Evaluating the Comparative Self-Controlled Case Series Method

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BACKGROUND

- New user cohort design evaluates the risk of health outcomes in a treatment group relative to a comparator group; selection effects drive treatment assignment and are mitigated by propensity score methods using observed covariates[1,2]
- Self-controlled case series (SCCS) design evaluates the risk of health outcomes in cases only by comparing event rates in unexposed and exposed time; implicitly controls for fixed and unobserved covariates[1,3,4]
- The novel comparative self-controlled case series (CSSCS) combines advantages of new user cohort and SCCS designs; treatment and comparator groups balanced on observed covariates, estimate treatment and comparator effects in balanced groups while controlling for unobserved covariates

OBJECTIVES

- Design a statistically efficient, low residual bias method for estimating treatment effect that controls for observed and unobserved covariates
- Compare direction, magnitude, and precision of CSCCS effect estimates relative to those generated by new user cohort design
- Evaluate CSCCS with model calibration[5] and discriminative performance metrics[1,2,4]

METHODS

- Preliminary CSCCS approach is demonstrated by comparing celecoxib and non-selective non-steroidal anti-inflammatory drugs (nsNSAIDs) for risk of myocardial infarction (MI) and gastrointestinal hemorrhage (GI bleed) in osteoarthritis patients
- Method executed against Truven MarketScan Multi-State Medicaid (MDCD) and Truven MarketScan Medicare Supplemental Beneficiaries (MDCR)
- The SCCS design is extended to the treatment vs. comparator framework by executing parallel SCCS analyses on propensity score balanced incident new user cohorts; relative outcome risk is the ratio of rate ratios (RRR)[6]

RESULTS

- Many fewer patients needed for CSCCS than new user cohort design (Table 1) to achieve comparable or improved precision
- average uncertainty of effect across all outcomes in CSCCS is 10.6% lower than new user cohort in MDCD; 5.6% lower in MDCR

Table 1.Incident exposure and outcome counts for new user cohort and CSCCS designs comparing celecoxib vs. nsNAIDs on MI and GI bleed

			Celecoxib			nsNAIDs	
DB	Design	Exposed, n	MI, n(e)	Gib, n(e)	Exposed	MI, n(e)	Gib, n(e)
MDCD							
	New User Cohort	13737	19(19)	32(32)	13737	11(11)	21(21)
	SCCS, MI	260	260(402)	-	252	252(428)	-
	SCCS, Gib	327	-	327(508)	297	-	297(447)
MDCR							
	New User Cohort	57547	115(115)	155(155)	57547	69(69)	153(153)
	SCCS, MI	1435	1435(2651)	-	1460	1460(2665)	-
	SCCS, Gib	1853	-	1853(2999)	1744	-	1744(2825)

*DB=database, SCCS=self-controlled case series, CSSCS=comparative self-Controlled case series, nsNSAID=non-selective NSAID, GIb=gastrointestinal bleed, MI=myocardial infarction, n(e)=patient count(event count)

- Inconsistent results between new user cohort and CSCCS designs for 3 of 4 test cases (MI and GI bleed in MDCD, MI in MDCR) (Table 2, Figure 1a, 2a)

RESULTS, cont'd.

- New user cohort and CSSC results consistent for GI bleed on MDCR (Table 2, Figure 2a)
- RRR<1 does not imply celecoxib reduces risk of outcome
- CSCCS and new user cohort comparably negatively biased (Figure 1b, 2b)
- CSCCS null mean = -0.18 (SD=0.22); new user cohort null mean = -0.20 (SD=0.15)
- Coverage probability: MDCD 64%, MDCR 44%

Table 2. Effect estimates of celecoxib vs. nsNSAIDs on MI and GI bleed from comparative new user cohort and CSSCS designs on Truven Medicaid and Medicare databases

DB	Design	Measure	MI β	95% CI lb	95% CI ub	GI bleed β	95% CI lb	95% CI ub
MDCD								
	New User Cohort	RR	1.50	0.54	4.47	1.21	0.60	2.50
	SCCS, celecoxib	IRR	1.27	0.92	1.73	1.63	1.20	2.19
	SCCS, nsNSAIDs	IRR	1.48	1.05	2.06	1.89	1.26	2.75
	CSCCS	RRR	0.86	0.55	1.35	0.86	0.54	1.39
MDCR								
	New User Cohort	RR	0.89	0.61	1.31	0.58	0.43	0.77
	SCCS, celecoxib	IRR	1.49	1.30	1.71	1.35	1.18	1.54
	SCCS, nsNSAIDs	IRR	1.43	1.20	1.69	2.55	2.22	2.91
	CSCCS	RRR	1.05	0.84	1.30	0.53	0.44	0.64

*DB=database, SCCS=Self-Controlled Case Series, CSSCS=Comparative Self-Controlled Case Series, RR=Relative Risk, IRR=Incident Rate Ratio, RRR=Rate of Rate Ratios, SCCS = self-controlled case series, CSCCS = comparative self-controlled case series, nsNSAID = non-selective NSAID, GI Bleed = Gastrointestinal Bleed, MI = Myocardial Infarction

Figure 1a. Effect estimates of new user cohort and CSCCS designs in MDCD

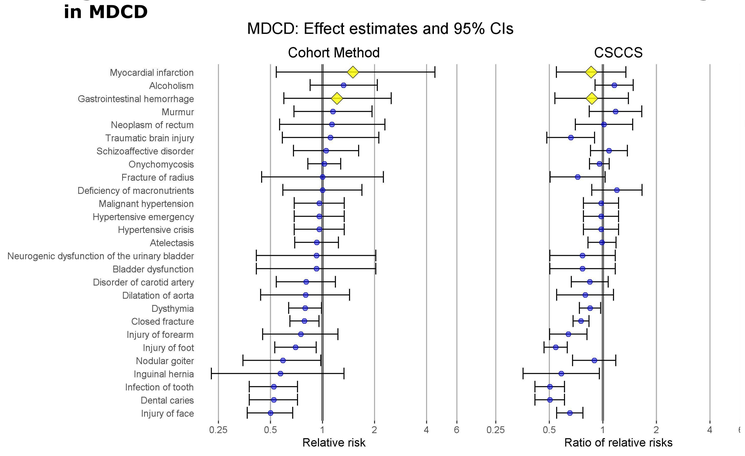


Figure 1b. Bias in new user cohort and CSCCS designs in MDCD

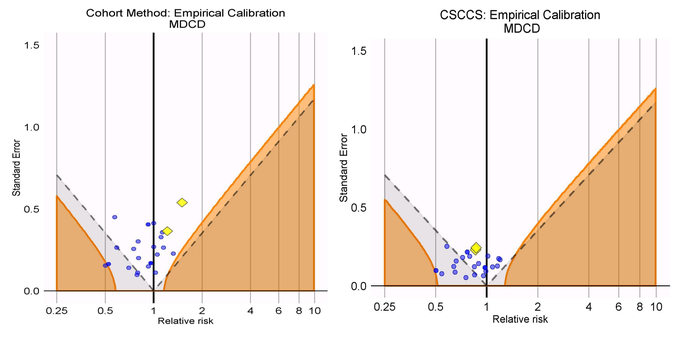


Figure 2a. Effect estimates of new user cohort and CSCCS designs in MDCR

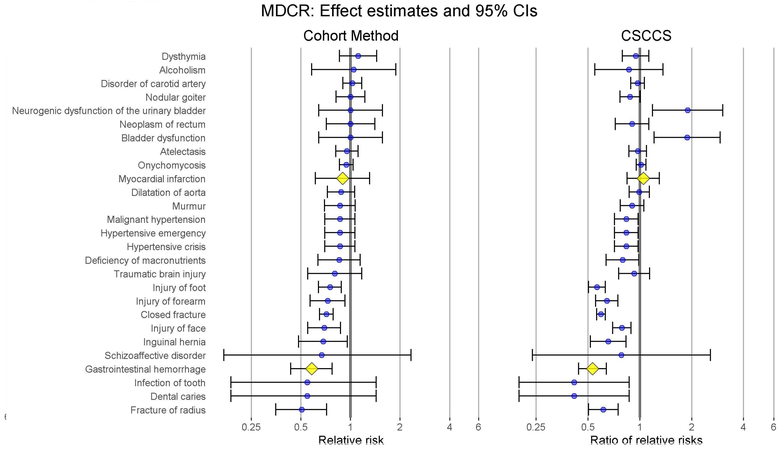
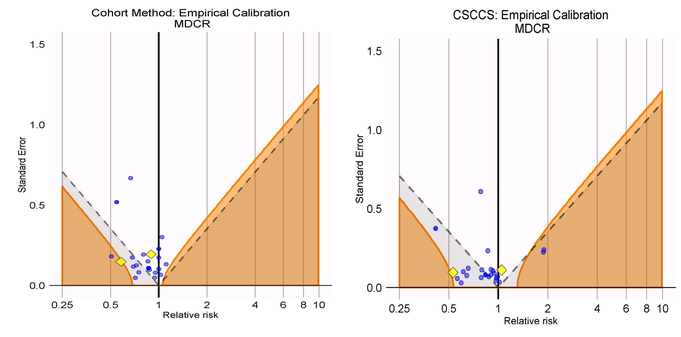


Figure 2b. Bias in new user cohort at CSCCS designs in MDCR



CONCLUSION

- Preliminary results are inconclusive; unable to conclude that CSCCS effect estimates are comparable to those from new user cohort design
- Execution across many drug-outcome pairs of known positive and negative signal across a database network necessary for full evaluation
- Statistical efficient advantages for estimating comparative treatment effects on low-prevalence outcomes

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CONFLICT OF INTEREST

- JW, MS, EV, and PR are full time employees of Janssen Research and Development, a unit of Johnson and Johnson. The work of this study was part of their employment. They hold pension rights from the company and own stock and stock options.