

Comparing Self-Controlled Case Series and Cohort Designs for Estimating Pancreatitis Risk Associated with GLP-1 Receptor Agonists: A Monte Carlo Simulation Study

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Background/Objectives

Background

- Prior studies of GLP-1 therapies and acute pancreatitis have shown mixed results; pancreatitis remains an uncommon event
- Pancreatitis typically occurs early after therapy initiation
- Unmeasured confounding is a major source of bias in observational studies

SCCS design:

- Within-person design for evaluating time-varying exposures and uncommon outcomes
- Each patient serves as their own control
- Controls for fixed, time-invariant measured and unmeasured confounders
- Efficient when exposure periods are short relative to the observation period

Study objective:

- To compare SCCS with cohort methods (PSM and IPW) for estimating associations between time-varying exposures and uncommon outcomes, using GLP-1-associated pancreatitis as a use case

Methods

Design: Monte Carlo simulation (72 months; 500,000 patients, 500 replications) comparing SCCS vs cohort methods (PSM, IPW) for pancreatitis risk after GLP-1 initiation (true IRR = 1.10)

Data generation: Baseline covariates and latent confounding fixed across replications; GLP-1 initiation (exposure) and pancreatitis events (outcome) simulated using patient characteristics and piecewise declining baseline hazard

Scenarios:

- A: time-invariant confounding
- B: + unmeasured time-varying confounding
- C: + measured time-varying confounder adjustment

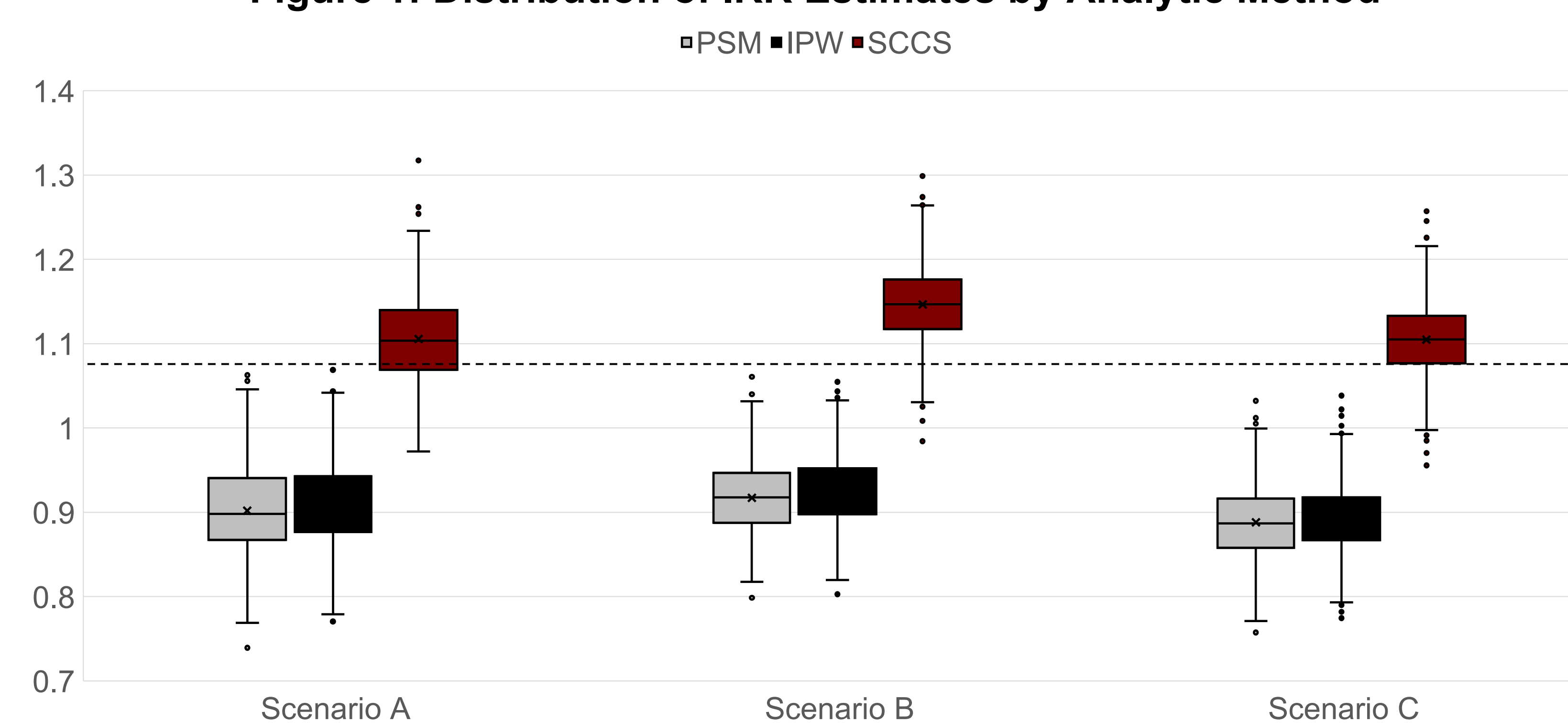
Risk windows: Overall, 1–6, 7–24, ≥25 months since initiation

Analyses:

- SCCS: fixed-effects Poisson models with calendar-time adjustment
 - PSM: 1:1 nearest-neighbor matching using a 0.02 PS caliper
 - IPW: stabilized inverse probability weights, trimmed at 1st/99th percentiles
 - PSM/IPW outcomes: Poisson models adjusted for baseline covariates
- Statistical analysis:** Analyses conducted in Stata MP (StataCorp LLC, College Station, TX, USA). Primary performance metrics were bias, Root Mean Square Error (RMSE), and 95% CI coverage.

Results

Figure 1: Distribution of IRR Estimates by Analytic Method



Boxplots show estimated IRRs across 500 replications. The dashed horizontal line indicates the true IRR of 1.10.

Table 1: Covariate Balance Before and After PSM/IPW

Scenario	Method	Mean SMD	Max SMD	% Covariates with SMD ≥ 0.10
A	Pre-adjustment	0.289	1.654	50.0
A	PSM	0.028	0.081	0
A	IPW	0.020	0.048	0
B	Pre-adjustment	0.292	1.743	50.0
B	PSM	0.028	0.080	0
B	IPW	0.018	0.047	0
C	Pre-adjustment	0.308	1.744	55.6
C	PSM	0.022	0.063	0
C	IPW	0.027	0.069	0

Balance assessed using standardized mean differences; adequate balance defined as |SMD| < 0.10. Scenario C includes the measured time-varying confounder at index.

Table 2: Overall Performance by Scenario and Method

Scenario	Method	Mean IRR	Bias in log(IRR)	RMSE	95% CI Coverage
A	SCCS	1.106	0.004	0.049	94.0%
A	PSM	0.902	-0.200	0.208	5.2%
A	IPW	0.910	-0.191	0.198	4.8%
B	SCCS	1.146	0.041	0.057	83.0%
B	PSM	0.917	-0.183	0.189	3.6%
B	IPW	0.926	-0.173	0.179	3.2%
C	SCCS	1.105	0.004	0.040	95.6%
C	PSM	0.888	-0.215	0.221	1.4%
C	IPW	0.893	-0.209	0.214	1.0%

True IRR = 1.10. Bias, RMSE, and coverage evaluated on the log-IRR scale.

Note: Simulation coding was refined after abstract submission to improve exposure-window alignment, covariate balance, and time-varying confounder adjustment; numeric results may differ from the submitted abstract, but conclusions are unchanged.

Table 3: Mean IRR by Risk Window

Scenario	Method	Overall	1-6 Months	7-24 Months	≥25 Months
A	SCCS	1.106	1.104	1.105	1.109
A	PSM	0.902	0.941	0.940	0.939
A	IPW	0.910	0.961	0.958	0.952
B	SCCS	1.146	1.223	1.103	1.113
B	PSM	0.917	1.044	0.940	0.931
B	IPW	0.926	1.054	0.950	0.947
C	SCCS	1.105	1.104	1.103	1.111
C	PSM	0.888	0.939	0.931	0.929
C	IPW	0.893	0.961	0.942	0.941

Balance assessed using standardized mean differences; adequate balance defined as |SMD| < 0.10. Scenario C includes the measured time-varying confounder at index.

Key Findings

- SCCS accurately recovered the true IRR under time-invariant confounding: IRR 1.106 vs true IRR 1.10.
- Unmeasured time-varying confounding biased SCCS upward, especially during 1–6 months after initiation.
- Adjusting for the measured time-varying confounder restored SCCS performance: IRR 1.105; 95% CI coverage 95.6%.
- PSM and IPW remained attenuated across scenarios, with poor empirical CI coverage.

Conclusion

SCCS provided substantially less biased and better-calibrated estimates than PSM/IPW for uncommon event outcomes when confounding was time-invariant or measured over time. However, SCCS remained vulnerable to unmeasured time-varying confounding.

References and Supplemental Materials

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