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Journal of Clinical Epidemiology 67 (2014) 325−334

Journal of Clinical Epidemiology

Incorporating uncertainty regarding applicability of evidence from meta-analyses into clinical decision making

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Accepted 13 September 2013; Published online 12 December 2013

Abstract

Objectives: Judging applicability (relevance) of meta-analytical findings to particular clinical decision-making situations remains challenging. We aimed to describe an evidence synthesis method that accounts for possible uncertainty regarding applicability of the evidence.

Study Design and Setting: We conceptualized uncertainty regarding applicability of the meta-analytical estimates to a decision-making situation as the result of uncertainty regarding applicability of the findings of the trials that were included in the meta-analysis. This trial-level applicability uncertainty can be directly assessed by the decision maker and allows for the definition of trial inclusion probabilities, which can be used to perform a probabilistic meta-analysis with unequal probability resampling of trials (adaptive meta-analysis). A case study with several fictitious decision-making scenarios was performed to demonstrate the method in practice.

Results: We present options to elicit trial inclusion probabilities and perform the calculations. The result of an adaptive meta-analysis is a frequency distribution of the estimated parameters from traditional meta-analysis that provides individually tailored information according to the specific needs and uncertainty of the decision maker.

Conclusion: The proposed method offers a direct and formalized combination of research evidence with individual clinical expertise and may aid clinicians in specific decision-making situations.

Keywords: Evidence-based medicine; Meta-analysis; Heterogeneity; Uncertainty; External validity; Decision making; Statistical data interpretation

> *"Identifying when it is appropriate to generalize from the abstract to the actual patient remains the central problem of any form of scientific clinical practice" [1, p. 289].*

1. Introduction

Evidence-based clinical decisions at the bedside should integrate individual clinical expertise with findings from clinically relevant research [2−4]. This integration requires an evaluation (critical appraisal) of the external evidence by the clinician [3,5]. Currently, systematic reviews and meta-analyses of randomized controlled trials are considered the highest level of evidence to inform treatment-related decisions, and several resources are available that support the clinician in the appraisal of such studies [5−10]. While evaluating a meta-analysis, a clinician is likely to be confronted with the assessment of both internal and external validity of the findings. Internal validity can be described as methodological rigor or low risk of systematic internal bias in the estimation of the target parameter of interest, usually the treatment effect. In fact, most evaluation guidelines have a strong focus on internal validity, whereas external validity has remained somewhat neglected [11−14].

Publications considering external validity used a multitude of terms such as generalizability, robustness, applicability, transferability, or relevance. It is rarely noted that these terms, if used synonymously, mix two major perspectives [12]. The first perspective describes external validity of findings as the extent to which they show generalizability to (or robustness across) other circumstances (eg, populations, outcomes). With regard to this aspect, strategies have been developed for the identification, reporting, and synthesis of information to support decision makers [13]. However, for a clinician making a bedside decision, external validity does not need to be assessed globally but rather with reference to the particular situation in which a decision is to be made. This second aspect describes applicability

Conflict of interest: The authors report no potential conflicts of interest.
Funding: No external funding was received for the study.

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0895-4356/$ - see front matter
http://dx.doi.org/10.1016/j.jclinepi.2013.09.010

What is new?

What this adds to what was known?

- Judging applicability of evidence to specific target settings is essential in evidence-based medicine.
- Particularly, the application of findings from broad-spectrum meta-analyses remains challenging.
- Adaptive meta-analysis enables the formal incorporation of the clinician's judgment of applicability (relevance) of meta-analytical evidence to a particular setting and the degree of accompanied uncertainty into clinical decision making.
- Uncertainty regarding applicability of evidence may, but not must, increase decision uncertainty.
- Modeling uncertainty as an information-theoretical measure (eg, entropy) seems a promising way of formalization.
- The proposed method can be generalized to deal with any trial pool beyond meta-analysis.

(transferability or relevance) of the evidence to a specific decision-making setting. The distinction between the two perspectives of external validity becomes clear if one considers that even if a research finding is widely generalizable to several situations, it still can have a remarkably little applicability in a particular setting and vice versa [15].

In the present study, we investigated the second perspective of external validity, that is, applicability. We considered research findings as potential information for clinical decision making and focused on decisions concerning the choice among available treatments for a particular patient in a given clinical context. A clinical decision-making context can be characterized by a variety of attributes. Traditionally, a limited number of central attributes have been considered crucial for clinical decision making, frequently referred to as the population, intervention, comparator, and outcome (PICO) scheme [13,16]. In this scheme, populations are described primarily by diagnostic categories and other clinical and/or demographic characteristics, interventions and comparators by agents or elements that are believed to be the key determinants of the causal effect, and outcomes by (changes in) the patient's state or condition during or after the received intervention. We believe that the skill to decide which attributes are relevant to characterize a decision-making situation and which depth of differentiation is needed within the single attributes is part of the clinical expertise as defined in evidence-based medicine [4]. However, the perception of most clinical decision-making situations may vary among clinicians. Hence, we suppose that for most decision-making situations, a globally valid characterization, or definition, does not exist.

When a clinician attempts to apply results of a meta-analysis at the bedside, users' guides suggest seeking answers to questions such as "Can the results be applied to my patient care?", "Is my patient so different from those in the study that results cannot be applied?", and "Is the treatment feasible in my setting?" [7,10]. Judgment on applicability can be somewhat difficult, (1) if the central attributes of the meta-analysis and the target decision-making situation differ completely or in parts (eg, they refer to different age groups) or (2) if the meta-analysis has a broad scope covering several decision-making situations and not only the one of interest (eg, it refers to many different age groups without differentiating between them). Concerning the first difficulty, "mechanistic" knowledge may be used to justify extrapolation (or particularization) of study results by judging to what extent the causal (eg, pathophysiological) mechanisms of the effects in the study population are shared with the patient of interest [17,18]. Here, we focus mainly on the second difficulty of applying findings from broad-spectrum reviews, which are not uncommon [19] and include trials that are likely to be considered clinically heterogeneous [20]. Assessment of clinical heterogeneity can be seen as judging about differences. From the perspective of the meta-analyst, already Lipsey and Wilson [21, p. 3] noted that "the definition of what study findings are conceptually comparable for purposes of meta-analysis is often fixed only in the eye of the beholder. Findings that appear categorically different to one analyst may seem similar to another." Not only researchers (as authors of meta-analyses) but also clinicians (as end users of them) may vary according to their view on clinically relevant similarities and differences across decision-making situations [20]. As stated, we consider this variation to be meaningful and part of the clinical expertise necessary for high-quality health care.

Currently, judgment on the applicability of a meta-analysis to a bedside situation is likely to lead to a dichotomous (evidence applicable vs. not applicable) decision by the clinician. However, especially in case of broad-spectrum reviews, this decision can be accompanied by considerable uncertainty. This decision uncertainty will largely depend on the way the reviewers dealt with clinical heterogeneity present among the trials included in the review, the clinical heterogeneity as subjectively perceived by the decision-making clinician, and the concordance between the two. In some cases, the decision of whether a meta-analysis is applicable will not be unequivocal, and forcing the clinician to choose between completely accepting and ignoring the findings may either lead to residual uncertainty or result in substantial information loss, respectively.

Although this field is largely underresearched, some approaches have been developed to address applicability of empirical findings (along with their uncertainty) to support decision making [22–24]. These methods consider