often intended to be used permanently (statins, insulin, and thyroxin) and three outcomes (retinal detachment, wrist fracture, and ischemic stroke), where the true causal relations were expected to be null. Controls were matched on age, gender, and index date, and exposure was ascertained at 2-month intervals over the preceding 12 months.

**Results:** For retinal detachment, the case–crossover OR was 1.60 (95% confidence interval (CI): 1.42–1.80) for statins, 1.40 (CI: 1.02–1.92) for thyroxin, and 1.53 (CI: 1.04–2.24) for insulin. Estimates for the control population were nearly identical, leading to near-null case–time–control estimates for the three drug classes. For the wrist fracture and stroke outcomes, case–time–control ORs were consistently above unity (1.09, 1.51, and 1.15 for wrist fracture, and 2.27, 1.87, and 1.67 for stroke), suggesting significant residual bias.

**Conclusions:** In case–crossover studies of drugs, permanent users confer a moderate bias upward, which is partly remedied by using a control group. Additional research is needed to identify the optimal strategy for selecting this control group.

## 3. Controlling for Frailty in Cancer Comparative Effectiveness Studies of Older Adults

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**Background:** Older cancer patients often have multiple comorbidities and functional deficits, which likely impact treatment decisions and outcomes. Using databases that lack functional information may lead to biased estimates of real world comparative effectiveness (CE).

**Objectives:** The aim of this study was to evaluate the impact of controlling for markers of frailty in a CE study of adjuvant chemotherapy for non-metastatic rectal cancer.

**Methods:** We identified a cohort of 1404 older (65 + years) non-metastatic rectal cancer patients from 2004 to 2009 using the Surveillance, Epidemiology and End Results-Medicare data, who underwent neoadjuvant therapy and surgery and survived 120 days. Using propensity score methods, we evaluated the CE of adjuvant chemotherapy versus observation on mortality, incrementally adding (i) basic confounders (demographics, cancer features, neoadjuvant treatment, comorbidities); (ii) 17 claims-based frailty indicators (e.g., oxygen use, sepsis); and (iii) 30-day post-surgical hospitalization. Among those receiving adjuvant chemotherapy, we evaluated the CE of adjuvant oxaliplatin versus 5-flurouracil (5-FU) on mortality using the same confounder sets. Standardized mortality ratio weighted Cox proportional hazards models were used to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals.

**Results:** In total, 738 patients (52%) received adjuvant chemotherapy; 52% received oxaliplatin. Overall mortality was 9.8 per 100 person-years (mean follow-up: 3 years). The crude HR for adjuvant chemotherapy versus observation and mortality was 0.68 (0.56, 0.83); after basic confounder adjustment, the estimate was stable (aHR = 0.68 (0.54, 0.85)). Adjustment for frailty markers attenuated the aHR (0.71 (0.56, 0.90)), and inclusion of post-surgical hospitalization led to further attenuation (aHR = 0.75 (0.59, 0.95)). Among patients receiving adjuvant chemotherapy, the crude HR comparing oxaliplatin versus 5-FU on mortality was 1.0 (0.72, 1.39); adjustment for basic confounders and additional frailty markers produced similar results.

**Conclusions:** Our results suggest that adjustment for markers of frailty and post-surgical hospitalization may improve the validity of cancer CE studies using non-active comparators.

## 4. Impact of Violations of the Assumptions of the Self-controlled Case Series Design in Pharmacoepidemiological Studies: An Example of Antidepressants Use and the Risk of Hip Fracture

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**Background:** The self-controlled case-series (SCCS) design has been applied to control for time-fixed (un)




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measured confounding in pharmacoepidemiological studies. Although previous studies acknowledged that violations of the key SCCS assumptions lead to biased exposure effects, little is known about the impact of the violations in empirical studies.

**Objectives:** The aim of this study was to evaluate the impact of various levels of violation of assumptions of the SCCS design and different definitions of observation/risk periods in a study of antidepressants use and the risk of hip/femur fracture (HF).

**Methods:** Information on adults with an HF who used antidepressants at any time during the observation period 2001–2009 was extracted from the UK THIN (6632 cases) and the Dutch Mondriaan (136 cases) databases. The incidence rate ratio (IRR) using this design was defined as the rate of events during exposed periods and during all other observed periods. The IRR of HF was estimated using conditional Poisson regression.

**Results:** The IRRs appeared extremely biased when all subjects were censored at their first/last HF or when the analysis was restricted to subjects experiencing hip fracture after initiating antidepressant use. For example, in THIN, IRRs for >365 days of exposure were 1.26 [1.13–1.42] when complete follow-up was considered and 40.1 [32.2–49.9] when censoring was at the first event. However, modest censoring at the first or last event (up to 20%) had a minor impact on the IRRs. Additionally, results were consistent when including subjects who were exposed at the start of follow-up and for different risk period definitions.

**Conclusions:** The SCCS design is sensitive to violations of the assumptions and yields apparently biased estimates when a significant number of subjects are censored at the event or when the analysis is restricted subjects who experienced hip fracture after initiating antidepressants. The performance of this design may differ across studies and across databases. Therefore, in each SCCS study, correct specification of the SCCS design should be carefully assessed and reported.

## 5. Probabilistic Multiple-Bias Analyses of Observational Studies on Narcolepsy Following Vaccination with GlaxoSmithKline's Inactivated Adjuvanted (AS03) A/H1N1pdm09 Pandemic Influenza Vaccine

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**Background:** An increase in the incidence of narcolepsy was first observed in Finland and Sweden towards the end of the 2009 H1N1 influenza pandemic. Preliminary epidemiological studies suggested a temporal association with GlaxoSmithKline's (GSK) Dresden-manufactured A/H1N1pdm09 vaccine, leading to a number of additional studies across Europe. Given the public health urgency to investigate the signal, these studies used readily available retrospective data from various sources. The potential for bias in such settings was generally acknowledged. Although several health authorities advocate quantifying the potential impact of biases, this was not systematically carried out in any of the narcolepsy studies.

**Objectives:** The aim of this study was to quantify the impact of a cascade of potential bias and confounding on the association between GSK's A/H1N1pdm09 vaccine and narcolepsy.

**Methods:** We apply bias-level multiple-bias analyses to two published studies on the association of the vaccine with narcolepsy: a paediatric cohort study from Finland and a case–control study from France. In particular, we developed Monte Carlo simulation models based on formal models of bias and confounding to evaluate a potential cascade of biases, including confounding by indication and natural H1N1 influenza infection, selection bias, and disease and exposure misclassification. All bias parameters were evidence based to the extent possible.

**Results:** Given the assumptions made and when accounting for all potential sources of bias, the rate ratio of 13.78 (95%CI: 5.72, 28.11) in the Finnish study was reduced to 4.88 (2.5th to 97.5th percentile: 1.91, 10.84) and the odds ratio of 5.43 (95%CI: 2.6, 10.08) in the French study to 1.93 (2.5th to 97.5th percentile: 0.78, 4.04).

**Conclusions:** The observed association between GSK's A/H1N1pdm09 vaccine and narcolepsy persists in a multiple-bias sensitivity analysis in the Finnish study but not in the French study. We advocate the use of multiple-bias analyses to better understand the robustness of study findings, and to increase accuracy of data used to inform subsequent benefit-risk decision.