new hypotheses, to motivate and direct further research and to form a firm, evidence-based platform for nutrition policy.

One of the purposes of this series on evidence-based nutrition[1,2] is to elucidate how students and researchers in nutrition, practitioners, health care providers and policy makers can apply basic principles and standardised methods to synthesise and make sense of large, often unmanageable amounts of information. This is necessary in order to draw conclusions from empirical studies and make decisions which will be evidence-based and not unduly influenced by bias and chance effects. The purpose of this paper in the series is to show how a meta-analysis can be used to do this by statistically combining results from independent but related studies into a composite measure of effect.

A meta-analysis is a statistical technique used to combine the results of studies addressing the same question into a one-number summary.[3,4] The meta-analysis method can be applied in the social-behavioural and biomedical sciences[5] and is therefore particularly suitable for nutrition data. The term meta-analysis should not be confused with a systematic review. Egger and Smith[4] suggest that the term *meta-analysis* should be used 'to describe the statistical integration of separate studies whereas *systematic review* is most appropriate for denoting any review of a body of data that uses clearly defined methods and criteria'. According to this definition a meta-analysis can, if appropriate, be part of a systematic review. It is always appropriate and desirable to systematically review a body of data, but it may at times be inappropriate to pool results from separate studies.[4] Because a systematic review is a structured, systematic qualitative and quantitative integration of comparable results of several independent studies, it can provide a firm basis for planning and policy recommendations.[6] A meta-analysis has been described as 'a quantitative approach to research reviews',[7] 'aggregating data',[8] 'the epidemiology of results'[5] and 'the application of statistical procedures to collections of empirical findings'.[3] A meta-analysis uses specific statistical methods to combine, summarise and integrate comparable results from different studies. The unit of observation is therefore the study. A major purpose of pooling results in a meta-analysis is to increase statistical power and precision of estimates in smaller studies.[3-9] There are excellent sources available[3-10] with detailed, step-by-step guidelines, recommendations and numerous examples of how to do a meta-analysis. In this paper the advantages and limitations of a meta-analysis and the process of conducting one will be outlined briefly to motivate nutritionists when and how to use it in their interpretation of the literature, in drawing conclusions from studies with conflicting results, and in policy formulation.

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Characteristics and advantages of a meta-analysis

'Traditional' reviews of the literature may have problems with selective (biased) inclusion of studies, differential subjective weighting of studies in the interpretation of a set of findings, misleading interpretations, failure to examine characteristics of included studies as potential explanations for either disparate or consistent results across studies, and failure to examine moderating variables in the relationship under examination.[5,11] The idea that pooling or combining data might be better than selecting data was an early attempt by astronomers in the 17th century to address selective bias.[11] Karl Pearson, probably the first medical researcher, in 1904 used formal techniques to combine data from different studies to evaluate the preventive effects of inoculations against enteric fever (reviewed by Egger and Smith[11]). The technique of the meta-analysis, in which statistical methods are used to combine comparable data, gradually developed and is now especially used and validated for randomised, controlled clinical trials in medicine. However, as can be seen in several examples from the social sciences[5,12] it has also found a wider application. A meta-analysis addresses the potential problems of traditional reviews because of the following characteristics and advantages, [4-13] which help to minimise bias in results:

- It examines variability between studies.
- It increases statistical power and precision by combining results from different studies, compensating for low-powered research and small effect sizes which are often too small to give statistically significant results.
- In observational studies it allows subgroup analysis and dissecting out of moderator or confounding effects, particularly when included studies were conducted with different levels of potential moderators.
- It accumulates, integrates and summarises results from different studies. In addition to providing evidence-based data for policy and practice, results from a meta-analysis can be used to formulate new hypotheses and to direct new research in the particular field.

Meta-analysis reviews can therefore be used to confirm information, to find errors in existing information, and to search for additional findings.

The process of conducting a meta-analysis

A meta-analysis tries to answer questions on how variables are related (exposures with other exposures, exposures with outcomes and outcomes with other outcomes), how strong the evidence for these relationships are, and, in observational studies, which factors (modulators, confounders) influence these relationships.[6-9] To ensure the best possible and valid synthesis from available information, a structured methodology in conducting the meta-analysis should be followed and documented. As mentioned, a number of sources,[5-14] including the *Cochrane Reviewers Handbook*,[9] have described this method for different domains in both the social[3,8,9] and biomedical[14,10,12] sciences. The different steps can be summarised as follows:

Step 1: Formulating or defining objectives (research questions)

There must be clear objectives regarding what the meta-analysis outcomes should be: is the focus on producing a single, pooled result, or on sub-group differences, or on explaining contradictory results? Are the research questions/hypotheses and/or the major variables of importance clear? Is the literature to be reviewed defined? Does the formulation of the objective(s) capture the important literature in the field? Are reasonable inclusion and exclusion criteria for studies defined and compatible with the objectives?

Step 2: Literature search and selection of studies

A computer literature search with appropriate search words is a starting point, but will not necessarily lead to an unbiased sample of studies, because many journals (especially local ones) are not indexed on the major databases. There may be studies not published because of inconclusive or negative results. To prevent publication bias and obtain a representative sample of studies, the meta-analysis researcher should use a combination of methods to search for literature. For example, research organisations (listing funded projects), universities and government departments as well as other researchers could be contacted. The *Cochrane Reviewers Handbook*[9] gives useful guidelines to locate studies. For inclusion in the meta-analysis, full publications and/or results of the studies should be obtainable. In the final report, the researcher should give an indication of the search methods and literature that could not be obtained, as well as possible selection bias. The researcher should state whether foreign language studies have been included. Studies published in non-English journals may be inconclusive or have negative results compared with those published in English language journals. Jüni *et al.*[15] recently examined the possibility that excluding clinical trials reported in languages other than English from meta-analyses may introduce bias and reduce precision of combined estimates of treatment effects. Although they showed that excluding these trials generally had little effect, they warn that the importance of non-English language trials is difficult to predict. They recommend comprehensive literature searches followed by a careful assessment of trial quality, independent of language of publication.

The studies to be used in the meta-analysis can then be selected by applying the inclusion and exclusion criteria. Yach[6] describes this step as a qualitative assessment of the literature, in which the reviewers may be blinded to the results. Articles may be excluded because of inappropriate design, methodology or types of subjects, exposures, outcomes or other variables in the particular study. An assessment of the study quality is necessary before inclusion, reducing bias in the review.

Step 3: Coding of studies

The objective of the meta-analysis should guide decisions on which variables to code. These variables should figure prominently in the subsequent statistical analysis. The type of variables will be different for randomised controlled trials and observational studies. Variables that are usually coded include study context (year, country, setting, source of publication, authors, etc.), methodological characteristics such as sampling procedures, type of study (long-term, acute, prospective, cross-sectional, retrospective, case-control, intervention and type of intervention, etc.), subject characteristics (gender, age, ethnicity, medical history, etc.), type of control groups, measuring methods, statistical methods and key outcomes (effect sizes). A category for unreported or uncertain information is essential in meta-analyses. Coding can be a time-consuming exercise, and coders should be trained (using a coding manual) and able to make informed judgements. To reduce errors each study is coded by at least two reviewers and the results compared with the help of a third reviewer if necessary. Reliable coding of effect size, the key variable of the meta-analysis, is important. The various reported statistical outcomes of different studies should be aggregated into a common, quantitative unit — the index effect. This quantitative unit will depend on the type of studies in the meta-analysis. For example, when combining prospective studies (randomised controlled trials), a relative risk should be calculated and used, but an odds ratio can also be used. When observational studies are included in the meta-analysis, such as case-control studies, the odds ratio will be the appropriate unit. For the meta-analysis, a common measure of effect should be chosen, re-calculated and coded for each study.

Step 4: Statistical analysis

This step can be described as a quantitative assessment in which a pooled effect size, statistical heterogeneity between studies and interactive effects between groups are calculated. A variety of techniques may be used, dictated by the type of results (data) being analysed. A conceptual understanding of the principles is more important for the reviewer than detailed knowledge of the techniques. Appropriate statistical methods for dichotomous data include the odds ratio, relative risk and risk difference, and for continuous data the most appropriate measures of effects are the weighted mean difference and standardised mean difference. A test for heterogeneity between studies is necessary and should influence the statistical approach for conceptual understanding. Most reviewers of nutrition- and health-related studies would need the assistance of a statistician to ensure that an appropriate statistical model is used that correctly specifies the obtained data.

Step 5: Displaying and interpretation of results and drawing conclusions

Again, there are various ways to display results from a meta-analysis. The Cochrane Review method[9] uses a special programme to generate tables and graphs. In addition to graphs displaying results from individual studies as well as the pooled result, a table describing the characteristics of the reviewed studies could be helpful to indicate missing information in some studies. In the interpretation of the pooled results, the issue of power should be addressed. The individual and pooled results can be used to show a general trend, to assess disparities and incongruities, to indicate outlying studies and to formulate new hypotheses. As in all scientific papers, the conclusions should be restricted to the study objectives, and in the case of the meta-analysis, to the literature reviewed.

In Fig. 1, the consecutive steps for conducting a meta-analysis are outlined (adapted from Jenicek[13]). Fig. 2 gives an example of a meta-analysis for four studies. This type of graphical display is called a forest plot. The results of each individual study along with their confidence intervals are shown. The midpoint of the box in the middle represents the effect size (the difference in the measure between dietary advice and control) and the horizontal line the confidence interval. The size of the boxes relates to the weight each study has in the analysis. The weights assigned are usually in inverse proportion to their variance, a method that gives more weight to larger studies. The summary statistic of the four studies is shown by the diamond, which represents the mean difference (between dietary advice and control) and confidence interval. The vertical line that crosses through in the centre of the plot is equal to zero and is the line of no effect such that a diamond placed on this line will indicate that there is no difference between the intervention and control groups. In Fig. 2 the diamond does not cross the vertical line and the summary result is statistically significant (shown in the figure by test for overall effect). A simple rule of thumb to determine whether there are differences between the studies (heterogeneity) is to see if it is possible to draw a vertical line that would pass through the confidence intervals of all the studies. This analysis does not show heterogeneity, also indicated by the statistical test for heterogeneity given in the figure.

Limitations of a meta-analysis

The limitations and possible problems of a meta-analysis have been well recognised.[16-20] Some of these problems may have

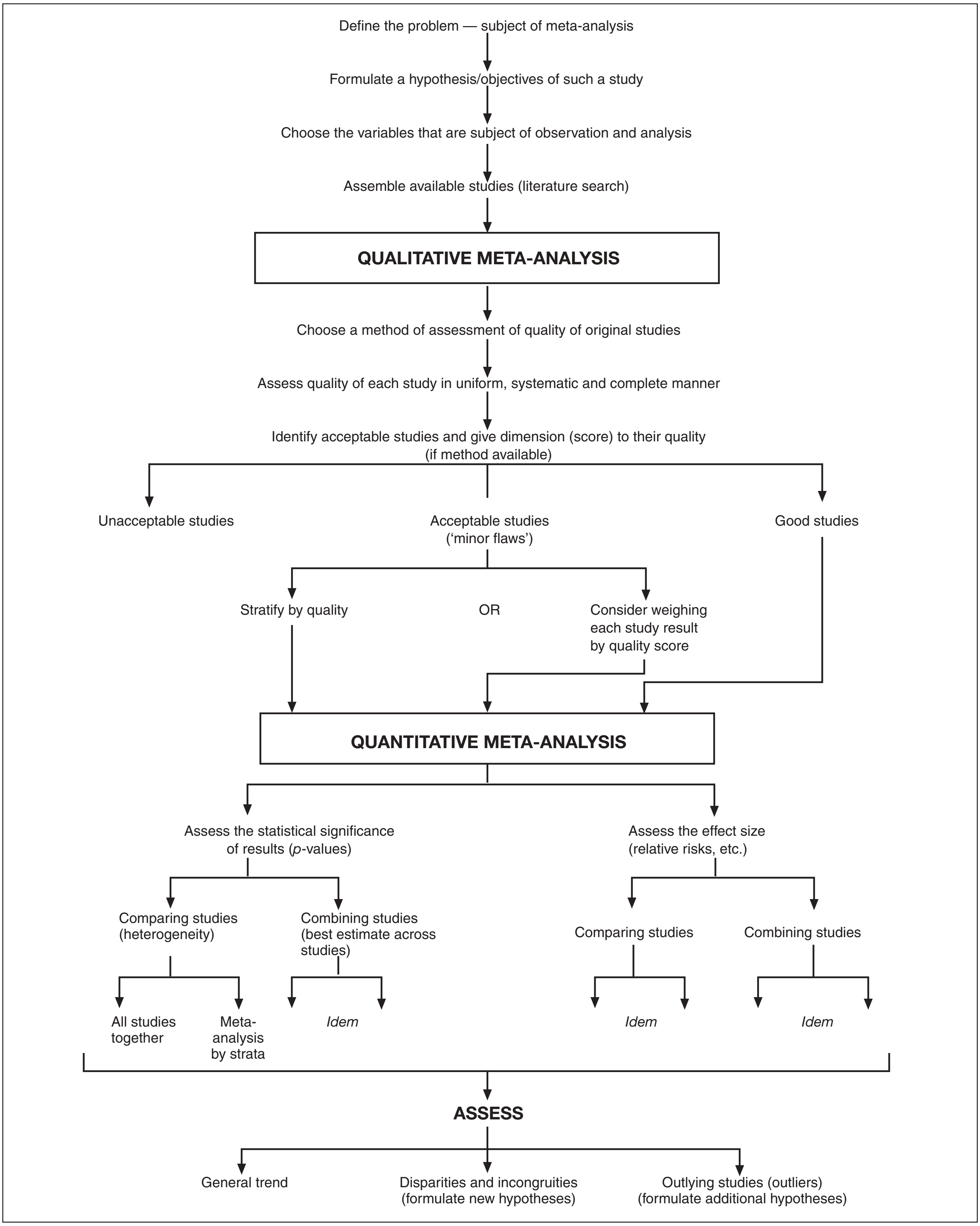

Fig. 1. Consecutive steps in a meta-analysis (adapted from Jenicek[13]).

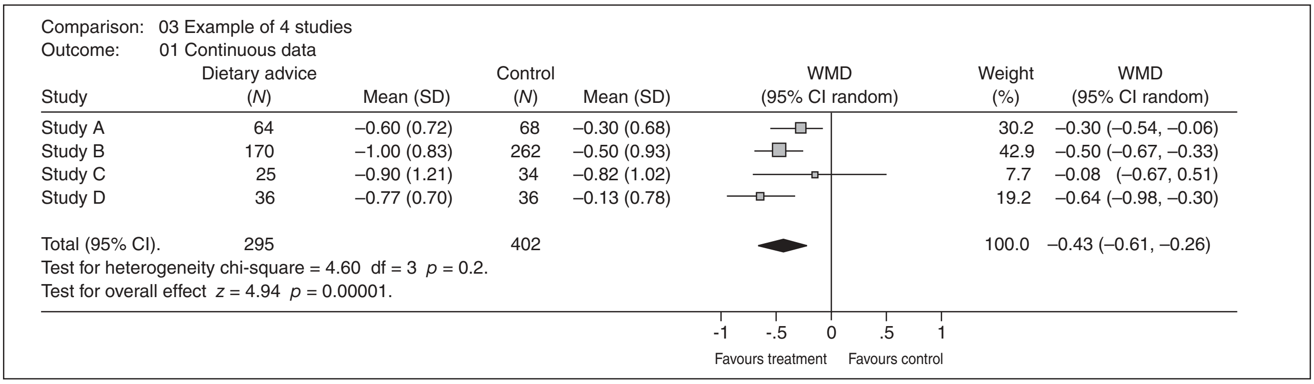

Fig. 2. Example of a meta-analysis.

their roots in poor quality of the original studies, while others may be related to statistical inference. Special care should therefore be taken in the selection of studies to include in the analysis, using well-defined strategies to overcome publication and reviewer (observer) bias. The reviewer should ensure that studies are sufficiently similar with regard to design, methods and outcomes measured to be comparable. There should be a clear distinction between randomised controlled trials and observational studies (are oranges compared to oranges or to apples?). This is a different concept to the assessment of statistical heterogeneity and should be considered even if statistical heterogeneity is not shown to be present. Issues such as size of studies (small and large studies), quality of studies, randomisation in selection of subjects, time spans, etc. should be defined and described in the systematic review. The reviewer may for example decide to exclude very small or non-randomised studies, or to weigh and rank studies according to quality in a sensitivity analysis.

Application of the meta-analysis in nutrition

From the above discussion it should be clear that a meta-analysis can be used to review the literature which reports on the relationships between any nutrition exposure (habitual diet, dietary patterns, specific nutrient intakes, nutritional interventions) and health outcomes (nutritional status, blood variables such as markers or risk factors for disease, morbidity, mortality). In addition to reviewing the literature for policy decisions, the meta-analysis method can also be used to train postgraduate students.[21] A meta-analysis could replace the traditional reviews of the literature in student dissertations. The results can be used to formulate new hypotheses and to motivate the empirical research.

There are several examples of meta-analysis reviews in the biomedical sciences, especially of clinical drug trials. It is surprising that a method potentially extremely suited to review nutrition studies has not been used extensively. We hope that this contribution will motivate students, scientists and practitioners in nutrition to review nutrition studies in this structured way.

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PLEASE ANSWER ALL THE QUESTIONS

(There is only ONE correct answer per question.)

1. A meta-analysis is the structured result of a literature review in which results from several independent but related studies are systematically and statistically combined to increase statistical power and precision of estimates in smaller studies.
   [a] True
   [b] False

2. After assessment of the literature, variables in each study are coded by at least two reviewers and the results compared.
   [a] True
   [b] False

3. The appropriate common measure of effect in a meta-analysis, which includes case-control studies, is an odds ratio.
   [a] True
   [b] False

4. In a meta-analysis the heterogeneity of studies is tested, study results are pooled and the combined level of effect calculated.
   [a] True
   [b] False

5. A diamond on the vertical line in the centre of a forest plot indicates there is a difference between the intervention and control groups.
   [a] True
   [b] False

6. Differences between studies (heterogeneity) can be determined by drawing a vertical line through the confidence intervals of all the studies.
   [a] True
   [b] False

7. A meta-analysis is regarded as a
   [a] Quantitative approach to research reviews
   [b] Qualitative approach to research reviews

8. The meta-analysis method can be used to review the literature to form a firm, evidence-based platform for nutrition policy.
   [a] True
   [b] False

9. A meta-analysis is a
   [a] Systematic review of results from several studies
   [b] Statistical integration of comparable numerical results from several studies

10. Inclusion of studies in "traditional" literature reviews may be biased.
    [a] True
    [b] False

11. When including results of randomised controlled trials in a meta-analysis, a relative risk should be calculated as the common measure of effect.
    [a] True
    [b] False

12. An assessment of quality of the original studies is not necessary before inclusion in a meta-analysis.
    [a] True
    [b] False

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1) a b	2) a b	3) a b	4) a b
5) a b	6) a b	7) a b	8) a b
9) a b	10) a b	11) a b	12) a b