Defining the valid analytic space for quantitative bias analysis in pharmacoepidemiology

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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 uncorrected odds ratios (OR) [10-1, 10-2, 10-3, 10-4, 10-5, 10-6]
  - 20 outcome odds ratios (OR) [1, 1.25, 1.50, 2, 4, 10]
  - Specificity precision is dependent on outcome IP; specificity values were generated within each level of IP: 20 specificity values were defined as 1-incidence to 1.00 by 5%
- 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

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=10-2, 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 ~10-4 with measurement error variability across databases.
- At higher uncorrected ORs, these measurement error values would considerably impact estimates.

DISCUSSION
- There is considerable IP-OR-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<10-3.
- Chart abstraction validation methods are unable to obtain specificity values at the necessary precision to appropriately correct rare outcome estimates.

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