ABC of Methodology

This is a new Section of *Epidemiologia e Psichiatria Sociale*, that will regularly cover methodological aspects related to the design, conduct, reporting and interpretation of clinical and epidemiological studies. We hope that these articles will help develop a more critical attitude towards research findings published in the international literature and, additionally, will help promote the implementation of original research projects with higher standards in terms of design, conduct and reporting.

Corrado Barbui, *Section Editor* and Michele Tansella, *Editor* EPS

What is an individual patient data meta-analysis?

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Dealing with meta-analytical studies, there is a variety of ways to collect data and bring them together in a statistical synthesis (Higgins & Green, 2006). These ways include extraction of data from published reports (the so called, *standard meta-analysis*) or collection of individual patient data that are combined in individual patient data meta-analysis (IPD-MA). IPD-MAs are sometimes called *pooled analysis* (mostly in the US). However, *pooled analysis* may additionally indicate re-analyses of aggregated data extracted from studies included in narrative (not systematic) reviews (Cipriani & Barbui, 2006a). This ambiguity may generate some confusion and readers of scientific reports should always pay careful attention to what researchers have actually done, irrespective of the terminology employed. The IPD methodology has been used in large-scale collaborative overviews in which data from all randomised trials in a particular disease area were brought together (Rothwell *et al.*, 2004) and also in more restricted reviews in which data from a relatively small number of trials assessing a specific healthcare intervention were collected and combined (Jeng *et al.*, 1995).

IPD-MAs usually require more time, resources and expertise than other forms of review, however the process brings with it a number of advantages (Stewart & Clarke, 1995). The main difference between a standard meta-analysis and an IPD-MA is that while the former is based on information that refers to each included *study* (for example, in study No 1 the mean age of the entire sample is 50 years), the latter is based on information that refers to each included *subject* (for example, in study No 1 the age of patient No 1 is 48 years, the age of patient No 2 is 52 years, and so on). Intriguingly, information that refers to each included *subject* refers to sociodemographic and clinical data but also to outcome data (for example, in study No 1 patient No 1 is a responder, patient No 2 is not a responder, and so on).

IPD-MA have advantages over other types of review. For example, IPD-MAs allows to describe the effects of competitive treatments over time (Jeng *et al.*, 1995). In fact, information that refers to the outcome of each included *subject* is usually collected not only at endpoint but also at various time intervals after random allocation. Kaplan-Meier analyses of event-free survival on the pooled data are therefore carried out, with stratification by trial where necessary. The finalised data for each study are then analysed separately to obtain summary statistics, which are combined to give an overall estimate of the effect of treatment. In this way, participants are only directly compared with others in the same study and the entire dataset is not pooled as though it came from a single, homogeneous study.

Collecting IPD rather than aggregate data brings additional advantages because sub-group analyses testing whether patient-related variables (sex, age, illness severity) are associated with the outcome of interest may be carried out. A practical example may illustrate these concepts. Imagine that we are interested in investigating whether there are clinical characteristics of depressed patients that

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predict response in trials comparing antidepressants with placebo. Based on clinical reasoning, we may decide to stratify the analysis according to the following patient-level variables in a forest plot (Cipriani & Barbui, 2006b) (see an hypothetical scenario in the Figure):

- Age at index episode.
- Gender.

The hypothetical example shows that antidepressants were more effective than placebo, as indicated by the Relative Risk (RR) reported in the last line of the Figure. However, IPD-MA allows us to check whether this finding similarly applies to all age groups and to both sexes. In terms of age, the Figure reveals that antidepressants were not more effective than placebo in those aged between 18 and 30 years and in those aged between 31 and 40 years. Conversely, the effect of antidepressants is evident in those over 40 years of age. In terms of gender, antidepressants resulted effective in both sexes, although the RRs were different.

Clearly IPD-MA are powerful tools that may help take decisions about optimal patient care. However, IPD-MA are problematic research exercises because individual patient data remain hardly accessible (Barbui & Cipriani, 2007).

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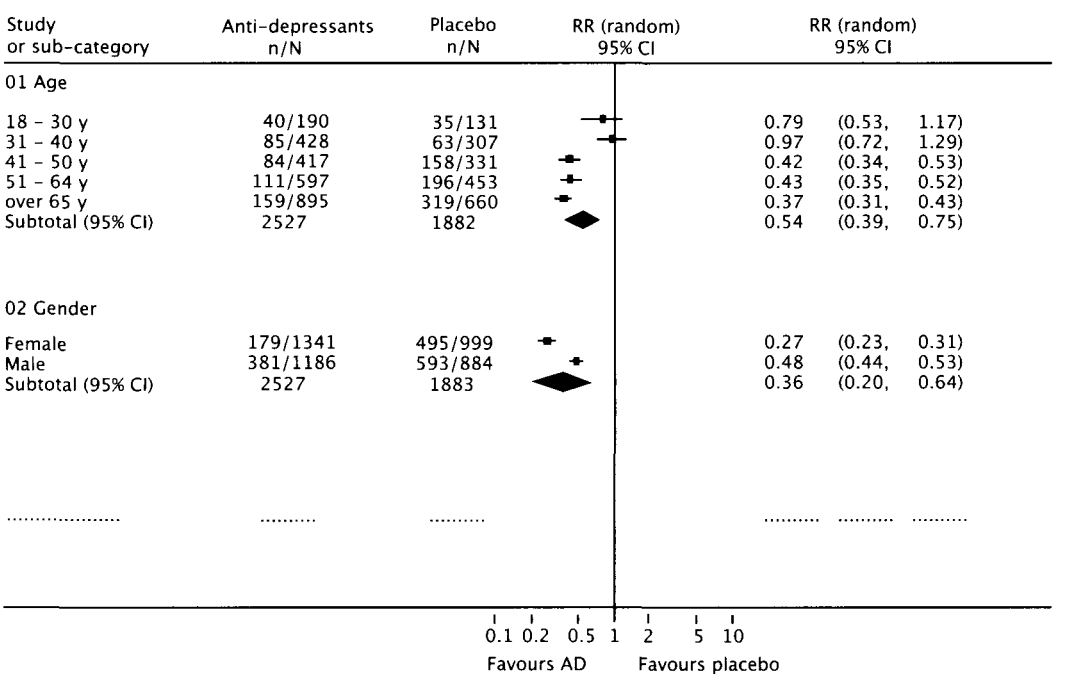
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Legend RR: relative risk; CI: confidence interval; Ad: antidepressant; Y: year.

Figure – *Hypothetical scenario of an individual patient data meta-analysis, with results stratified according to age and gender.*

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