Evaluation of Negative Control Selection as Method to Control for Systematic Bias in Real-World Assessment of Drug Benefits: REWARD-B Platform

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INTRO

- The **Real-World Assessment of Drug Benefits (REWARD-B) platform** utilizes a self-controlled cohort design to find associations between all drugs and all conditions as way to discover unknown benefits of existing therapies and requires negative control calibration to produce valid results.
- Self-controlled study designs produce less biased estimates than other study designs yet, remain prone to systematic bias.
- Applying negative controls is an effective way to control for systematic bias.
- However, manual selection of controls can be time consuming, resource-intensive, and prone to human error.
- The purpose of this research is to compare the performance of automated selection of negative control sets versus a hand curated set.

METHODS

- Benefits of existing medications for incident Bipolar Disorder were examined utilizing the REWARD-B platform.
- Analyses were performed in IBM MarketScan® Commercial Database (CCAE). Incident rate ratios were calculated, and calibrated p-values were generated by estimating the systematic error distribution using four sets of negative controls: three automated and one manually curated (Table 1).

Table 1: Description of Negative Control Sets

Negative Control Set	Description
Set 1	All drugs [a]
Set 2	All drugs with removal of ATC level 2 drug classes used to potentially treat Bipolar Disorder [b]
Set 3	Automated data processing and classification procedure [c]
Set 4	Manually curated and adjudicated [d]

a All drugs present in data, according to RxNorm, assuming that the probability of a causal relationship between any random medication and outcome is low.
b ATC classes removed: N03-Antiepileptics, N05-Psycholeptics, N06-Pyschoanaleptics
c Method previously developed & validated by Voss et al.- combines an automated search of literature, spontaneous reports, and product labels. Negative controls are selected when no evidence between medication and condition of interest exists.
d Adjudicated list of negative exposure controls (drugs not believed to cause Bipolar Disorder) reviewed by 2 clinicians

RESULTS

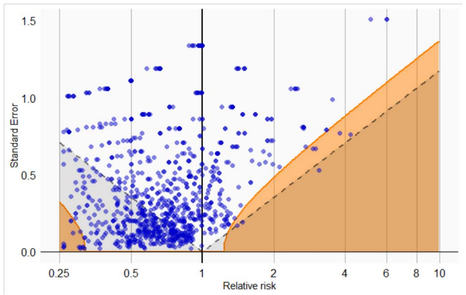
- A total of 2,592 medications were evaluated.
- The uncalibrated results using set 1 showed 15% (n=388) of medications had a statistical association with Bipolar Disorder ($p<0.05$), which is higher than the expected 5%, indicating bias in the study design (Figure 1); similar proportions were found in other sets.
- Results from each of the four negative control sets demonstrated strong negative bias and were similar between each of the 3 automated sets and the manually curated set (Figure 1).

Automated methods to generate negative controls for self-controlled cohort designs produce reliable results quickly.

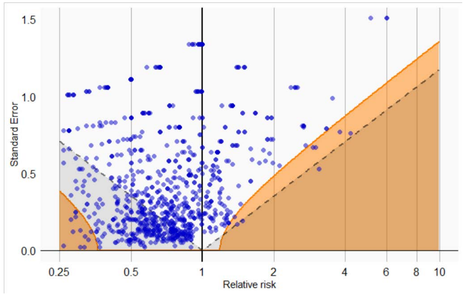
CONCLUSION

- Empirical calibration is necessary to adjust for systematic bias that arises from the self-controlled cohort design.
- When applied to the REWARD-B platform, we demonstrated that automated procedures used to generate negative controls perform as well as manually generated negative controls, while taking only a fraction of the time to implement.
- Further research is needed to explore these findings in other disease areas and for negative control outcomes.

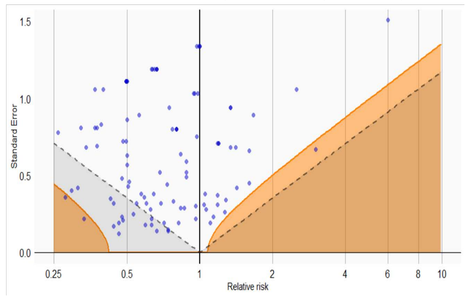
RESULTS



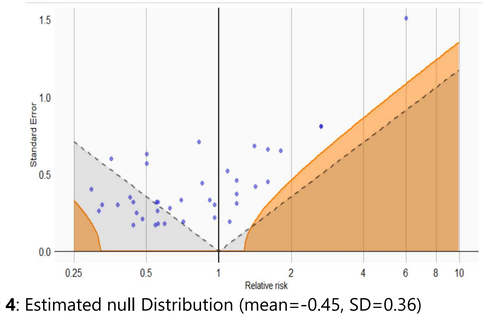
Set 1: Estimated Null Distribution (mean=-0.47, SD=0.35)



Set 2: Estimated null Distribution (mean=-0.43, SD=0.30)



Set 3: Estimated Null Distribution (mean=-0.40, SD=0.24)



Set 4: Estimated null Distribution (mean=-0.45, SD=0.36)

Figure 1. Null distribution plot and summary statistics for the negative control sets evaluated. Estimates below the gray dashed lines have an uncalibrated p-value <0.05. Estimates within the orange areas have a calibrated p-value <0.05.

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