Understanding heterogeneity in meta-analysis: the role of meta-regression

W. L. Baker,1,2 C. Michael White,1,2 J. C. Cappelleri,3 J. Kluger,1,2 C. I. Coleman,1,2 From the Health Outcomes, Policy, and Economics (HOPE) Collaborative Group

SUMMARY

Background: Meta-regression has grown in popularity in recent years, paralleling the increasing numbers of systematic reviews and meta-analysis published in the biomedical literature. However, many clinicians and decision-makers may be unfamiliar with the underlying principles and assumptions made within meta-regression leading to incorrect interpretation of their results. Aims: This paper reviews the appropriate use and interpretation of meta-regression in the medical literature, including cautions and caveats to its use. Materials & Methods: A literature search of MEDLINE (OVID) from 1966-February 2009 was conducted to identify literature relevant to the topic of heterogeneity and/or meta-regression in systematic reviews and meta-analysis. Results: Meta-analysis, a statistical method of pooling data from studies included in a systematic review, is often compromised by heterogeneity of its results. This could include clinical, methodological or statistical heterogeneity. Meta-regression, said to be a merging of meta-analytic and linear regression principles, is a more sophisticated tool for exploring heterogeneity. It aims to discern whether a linear relationship exists between an outcome measure and one or more covariates. The associations found in a meta-regression should be considered hypothesis generating and not regarded as proof of causality. Conclusions: The current review will enable clinicians and healthcare decision-makers to appropriately interpret the results of meta-regression when used within the constructs of a systematic review, and be able to extend it to their clinical practice.

Introduction

Evidence-based medicine is a process in which the best scientific evidence is combined with practitioner expertise to make decisions regarding the care of individual patients (1). Systematic reviews are a technique to identify, in a relatively unbiased manner, the evidence relevant to a specific research question. A systematic review has been defined by the Cochrane Collaboration as ‘a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review’ (2,3).

Meta-analysis, often an integral part of a systematic review, utilises statistical techniques to pool data on a common end-point from studies included in the review (4–8). Statistical heterogeneity in a meta-analysis concerns the variation in results across studies. This variation could result from clinical or methodological differences among the studies or could simply be because of chance (9). Clinical heterogeneity may result from differing patient populations, interventions, follow-up times, or choice and measure of outcomes between the included studies. Differing study designs (i.e. active vs. placebo controlled) and study quality issues (i.e. presence or absence of double-blinding) can, for example, result in methodological heterogeneity.

The Quality Of Reporting Of Meta-Analysis as well as the Meta-analysis Of Observational Studies in Epidemiology groups recommends reporting the methods used in a systematic review of randomised clinical trials and observational trials, respectively, to assess for clinical and methodological heterogeneity (10,11). Currently, accepted methods for assessing statistical heterogeneity include visual assessment of graphics such as forest and L’Abbe plots (Figure 1), as well as statistical tests including the Cochran’s Q or $I^2$ statistic (12–15).
A commonly utilised approach to address heterogeneity of effect between studies is the use of meta-regression. Meta-regression has been described as the merging of meta-analytic techniques with linear regression principles (predicting treatment effects using covariates) (16). Briefly, meta-regression explores whether a linear association exists between variables and a comparative treatment effect, along with the direction of that association. Meta-regression is a more sophisticated method than subgroup analysis for exploring heterogeneity and has the potential advantage of efficiently allowing the evaluation of one or more covariates simultaneously. While sophisticated, the associations found in meta-regression are considered hypothesis generating only and cannot be regarded as proof of causality.

The current review will discuss the appropriate use and interpretation of meta-regression in the medical literature, including cautions and caveats to its use, to explore heterogeneity of treatment effect across studies. It is intended to provide the clinical practitioner or decision-maker with the necessary information to interpret appropriately the results of meta-regression when used within the constructs of a systematic review, and be able to extend it to clinical practice.

**Meta-regression example**

To better illustrate what meta-regression analyses are and the cautions and caveats associated with their use, we will focus on the results of a published meta-regression analysis by Bonovas and Sitaras (B&S) throughout this review (17).

B&S reported the results of a meta-analysis examining the impact of pravastatin on cancer incidence and whether this effect varied by patient age (17). They state that the results of two published clinical trials, the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial and the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial, were the impetus for their analysis (18,19). In the LIPID trial, there was a subgroup analysis, whereby those aged 31–64 years were analysed separately from those aged 65–75 years. The incidence of cancer in the older-aged subgroup was found to be higher than the lower-aged subgroup, as expected (19). The PROSPER trial enrolled only patients aged between 70 and 82 years old and suggested, through a *post hoc* analysis, a potential relationship between pravastatin use and cancer risk (18).

The investigators identified a total of 12 trials examining the use of pravastatin and reporting results on cancer incidence, including a total of 42,902 patients. Using standard meta-analytic techniques, they failed to show a significant association between pravastatin use and cancer (random-effects relative risk = 1.07, 95% confidence interval: 0.98–1.17, p = 0.12). However, upon meta-regression, they demonstrated a significant positive association between the mean age of study participants and cancer risk resulting from the use of pravastatin \[ \text{log risk ratio (LRR)} = 0.854 + 0.014 \times \text{age}; p = 0.006 \]. This meta-regression suggested that the cancer risk resulting from pravastatin use increases as the age of the population increases.

**Issues regarding the conduction of meta-regression**

**Methods for assessing heterogeneity within meta-analysis**

As mentioned before, there are numerous methods, including both graphical and statistical, which are available to characterise and quantify the existence and extent of heterogeneity (differences in magnitude...
The role of meta-regression

and/or direction) of results across studies in a given meta-analysis. It is more clinically relevant to practitioners to identify potential sources of heterogeneity rather than simply quantify its existence. After all, the question is not whether heterogeneity of results across studies exists but rather to gauge the extent and meaning of heterogeneity (15). As such, examining for potential clinical and methodological differences between studies should be conducted rather than simply relying on tests to report the presence of heterogeneity. It is important to recognise that a non-significant test for heterogeneity does not guarantee homogeneity between all trials included in a meta-analysis (20). For example, in the B&S example (17), they report a Cochran’s Q statistic and an  I^2  = 15%. These statistical tests suggest little statistical heterogeneity between trials, yet they were able to show differences in treatment effect based on the age when they conducted meta-regression. This example illustrates the relatively low power of these tests to demonstrate statistical heterogeneity, and the need to evaluate for clinical and methodological heterogeneity even in the face of little statistical heterogeneity between trials, assuming appropriate and responsible use of current methodologies allow for it (15).

Meta-regression to explain heterogeneity

Ideally, possible sources of clinical or methodological heterogeneity should be identified before the results are pooled in a meta-analysis, based on a review of the included studies’ demographics and methodology, as well as application to known pharmacological and (patho)physiological phenomenon (14).

There should generally be a sound rationale when deciding to undertake a meta-regression, not simply because the results of a meta-analysis were suggestive that an association might exist or because the ability to run multiple unfounded meta-regressions exists (9,21). In the B&S (17) example, it would be difficult to justify a meta-regression examining the effect of year of publication on the incidence of cancer with pravastatin use, as it is unlikely that pravastatin’s propensity to cause cancer changed from year-to-year. Consequently, even covariates defined a priori need to be considered hypothesis generating rather than being definitive.

Required information for conducting meta-regression

As previously stated, the aim of meta-regression is to discern whether a linear relationship exists between an outcome measure and one or more covariates. In the B&S (17) meta-regression, the underlying assumption being tested was whether a linear relationship existed with pravastatin use between the dependent variable (LRR for cancer) and the covariate (mean age in a study). It is also important to recognise that different results can be seen if aggregate level data, such as the mean age of the total population, are used rather than individual patient data, the age of each individual patient, in the meta-analysis (22–26). The latter, if available from individual patient data, is much preferred over the former. Schmid et al. noted that aggregate data (for use in both meta-analysis as well as meta-regression) are useful for exploring heterogeneity within study-level factors (e.g. type of controls used, study blinding, planned follow-up), whereas individual patient data are preferred for exploring patient-level factors (e.g. age, blood pressure) (27).

The main difference between meta-regression and linear regression, which clinicians and decision-makers may be more familiar with, is that meta-regression uses weighted data from multiple clinical trials (where each study is a data point in the regression analysis) rather than individuals patient data from a single study (where each person is a data point in the regression analysis) (28–30).

As seen with common regression, meta-regression produces a mathematical equation for a ‘best fit’ line to describe the relationship between an outcome variable and a covariate. A scatter plot can portray this visually with a line running through it as shown in Figure 2 (17). The regression coefficient provided in published meta-regressions describes how the outcome variable (or treatment effect) changes with a unit increase in the covariate. It is important to note the sign of the regression coefficient. A negative sign for the coefficient corresponds to a reduction in the outcome variable for given increases in the covariate. A positive sign corresponds to an increase in the outcome variable. The information provided in Figure 2, as reported by B&S (17), suggests that there

Figure 2

Graphical representation of effect size vs. a study-level variable. The symbol for each study is sized proportionally to the precision of the study (inverse-variance weighting). Adapted with permission from Bonovas and Sitaras (17). LnRR = Logarithm risk ratio.
is a 1.4% increase in the log of cancer risk for every 1-year increase in patient mean age while receiving pravastatin therapy.

Random vs. fixed-effects regression models

The two commonly applied statistical models for both meta-analysis and meta-regression include fixed-and random-effects models. A fixed-effect model assumes a common effect size between studies, with any differences seen between the studies considered due simply to chance. Alternatively, random-effects models assume that the treatment effect is not the same across studies, and adjusts not only for the within-study variance but also the between-study variance. Thus, depending on the amount of between-study variance (e.g. level of statistical heterogeneity), studies are given different weights resulting in wider confidence intervals using a random-effects model than under a fixed-effect model. The choice of which model to use is based on the assumption of whether the included studies represent a uniform population, for which a fixed-effect model would be appropriate, or a random sampling of populations, for which a random-effects model would be appropriate. The practice of starting with a fixed-effect model and switching to a random-effects model if significant statistical heterogeneity is present should be discouraged.

There has been considerable debate as to the most appropriate type of model to run when conducting meta-regression (31,32). The general consensus is that it is unreasonable to assume that, even with adjustment for multiple covariates all between-trial variation could be accounted for. As a fixed-effect model does not take into account variability in between-study differences, it is less appropriate than the preferable random-effects model (31–33). Of note, it has been shown that when results of individual studies are very homogeneous, random-effects meta-regression and fixed-effect meta-regression provide similar results (33).

Selection of covariates for investigation

Careful selection of appropriate covariates for inclusion into a meta-regression analysis is imperative for getting trustworthy results. Investigators often have a working knowledge of everything relevant in the literature of a given area, except for the individual trial results, that lead to the hypothesis that they are testing in their meta-regression. Thus, the choice of covariates should be grounded in knowledge of the subject matter. Other common issues related to the selection of covariates include the issues of multiplicity and prespecification (21). The issue of multiplicity relates to the investigation of too many covariates in individual analyses or a multivariable analysis. Convention tells us that assuming a p-value of 0.05 and that, if no true associations between any covariates and effect size exists, an investigator will find one false-positive result for every 20 covariates assessed. In other words, the more covariates evaluated, the higher the likelihood that a false-positive result will be seen.

One of the difficulties in interpreting the results when several covariates are tested is the inability for both the reader and the researcher to distinguish between the true effects and false-positive effects. The B&S (17) meta-analysis assessed age as their sole covariate, limiting the risk of false-positive findings. Readers of a meta-regression should consider the relationship between how many covariates were evaluated vs. how many were reported. Authors of systematic reviews should be forthcoming in reporting the actual number of covariates that were assessed in meta-regression models rather than simply reporting those with significant results. If numerous variables are investigated, the potential for false-positive results should be recognised by the authors and taken into consideration by the readers when interpreting the results of a study.

Prespecification (a priori identification) of which covariates are to be investigated is another way to safeguard against biased conclusions (26). However, logistical difficulties arise from requiring a priori protocol development for meta-analytic projects. For a vast majority of meta-analyses published in the medical literature, a platform for documenting these protocols does not exist. The Cochrane Collaboration is one of the few organisations that publish protocols for ongoing projects that are publicly available. In order for these protocols to be truly a priori, the investigators should not have a working knowledge of the results for any of the trials included in their meta-regression. This is unlikely to be achieved in current practice because of the retrospective nature of meta-analysis and meta-regression. Prospective meta-analysis, which involves the planning of clinical trials in the context of knowing that they will be included in a meta-analysis, is a potential methodology for conducting true a priori analyses (34,35). However, large-scale collaboration is usually required and thus presents logistic challenges.

In addition, the availability of a published protocol for a meta-analysis does not guarantee that the protocol will be followed. Higgins et al. (36) conducted an investigation of 39 systematic reviews in the Cochrane Database of Systematic Reviews, for which 28 had prepublished protocols. They compared the covariates that were prespecified in the protocol to be investigated, either by subgroup analysis or
meta-regression, to the analyses that were actually undertaken in the final manuscript. Of the 15 protocols that prespecified subgroup analyses or meta-regression, seven did not undertake any of the planned analyses, three only undertook post hoc analyses, three undertook post hoc analyses in addition to the prespecified ones and two undertook only those analyses that were prespecified (36). It is also important to keep in mind that the prespecification of covariates for investigation does not protect against issues of multiplicity.

With respect to selecting appropriate covariates for investigation, a few key points are important to keep in mind when either conducting or evaluating a meta-regression manuscript: (i) the presence of statistical heterogeneity is not required for, and its absence should not preclude the conduction of, subgroup analyses or meta-regression; (ii) along with the a priori identification of which covariates are to be investigated is desirable, a defensible scientific rationale for each should be presented; and (iii) it is important to limit the number of covariates that are evaluated in a meta-regression to avoid the problem of multiplicity and false-positive findings. Having said that, it should also be emphasised that these analyses are exploratory and it is the magnitude of effect and its 95% confidence interval that are more relevant than whether a p-value is less than or greater than 0.05.

**Aggregation bias (ecological fallacy)**
Meta-regression is often used to investigate the relationship between treatment effects and covariates reported as aggregated data, such as average age. These analyses must be interpreted cautiously as the average age seen within a study may not accurately reflect the ages of all the patients within a study and their propensity to experience the outcome of interest. This can result in bias that is often referred to as aggregation bias or ecological bias (26,37). For example, if a clinical trial enrols patients between the ages of 20 and 80 years, with an average age of 50 years, it is inappropriate to assume that all of the participants of the trial will behave (medically) like a 50-year old, but rather the 20-year olds will have the risk of a 20-year old and the 80-year olds will have the risk of an 80-year old. This relationship can be graphically displayed.

Figure 3 pictorially demonstrates this concept using a hypothetical situation. In the top panel (Figure 3A), a positive relationship for patient age is demonstrated between or across studies (depicted by an upwardly sloping solid line); however, no relationship is seen within any of the studies (depicted by a horizontal dotted line). The opposite relationship is seen in the middle panel (Figure 3B), where a
positive relationship is observed within studies (depicted by an upwardly sloping dotted line); yet no relationship is seen between studies (depicted by a horizontal solid black line). This situation is very difficult to examine without having the benefit of individual patient data on age along with treatment and outcome. The bottom panel (Figure 3C) shows the optimal situation, whereby a positive relationship is observed between age and treatment effect both within (upwardly sloping dotted line) and across studies (up-sloping solid line).

The B&S (17) example demonstrated a positive relationship across studies between patient age and cancer risk in patients receiving pravastatin. A similar association between age and cancer risk was seen within the LIPID trial (19), which demonstrated higher cancer risk in older patients receiving pravastatin compared with younger patients. A caveat was that LIPID was the only trial allowing for such an assessment and may not necessarily be representative of all the trials included in the meta-analysis.

### Presentation and interpretation of meta-regression

#### Graphical presentation of results

An appropriate visual presentation of the results of a meta-regression is important for the proper interpretation of a study. Diagrams should include a plot of effect size vs. the desired covariate. A symbol for each study can be proportionally sized to the precision of the study (inverse-variance weighting). The lack of a proper measure of precision would provide misleading information as to which studies were providing the most weight to the analysis. Unlike standard forest plots of meta-analysis results (Figure 1A), confidence intervals surrounding each point estimate are not recommended in meta-regression diagrams as they draw more attention to studies with low precision (large confidence intervals) rather than the more influential studies (Figure 4B). Rather, each symbol should reflect the weight the study was given in the meta-analysis, such that studies with greater weight and more precision of effect (less variance) are given larger symbols (Figure 4A). In addition, a regression line and equation should be provided with each diagram.

#### Interpretation of meta-regression results

An important limitation to retrospective meta-regression is the appreciation for the observational nature of the analysis. Meta-regression describes an observational association across trials and thus does not lend itself to demonstrate a causal relationship. As with all observational studies, meta-regression can also suffer from confounding. To be a confounder in this context, the variable has to be associated with treatment effect, and separately, with the covariate (age). It is possible that an association identified between a covariate and a treatment effect may in fact reflect an association with another unidentified study-level variable, a confounder. For example, in the B&S study (17), if patients in the pravastatin group had been found to have a higher incidence of previous cancer than the placebo group, then it is plausible that the association found between pravastatin and cancer may simply have reflected the higher baseline risk in the treatment group rather than a true causative association. Other validity concerns, such as selection bias, can creep in as well with an example being that those participants who remain
The role of meta-regression

long enough in the study to be evaluated are relatively healthy compared with those who discontinue. In essence, studies of longer duration may have more profound benefit or lower reporting of harms, which is not related to treatment duration but to the population remaining in the study.

The B&S (17) example appropriately addressed their results by stating that their ‘findings suggest an association between pravastatin therapy and cancer in elderly patients’. Clearly, it is important for the results of a meta-regression not to overemphasise unwarranted conclusions for the sake of getting them published (20). Statistical tests remain only a tool for analysing study results and should not trump clinical judgment and context.

Like with subgroup analyses within individual trials, meta-regression analyses may suffer from low power (38). However, unlike subgroup analyses which depend on the total number of patients in an evaluation for power, meta-regression depends on the number of trials in the analysis. As such, non-statistically significant relationships should not always be interpreted as a lack of a true relationship, as the number of studies or the sample size in a particular covariate subgroup may be too sparse for reliable inference (38).

To help address this concern, most experts recommend that not more than 1 covariate be evaluated in a single model/analysis for every 10 studies in the meta-analysis (2). This would mean that at least 20+ studies would be required to run a ‘multivariable’ (i.e. two or more covariates being addressed at the same time) meta-regression. The advantage of such a multivariable analysis is that it may better control for confounding by addressing multiple covariates at once (i.e. age and gender), thus yielding more accurate estimates of association. However, when the ratio of covariates to studies becomes too large (> 1 : 10), results are less likely to be useful because of the analyses’ underpowered nature. In the B&S (17) meta-analysis, they assessed age as their sole covariate and included a total of 12 studies, conducting 13 analyses, which falls within the recommended range. Thus, it was less likely that their analysis was at risk of being underpowered.

Furthermore, a biologically or pharmacologically plausible mechanism should exist to explain the analyses and findings within a meta-regression. For example, the B&S (17) example would have been more convincing if a biological mechanism was provided to explain the apparent increases in cancer incidence seen with pravastatin and its relationship to age. It is much more difficult to accept the findings of an analysis if no explanation or rationale for the results is provided.

In addition to the interpretation of the validity of the results of a meta-regression, the clinical relevance must also be considered. Clinical significance in addition to statistical significance is important, especially in studies where only associations, not causality, can be demonstrated. As described in B&S (17), the number needed to harm (NNH) (which indicates how many patients need to be exposed to a risk-factor to cause harm in one patient that would not otherwise have been harmed) can be calculated for pravastatin use by age category. Assuming their stated overall cancer control event rate (CER) of 7.0% over a mean of 4.5 years, with the equation NNH = 1/[CER – relative risk (RR)] × CER, the following NNH are calculated: 65 years of age NNH = 238, 70 years of age NNH = 110, 75 years of age NNH = 65.

Thus, fewer patients need to be exposed to pravastatin to encounter one additional case of cancer as age increases. However, this must be balanced by the possible benefits of pravastatin, such as a reduction in primary and secondary major coronary events, which would be encountered more frequently, as evidence by a number needed to treat of 60 and 33, respectively (39). Even though B&S (17) showed an association between pravastatin use and cancer in older patients, it could be questioned whether clinicians should stop using this statin in an at-risk population based upon the results of this study and its implications.

As was mentioned earlier, meta-regression assumes a linear relationship between the treatment effect and the covariate in question. However, this assumption should be used with caution, as a linear relationship may not always exist, even when an important and clinically important relationship does exist. We recently conducted a meta-analysis examining the impact of peri-operative corticosteroid use on post-operative atrial fibrillation in patients undergoing cardiothoracic surgery (40). In a prespecified subgroup analysis evaluating low, medium and high-dose corticosteroids (in dexamethasone equivalents), we found that a dose–response relationship exists between corticosteroids and postoperative atrial fibrillation, but it was parabolic (U) shaped rather than linear (Figure 5). Reductions in the incidence of postcardiothoracic surgery atrial fibrillation appeared the greatest in patients receiving intermediate doses of corticosteroid (50–210 mg dexamethasone equivalent), while both lower (likely because of insufficient anti-inflammatory effects) and higher (likely because of increased fluid retention and overload) dosing resulted in blunted effects (40). Thus, linear meta-regression would not be appropriate for analysing this data (more complicated models such as a
The role of meta-regression

meta-regression with a quadratic or a log transformation on the covariate would be more appropriate).

**Key points for assessment of meta-regression**

Based on the information provided above, the following checklist can be used to help interpret the results of a published meta-regression analysis:

- Sources of statistical heterogeneity in a meta-analysis should be explored.
- A sound rationale for conducting the meta-regression should be provided.
- Aggregate data are best used for study-level factors, and individual patient data are best for patient-level factors.
- A random-effects model is preferable when heterogeneity is present.
- Covariates should be determined *a priori*.
- Limit the number of covariates to avoid false-positive findings.
- Take care in study interpretation if aggregation bias is likely.
- Results should be displayed graphically with each symbol reflecting the weight given to the study (avoid confidence intervals).
- Interpret results as an observational association rather than a causal relationship.
- Address potential limitations to the analysis.
- Consider the clinical relevance of the results.

**Conclusions**

Meta-regression is a useful technique to explore whether an association between an outcome measure and a covariate can be demonstrated. Given its observational nature in addition to the fact that traditional meta-regression uses aggregate (and not patient-level) data, meta-regression cannot determine causality and may often be viewed as hypothesis generating only although exceptions exist. There are many cautions and caveats when performing or evaluating meta-regressions. The confidence in the results is inexorably linked to the studies underlying the meta-regression and how the meta-regression is conducted.

**Acknowledgements**

None.

**Funding**

This review was funded by a contract from Pfizer Inc.

**References**

1. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn’t. *BMJ* 1996; 312: 71–2.
2. Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.6 [Updated September 2006]; In: The Cochrane Library, Issue 4. Chichester, UK: John Wiley & Sons, Ltd, 2006.
3. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med* 1997; 126: 376–80.
4. Cappelleri JC, Ioannidis JPA, Lau J. Meta-Analysis of Therapeutic Trials. In: Chow S-C, ed. *Encyclopedia of Biopharmaceutical Statistics*, 2nd edn. Revised and Expanded. New York, NY: Marcel Dekker, Inc., 2003: 586–98.
5. Normand SLT. Meta-analysis: formulating, evaluating, combining, and reporting. *Stat Med* 1999; 18: 321–59.
6. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997; 315: 1533–7.
7. Thompson SG, Higgins JPT. Can meta-analysis help target interventions at individuals most likely to benefit? *Lancet* 2005; 365: 341–6.
8. Cleophas TJ, Zwinderman AH. Meta-analysis. *Circulation* 2007; 115: 2470–5.
9. Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. *BMJ* 1994; 309: 1351–5.
10. Moher D, Cook DJ, Eastwood S et al. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement. *Lancet* 1999; 354: 1896–900.
11. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000; 283: 2088–12.
12. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327: 557–60.
13. Song F, Sheldon TA, Sutton AJ, Abrams KR, Jones DR. Methods for exploring heterogeneity in meta-analysis. *Eur Health Prof* 2001; 24: 126–51.
14. Thompson SG, Sharp SJ. Explaining heterogeneity in meta-analysis: a comparison of methods. *Stat Med* 1999; 18: 2693–708.
15. Ioannidis J, Patsopoulos N, Rothstein H. Reasons or excuses for avoiding meta-analysis in forest plots. *BMJ* 2006; 336: 1413–5.
16. Sutton AJ, Higgins JPT. Recent developments in meta-analysis. *Stat Med* 2008; 27: 625–50.
17. Bonovas S, Sitaras NM. Does pravastatin promote cancer in elderly patients? A meta-analysis. *CMAJ* 2007; 176: 469–54.
18. Shepherd J, Blauw GI, Murphy MB et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomized controlled trial. *Lancet* 2002; 360: 1623–30.
19. The LIPID Study Group. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. *Lancet* 2002; 359: 1379–87.
20 Oxman AD, Guyatt GH. A consumer’s guide to subgroup analyses. Ann Intern Med 1992; 116: 78–84.
21 Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine – reporting of subgroup analyses in clinical trials. N Engl J Med 2007; 357: 2189–94.
22 Stewart LA, Clarke MJ. Practical methodology of meta-analyses (overviews) using updated individual patient data. Stat Med 1995; 14: 2057–79.
23 Camma C, Giunta M, Chemello L et al. Chronic hepatitis C: interferon retreatment of relapsers. A meta-analysis of individual patient data. Hepatology 1999; 30: 801–7.
24 Trikalinos TA, Ioannidis JP. Predictive modeling and heterogeneity of baseline risk in meta-analysis of individual patient data. J Clin Epidemiol 2001; 54: 245–52.
25 The Ace Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. Ann Intern Med 2001; 134: 370–9.
26 Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI. Individual patient- versus group-level data meta-regression for the investigation of treatment effect modifiers: ecological bias rears its ugly head. Stat Med 2002; 21: 371–87.
27 Schmid CH, Stark PC, Berlin JA, Landais P, Lau J. Meta-regression detected associations between heterogeneous treatment effects and study-level, but not patient-level, factors. J Clin Epidemiol 2004; 57: 683–97.
28 Abarca J, Armstrong EP. How to use multiple logistic regression in retrospective database analyses. Formulary 2000; 35: 832–41.
29 Worster A, Fan J, Ismaila A. Understanding linear and logistic regression analyses. Can J Emerg Med 2007; 9: 111–3.
30 Slinker BK, Glantz S. Multiple linear regression: accounting for multiple simultaneous determinants of a continuous dependent variable. Circulation 2008; 117: 1732–7.
31 Thompson SG, Higgins JPT. How should meta-regression analyses be undertaken and interpreted? Stat Med 2002; 21: 1559–73.
32 Berkey CS, Hoaglin DC, Antczak-Bouckoms A, Mosteller F, Colditz GA. Meta-analysis of multiple outcomes by regression with random effects. Stat Med 1998; 17: 2537–50.
33 Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. Stat Med 1995; 14: 395–411.
34 Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. N Engl J Med 1992; 327: 248–54.
35 Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials: builds evidence for exemplary medical care. J Clin Epidemiol 1995; 48: 45–57.
36 Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic review of clinical trials: a critical appraisal of guidelines and practice. J Health Serv Res Policy 2002; 7: 51–61.
37 Morgenstern H. Uses of ecological analysis in epidemiologic research. Am J Pub Health 1982; 72: 127–30.
38 Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. JAMA 1991; 266: 93–8.
39 Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. Arch Intern Med 2006; 166: 2307–13.
40 Baker WL, White CM, Kluger J, Denowitz A, Konecny CP, Coleman CL. Effect of perioperative corticosteroid use on the incidence of postcardiothoracic surgery atrial fibrillation and length of stay. Heart Rhythm 2007; 4: 461–8.

Paper received June 2009, accepted July 2009