Defining the valid analytic space for quantitative bias analysis in pharmacoepidemiology

James Weaver[1,2,3], Patrick B Ryan[2,3,4], Victoria Strauss[1,3], Marc A Suchard[3,5], Joel Swerdel[2,3], Daniel Prieto-Alhambra[1,3,6]

[1]Centre for Statistics in Medicine, Nuffield Department of Orthopedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK; [2]Observational Health Data Analytics, Global Epidemiology, Janssen Research and Development, Titusville, NJ, USA; [3]Observational Health Data Sciences and Informatics, New York, NY, USA; [4]Department of Biomedical Informatics, Columbia University Medical Center, New York, NY, USA; [5]Department of Biostatistics, Fielding School of Public Health, and Department of Biomathematics, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA; [6]Medical Informatics, Erasmus Medical Centre, Rotterdam, Netherlands

BACKGROUND

- Bias from outcome misclassification is acknowledged but rarely corrected in observational comparative safety and effectiveness research
- Quantitative bias analysis (QBA) can correct effect estimates subject to outcome misclassification using incidence proportion and estimated measurement errors
- Certain QBA input combinations **can produce negative corrected event counts that invalidates results**

OBJECTIVE

- Determine which combinations of observed effect estimates, incidence proportions, sensitivity and specificity values produce valid and invalid corrections

METHODS

- Created grid space of:
  - 6 outcome incidence proportions (IP) [10^{-1}, 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6}]
  - 6 uncorrected odds ratios (OR) [1, 1.25, 1.50, 2, 4, 10]
  - 20 outcome sensitivity values [0.05 to 1.00 by 0.05]
  - Specificity precision is dependent on outcome IP, so specificity values were generated within each level of IP. 20 specificity values were defined as 1-incidence to 1.00 by 5%ile
- Complete space: 14,440 2x2 contingency tables, each with 1m target and 1m comparator exposures and associated inputs
- For each IP-OR combination, we computed a distribution of QBA-corrected ORs across combinations of sensitivity and specificity values and plotted their contours
- We estimated the sensitivity, specificity, and IP of ischemic stroke in 5 observational databases (labeled as Source in figure) using probabilistic reference standard validation and plotted their location on the analytic space

QBA produces implausible or invalid outcome misclassification-corrected estimates in most common comparative effect estimation scenarios

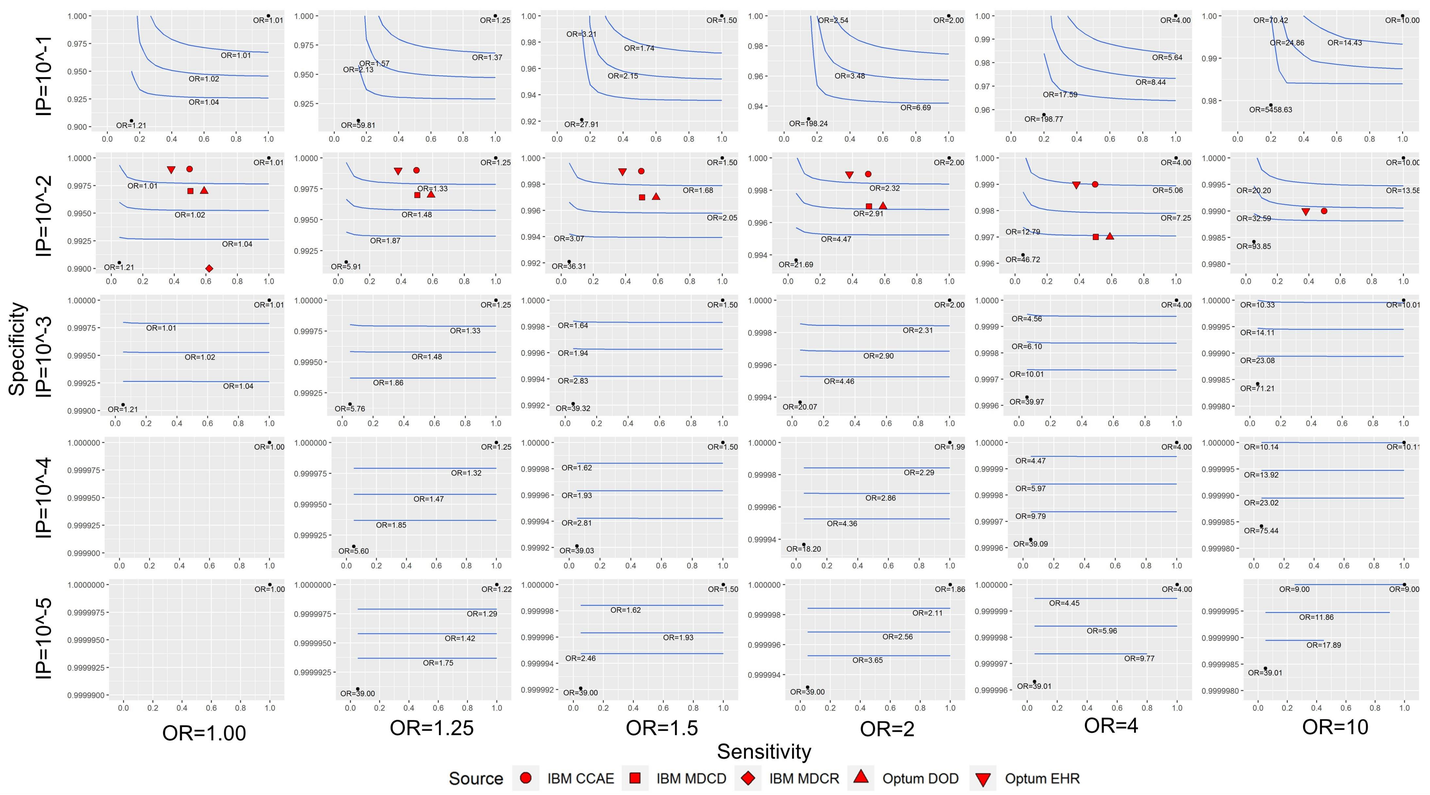

Figure 1. QBA-corrected OR contour plots across 4-dimensional grid space of IP, uncorrected OR, sensitivity, and specificity. Black data points are the uncorrected OR (sensitivity = specificity = 1) and maximum valid OR of the corrected OR distribution across sensitivity and specificity values for each IP-uncorrected OR combination. Blue lines display the corrected OR contour for the 25%ile, 50%ile, and 75%ile of the corrected OR distribution. Red data points are database-specific, empirical QBA-corrected estimates from a study assessing the risk of ischemic stroke between new users of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with hypertension.

RESULTS

- Minimum required specificity for valid QBA correction was inversely proportional to IP.
- Minimum specificity required for valid QBA correction is 0.91, observed where IP=10^{-1}.
- Where IP=10^{-5}, minimum required specificity is 0.9999911
- Lower value sensitivity variation at higher IP affected OR correction, but where incidence was ≤10^{-3}, only specificity materially affected correction
- Empirical results showed ischemic stroke IP as ~10^{-2} with measurement error variability across databases
- At higher uncorrected ORs, these measurement error values would considerably impact estimates
  - E.g., at uncorrected OR=4, the corrected estimate would be inflated >3x in three of five databases

DISCUSSION

- There is considerable IP-OR-sensitivity-specificity analytic space where QBA for outcome misclassification correction is implausible or invalid
- Correction with imprecise specificity is problematic because small specificity changes can make implausible large OR adjustments
- Impact of sensitivity on correction is limited where IP<10^{-2}
- Chart abstraction validation methods are unable to obtain specificity values at the necessary precision to appropriately correct rare outcome estimates

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