subsequent trials in 20 of the 26 meta-analyses studied (figure), the average difference in relative odds being 35% (95% CI 15–55).

There seems to be a systematic bias in reported treatment effect related to the order of publication of trials. This bias is independent of trial size, and is probably due, at least in part, to temporal trends in publication bias. If an initial trial of a treatment is positive, the trial would be more likely to be published than if it is negative. However, once a treatment is established, a negative trial showing that the treatment may, in fact, be ineffective is of more interest. Moreover, if initial trials are especially positive, further trials, and subsequent meta-analyses, are more likely to follow than if the initial trials are negative. Thus meta-analyses done early in the evolution of published trial data could overestimate the efficacy of treatment and should be interpreted with caution. Meta-analysists should consider the possibility that heterogeneity of treatment effect within meta-analyses might be related to the order of publication of trials as well as trial size.

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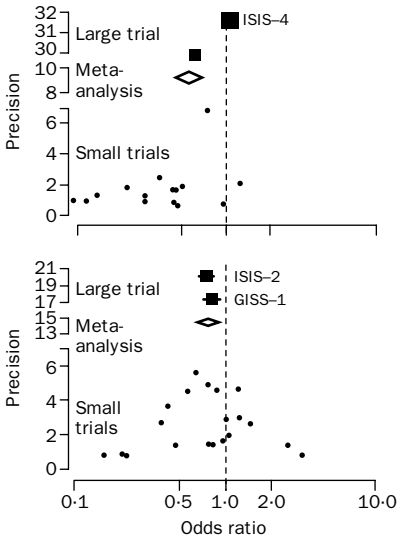
1 Editorial. Meta-analysis under scrutiny. *Lancet* 1997; **350:** 675.
2 LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomised controlled trials. *N Engl J Med* 1997; **337:** 536–42.
3 Villar J, Carroli G, Belizan JM. Predictive ability of meta-analyses of randomised controlled trials. *Lancet* 1995; **345:** 772–76.
4 Cappelleri JC, Ionnidis JPA, Schmid CH, de Ferranti SD, Aubert M, Chalmers TC, Lau J. Large trials vs meta-analysis of smaller trials: how do their results compare? *JAMA* 1996; **276:** 1332–38.
5 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315:** 629–34.

SIR—Your editorial,[1] inspired by LeLorier and colleagues'[2] report of serious discrepancies between meta-analyses of small trials and subsequent large trials, raised the question of whether meta-analyses can be trusted. Meta-analysis cannot be trusted when carried out mechanically and with no broader understanding of the issues under examination. For example, LeLorier and colleagues consider that meta-analyses of the influence of cholesterol lowering drugs on mortality were not supported by the outcome of later definitive studies. The drugs used in the earlier trials produced only small reductions in cholesterol compared with the substantial reductions produced by the statins. Meta-analyses had shown that the treatment effect was significantly related to the percentage reduction in cholesterol concentration[3] and therefore one would not predict that the same effect would be seen in the statin trials as were seen in earlier trials.



Funnel plot of small trials, and meta-analyses of small trials and individual large trials of magnesium (upper) and streptokinase (lower) in acute myocardial infarction

Circles=odds ratios (ORs) from trials included in meta-analysis; diamonds=combined odds ratios with 95% CIs from a meta-analysis; squares=ORs with 95% CIs from large trials appearing after the meta-analysis.

Do the earlier trials provide a basis for predicting the outcome of a current treatment regimen? There is an approach to the data included in a meta-analyses which can help here: inspection and statistical analysis of the funnel plot.[4] This plot allows examination of the association between the outcomes seen in trials (often odds ratios) and the statistical information (precision) contained within the trial, which is closely related to sample size. If an association is seen, with smaller trials producing larger beneficial effects, then the plot becomes asymmetrical and the meta-analyses may be seriously biased. The funnel plot of intravenous magnesium in the treatment of myocardial infarction is shown in the figure along with the meta-analysis and the latter large ISIS-4 trial, which failed to demonstrate the benefit seen in meta-analyses. The funnel plot is clearly asymmetrical, and a statistical test for asymmetry that we have developed[4] demonstrates significant (p=0·005) asymmetry. Conversely, in the case of streptokinase the funnel plot of trials published before the appearance of the large GISSI-1 and ISIS-2 trial was clearly symmetrical, with no statistical evidence of asymmetry in formal analysis. In this case the outcome of the large trials was almost identical to the result of the meta-analysis.

There are several possible causes of asymmetry in funnel plots,[4] including publication bias, location bias due to negative findings being preferentially published in non-English language journals or receiving fewer citations than positive trials, and data irregularities. True heterogeneity may also lead to funnel plot asymmetry, if the size of the effect really differs according to sample size because, for example, of a greater intensity of intervention occurring in smaller trials or smaller trials being done in patients at higher initial level of risk, who receive greater benefit. In all these cases of asymmetry the pooled effect from a meta-analysis will be misleading, with the degree of asymmetry indicating the likelihood that bias is substantial. We suggest that funnel plots and formal statistical testing for asymmetry is routinely included in the performance and the reporting of meta-analyses.

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1 Editorial. Meta-analysis under scrutiny. *Lancet* 1997; **350:** 675.
2 LeLorier J, Grègoire G, Benhaddad A, Kaouerre J, Derderian F. Discrepancies between meta-analysis and subsequent large randomized controlled trials. *N Engl J Med* 1997; **337:** 536–42.
3 Davey Smith G, Song F, Sheldon T. Cholesterol lowering and mortality: the importance of considering initial level of risk. *BMJ* 1993; **306:** 1367–73.
4 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315:** 629–34.

SIR—The following limerick may be of interest and amusement to your readers, especially those who share my skepticism about the arm-chair research done by meta-analysers:[1]

Meta-analysis

An ambitious physician in Boston
Wished to publish quickly and often
So he re-searched the lit
P'ed and R'ed it a bit
And first-authored a meta-concoction

Ciarán P Kelly

Beth Israel Deaconess Medical Center, Division of Gastroenterology, Boston, MA 02215, USA

1 Editorial. Meta-analysis under scrutiny. *Lancet* 1997; **350:** 675.

DEPARTMENT OF ERROR

Poppy Tea and the baker's first seizure—In this Research Letter by Mark A King and colleagues (Sept 6, p 716) the first sentence should have begun "A 26-year-old baker had a witnessed first tonic-clonic seizure" and the figure caption should have been "Morphine concentrations in blood".