

# Correspondence

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## Meta-analysis and the Hippocratic principle of *primum non nocere* — Authors' reply

The unequivocal rejection [1] of our meta-analysis of hypertension trials [2] by Egger and Davey Smith and their implicit advice to the reader rather than to consult another 'elegant recent meta-analysis' [3] indicates that we have hit upon a controversial issue. This is not unexpected. One of us (J.L.) has previously introduced the underlying thinking in 1988 on a small scale on the invited lecture circuit, always meeting with disbelief in some quarters. We are grateful that the editor of this journal has not only decided to publish our paper despite the criticism of one reviewer, but also asked this reviewer to comment, and has given us the opportunity to reply. Science is not about exorcism of various views but about conjectures and refutations aired during public discussion [4]. Hence, we gladly take the opportunity to refute (and accept the risk of being refuted in turn), not least because we believe the issue at hand to be of particular importance. The safety of innumerable people with elevated blood pressure is at stake as they risk being 'overtreated' by doctors who follow treatment recommendations based on data fitted to a model, rather than on a model fitted to data.

The main comments of Egger and Davey Smith concern the statistical methods we used in the meta-analysis and our selection of the trials. Central to the criticism of our statistical analysis is that 'random fluctuations in the control and treatment group mortality rates will tend to bias the slope of the regression line'. This is an important issue, that was, however, addressed extensively in the discussion section of our manuscript. As we discussed, 'a disadvantage of the regression analysis we used lies in the random error in the measurement of the mortality rate in the control groups of the trials', possibly leading to an underestimation of the weighted regression coefficients [5]. Importantly, this is a problem inherent in all meta-analyses based on regression analysis, including the 'metaregression' analysis of cholesterol-lowering trials by Davey Smith *et al.* [6]. The questions remain whether this problem led to considerable bias of our results, and which statistical techniques should be applied to overcome any bias. In our manuscript, an appropriate analysis was performed to estimate the magnitude of the problem resulting from this phenomenon (based on interchanging the dependent and independent variables), and we concluded that any bias that may have occurred is limited. Obviously, Egger and Davey Smith do not fully understand the statistical limitations posed by the

regression approach of meta-analysis, as their suggested solution to the problem — 'fitting linear regressions of the log of the odds ratio for total mortality, once taking control group and once taking overall (control and treatment groups combined) rates of vascular mortality as the explanatory variables' — does not apply to our meta-analysis. This approach was indeed used in the analysis of the cholesterol-lowering trials by Davey Smith *et al.* [6]. In that analysis, such a 'solution' was necessary because they used the (log) odds ratio as the dependent variable and, thus, artificially introduced a correlation between values of  $x$  (mortality in the control group) and  $y$  (log odds ratio) into the regression analysis [7]. By using mortality in the treatment group as the dependent variable, as in our meta-analysis, this problem does not arise. Importantly, the problem of random error in control group mortality was not addressed in the meta-analysis by Davey Smith *et al.*

It should further be noted that the assertion by Egger and Davey Smith that 'If, purely because of random variation owing to non-infinite sample sizes, the control group mortality in a trial happens to be particularly low, then the corresponding treatment group rate will, on average, appear to be high, even if there are no detrimental effects of treatment' may be true in a computer simulation, but is less relevant in the context of clinical trials. In a clinical trial, a group of subjects is enrolled that can be thought of as a random sample from some source population. By random permutation this group of subjects is divided between the treatments to be compared. This is quite different from drawing two independent samples from an imaginary population. It follows that, if the mortality rate among the trial subjects is low (or high) by chance owing to unlucky selection, this will, on average, be the case in both groups. Hence, if there is no treatment effect (i.e. under the null hypothesis) the mortalities in the treated and control groups will, on average, be equal to each other, irrespective of the value of the mortality in the control group. If this were not the case, treatment effect estimation from trials would be impossible (and sections in medical statistics books about hypothesis testing, sample size determination and treatment effect estimation in clinical trials would have to be rewritten).

Egger and Davey Smith further criticize our selection of the available randomised trials, notably the inclusion of the Multiple Risk Factor Intervention Trial (MRFIT)

and Hypertension and Follow-up Program (HDFFP), and our decision to exclude the trials in elderly hypertensives. We included in the meta-analysis all trials that did not meet one of five exclusion criteria. These criteria reflected methodological considerations (e.g. random allocation). We did not exclude the MRFIT and HDFFP studies, the two trials comparing 'special care' with 'referred care', and increased the comparability with the other hypertension trials by using only the mortality results for hypertensive patients that were not using antihypertensive drugs at entry in these two studies. Thus, the comparison in these trials was essentially antihypertensive treatment versus no treatment. Although drug treatment could also be initiated in the referred-care groups during the follow-up period of these trials, the latter is also the case in many (placebo-treated) control groups in the other hypertension trials. We do not believe that effects other than antihypertensive treatment explain the contrasting effect in referred-care trials. For example, this would not explain the contrasting effect in subgroups according to blood pressure level. In addition, our sensitivity analysis showed that exclusion of these trials did not materially change the findings. We excluded trials in elderly patients because the main outcome in our meta-analysis is increase in life expectancy, which in our view should be the main goal (and thus the main indication for initiation) of antihypertensive therapy in middle-aged patients. In the elderly, prevention of morbidity and increase in quality of life become more important goals of antihypertensive treatment and the decision to start antihypertensive treatment should not be based solely on increase in life expectancy.

The recommendations of Egger and Davey Smith to readers to consult the recent meta-analysis by Mulrow *et al.* [3] for 'an informed evaluation of current opinion concerning the costs and benefits of treating hypertension' deserves some comment. Although we agree that this meta-analysis is worth reading, in particular its comparison of trials in middle-aged and elderly hypertensives, it should be emphasized that the assumption of homogeneity underlying this type of meta-analysis does not hold true. As explained in our paper, we believe that the assumption that the treatment effects on mortality are similar and have the same direction across individual trials and subgroups of patients is *a priori* untenable. For low values of untreated risk of death this cannot possibly be the case, for the simple reason that the possibility that treatment does

harm in patients for whom the absolute risk is low can never be excluded. There are no treatments that work that are completely safe. We feel that meta-analyses based on an *a priori* untenable biological model forced on the data, that overlooks the fact that people who are not going to die do not need to be kept alive and can only be killed by an adverse effect of treatment, however rare, should be interpreted with caution. A violation of the Hippocratic principle *primum non nocere* ['first do no harm'] in clinical practice is a potential consequence of such an uncritical desire to pool data.

In conclusion, we are convinced that both the statistical analysis and the selection of the trials we used in our meta-analysis are appropriate, albeit that some limitations inherent to all meta-analyses using a regression approach remain. Finally, we strongly support the suggestion of Egger and Davey Smith that a collaborative meta-analysis based on the individual patient data from all available randomized hypertension trials would be useful to identify further those hypertensive patients who are most likely to benefit from the antihypertensive therapy. Perhaps the discussions included in this issue of the *Journal of Hypertension* will promote such an analysis.

## References

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## Does drug treatment improve survival in mild-to-moderate hypertension?

The meta-analysis by Hoes *et al.* [1] on the effect on mortality when treating mild-to-moderate hypertension deserves praise for introducing a weighted linear regression model of analysis. However, apart from a number of minor factual errors — for example, stating

that active therapy in the Veterans Administration study was hydrochlorothiazide or hydralazine (it was always a triple combination of reserpine, hydralazine and hydrochlorothiazide) — the authors have committed two serious errors.