confounding effect of these factors, it may introduce a new bias. If the matching factor is associated with the exposure of interest a crude case-control analysis may lead to a result that is confounded by the matching factor itself.[2] In such a case the confounding must be eliminated by stratified analysis or multivariate analysis.

Another potential problem is overmatching, which results from cases and controls being matched on variables that are highly related to the exposure. For example, suppose one matches on the variable "carrying a cigarette lighter" in a study of smoking and lung cancer. Matched analyses depend on the existence of discordant pairs of cases and controls, but few will exist in this situation because the confounder is closely related to the exposure. Overmatching will not bias the results, but it will make the analysis highly inefficient, which abrogates the main virtue of matching.[2]

In case-control studies investigators must use the technique of matching wisely since it is irreversible and its advantages may be limited by the problems we have highlighted.

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Numbers alone cannot determine rational treatment

EDITOR,—In the Editor's Choice in the issue of 12 November meta-analysis is embraced with enthusiasm as a means of determining effective treatment and solving therapeutic dilemmas. This approach should form part of the armamentarium of those interested in rational prescribing and seems to ensure that data from patients who have given up time and exposed themselves to risk by participating in clinical studies are used to full advantage. But how reliable are meta-analyses?

Recently it has been possible to compare the results of meta-analysis with those of a prospective study. For example, the fourth international study of infarct survival included over 50 000 patients, substantially more than the 1000-4000 combined to form meta-analyses of the same therapeutic area.[1 2] In many respects the results of the fourth international study of infarct survival and the meta-analyses are similar, but in others they differ: whereas meta-analysis showed clear benefit for intravenous magnesium and nitrates in treating acute myocardial infarction, the study of infarct survival did not. It is unlikely that the meta-analyses were "wrong" because of statistical problems as several groups came independently to the same conclusion. Furthermore, owing to the numbers involved, any subsequent analysis that included the fourth international study of infarct survival would reach the same conclusion as that study. A meta-analysis seems no more infallible than the clinical trials from which it is composed.

Emphasis has been placed on ensuring that only trials with the correct "statistical" design are included in meta-analyses, but less interest has been shown in "biological" design. The case of magnesium again illustrates the problem. In the second Leicester intravenous magnesium intervention trial, a large study of magnesium in acute myocardial infarction, the intravenous magnesium was given early and before thrombolysis, and benefit was seen.[3] In the fourth international study of infarct survival magnesium was given later and after thrombolysis, and no benefit was seen. Analysis based on numbers alone would suggest that magnesium has no advantage. However, analysis that takes into account the timing of administration suggests that early intervention might be beneficial,[4] a conclusion consistent with data from studies in animals indicating prevention of reperfusion "injury" by magnesium.[4]

Decisions on treatment should be based on best available evidence, and this often falls short of certainty. However, in the justifiable rush to establish evidence based treatment large numbers should not swamp critical clinical assessments. Meta-analyses and large trials are useful tools and have helped to shape rational treatment protocols, but greater account of therapeutic considerations should be taken when including or excluding trials. Prescribers should be prepared for frequent changes in treatment protocols as best available evidence is continually updated.

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Apolipoprotein e4 allele and cognitive decline

May be less relevant

EDITOR,—In their paper on the association of the e4 allele of apolipoprotein E and incidence of cognitive impairment in elderly men Edith Feskens and colleagues claim that 22% of incident cases of cognitive impairment can be attributed to the effect of the e4 allele.[1] This contrasts with much higher figures previously reported in patients with Alzheimer's disease,[2 3] but is in accordance with data that we collected on a series of patients with the disease.

Attributable fraction is the proportion of cases that would be avoided by reducing risk to the level found in the lower risk group, in this case subjects not carrying the e4 allele. Attributable fraction has been reported as ranging from 78% in familial Alzheimer's disease[3] to 53% in the sporadic disease,[2] indicating that a relevant proportion of cases of Alzheimer's disease might be due to the e4 allele and that other risk factors might have a minimal role. Attributable fraction was estimated, however, on the basis of the risk computed on prevalent cases (odds ratio)—that is, the risk of having the disease, assuming that disease duration was similar across e4 genotypes. In fact, prevalence, incidence, and disease duration are related in subjects homozygous for e4 (e4/e4) and in those not carrying the e4 allele (-/-) as follows:

$$\frac{P_{e4/e4}}{P_{-/-}} \quad \frac{I_{e4/e4}}{I_{-/-}} \quad \frac{D_{e4/e4}}{D_{-/-}}$$

that is, odds ratio = relative risk $\times \dfrac{D_{e4/e4}}{D_{-/-}}$

where P, I, and D are prevalence, incidence, and disease duration in patients with Alzheimer's disease for the relative e4 genotype. A corresponding relation applies to subjects heterozygous for the e4 allele. Longer disease duration in subjects with Alzheimer's disease carrying the e4 allele might lead to an overrepresentation of e4 in prevalent cases, thus resulting in odds ratios overestimating relative risk—that is, the risk of developing the disease. In this case, the relative risk, if computed on the basis of an inflated odds ratio, gives an inflated estimate of the attributable fraction. Even if as many as half of the cases of cognitive impairment are due to Alzheimer's disease and the e4 allele is not associated with other forms of dementia (which, however, does not seem to be true)[4 5] the proportion of cases of Alzheimer's disease attributable to the e4 allele according to Feskens and colleagues should not exceed 44%. This is in accordance with our own data on a hospital based series of 62 subjects with sporadic Alzheimer's disease that began at age 70 or over, which showed that the attributable fraction computed without taking longer disease duration in e4 carriers into account was 51% and 37% after correction for disease duration.[5]

Our and Feskens and colleagues' data show that the epidemiological relevance of the e4 allele in determining cognitive impairment might be lower than previously suggested, and that large, population based epidemiological studies need to be carried out to evaluate the risk of developing dementia in the many people who carry the e4 allele.

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Author's reply

EDITOR,—Firstly, we agree with Frisoni and colleagues that to calculate the attributable fraction the use of prospective data (incidence of disease) is much more informative than the use of cross sectional data (prevalence of disease). The duration of the disease, due to earlier onset as well as selective survival, is likely to affect the results. Population based prospective studies on the occurrence of Alzheimer's disease, however, are difficult to accomplish because of the large baseline population needed.

Secondly, on the basis of the prevalence data in our study the attributable fraction can be estimated to be about 10%. This is clearly lower than that calculated from our longitudinal data, in contrast with the hypothesis of Frisoni and colleagues. This is probably mainly a numerical issue: comparing prevalence rates of 31% (men without e4) and 41% results in a lower odds ratio than comparing incidence rates of 16% and 28%, although the