The value of negative controls for the self-controlled case series design

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The purpose of OHDSI

- To generate **reliable evidence** for the benefit of patients, providers, researchers, health care systems, industry, and government agencies

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Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection

Jeffrey C. Kwong, M.D., Kevin L. Schwartz, M.D., Michael A. Campitelli, M.P.H., Hannah Chung, M.P.H., Natasha S. Crowcroft, M.D., Timothy Karnauchow, Ph.D., Kevin Katz, M.D., Dennis T. Ko, M.D., Allison J. McGeer, M.D., Dayre McNally, M.D., Ph.D., David C. Richardson, M.D., Laura C. Rosella, Ph.D., M.H.Sc., Andrew Simor, M.D., Marek Smieja, M.D., Ph.D., George Zahariadis, M.D., and Jonathan B. Gubbay, M.B., B.S., M.Med.Sc.

RESULTS

We identified 364 hospitalizations for acute myocardial infarction that occurred within 1 year before and 1 year after a positive test result for influenza. Of these, 20 (20.0 admissions per week) occurred during the risk interval and 344 (3.3 admissions per week) occurred during the control interval. The incidence ratio of an admission for acute myocardial infarction during the risk interval as compared with the control interval was 6.05 (95% confidence interval [CI], 3.86 to 9.50). No increased incidence was observed after day 7. Incidence ratios for acute myocardial infarction within 7 days after detection of influenza B, influenza A, respiratory syncytial virus, and other viruses were 10.11 (95% CI, 4.37 to 23.38), 5.17 (95% CI, 3.02 to 8.84), 3.51 (95% CI, 1.11 to 11.12), and 2.77 (95% CI, 1.23 to 6.24), respectively.

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IRR: 6.05 (95% CI 3.86, 9.50)

Population-level effect estimation

- Methods for identifying causal relationships
  - Attempts to estimate unbiased, average effect of an exposure on an outcome
- Compares outcome occurrence between comparable populations
- Causal effect identification criteria
  - Consistency
  - Positivity
  - Exchangeability

Self-controlled case series design (SCCS)

- Compares outcomes *within* persons during time periods of differing exposure status
- Consistency:
  - Time-stamped risk intervals and outcome events
- Positivity:
  - Patients must have both exposed time and unexposed time
- Exchangeability:
  - Unexposed time = counterfactual approximation

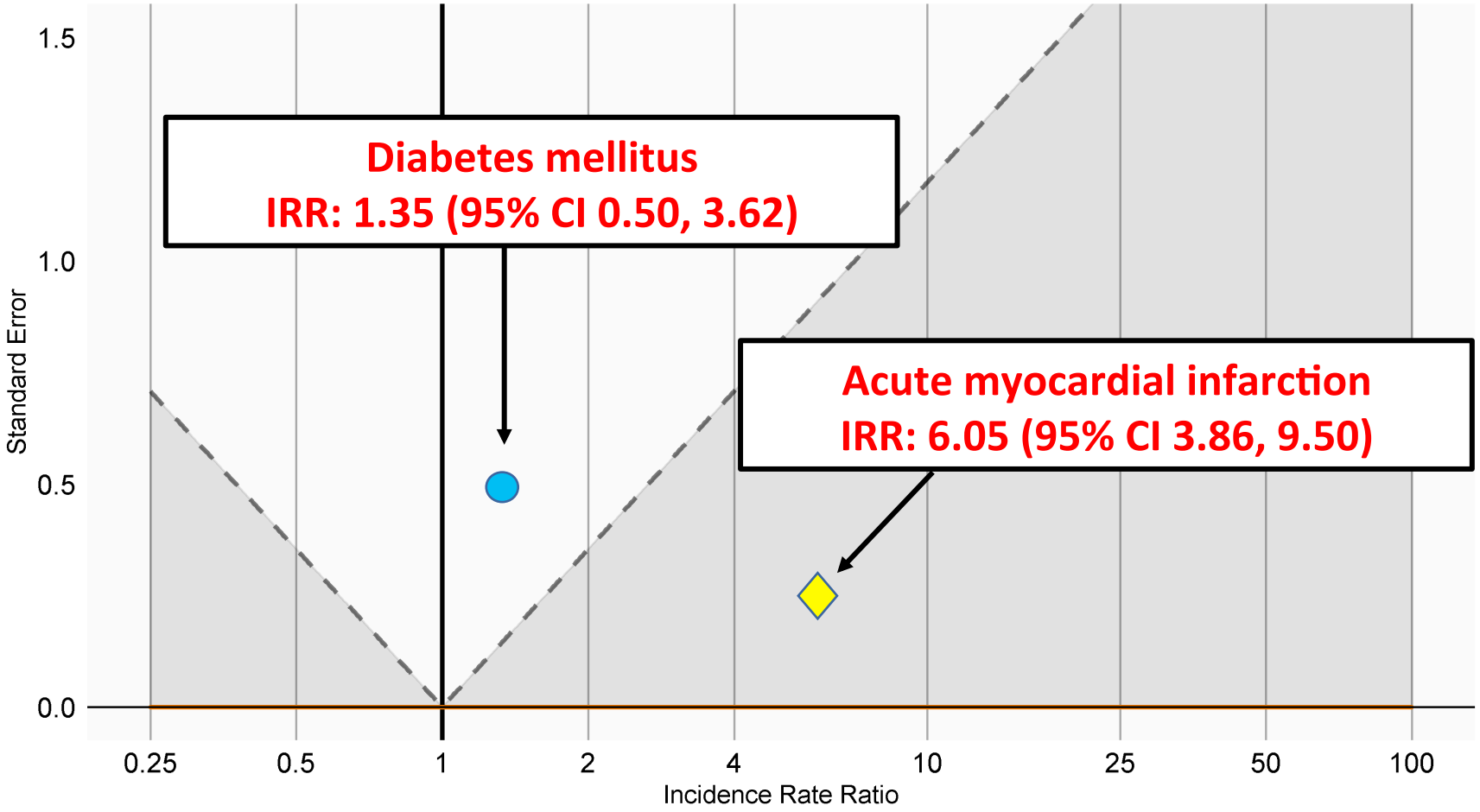
Replication study specification

- Exposure (influenza)
  - Dx code, +lab result
  - OP, any visit
  - No influenza past 60 days, no outcome during visit
- Risk interval
  - Influenza visit end date +1 day to visit start date +7 days
- Outcomes (first MI + 31 negative control outcomes)
  - IP, any visit
  - Primary position
- Analytic variants
  - Simple SCCS
  - Pre-exposure window
  - Age and seasonality adjustment
  - Event-dependent observation period correction

Negative control outcomes

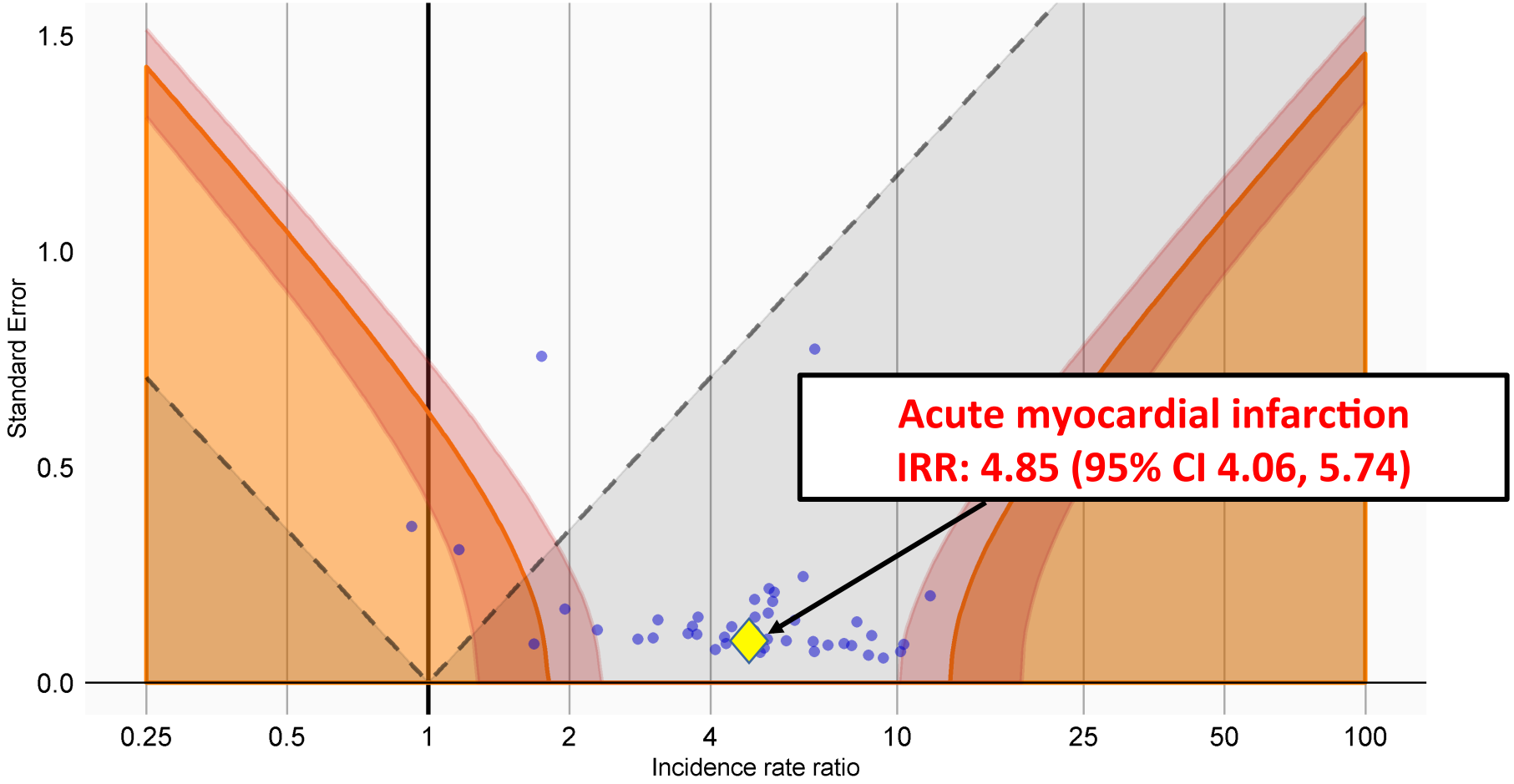
Lung cancer	Inflammatory disorder of digestive system
HIV	Infectious disease of genitourinary system
Depression	Infectious disease of abdomen
Ingrowing nail	Functional finding of gastrointestinal tract
Soft tissue lesion	Edema
Skin or mucosa lesion	Diabetes mellitus
Organic mental disorder	Chronic inflammatory disorder
Observation of colon	Chronic disease of genitourinary system
Neoplastic disease	Bleeding
Musculoskeletal and connective tissue disorder	Acute genitourinary disorder
Mass of trunk	Abscess
Mass of respiratory structure	Schizophrenia
Mass of lymphoreticular structure	Bipolar disorder
Lymphoproliferative disorder	Substance abuse
Lesion of brain	Traumatic injury
Inflammatory disorder of extremity	

NEJM results



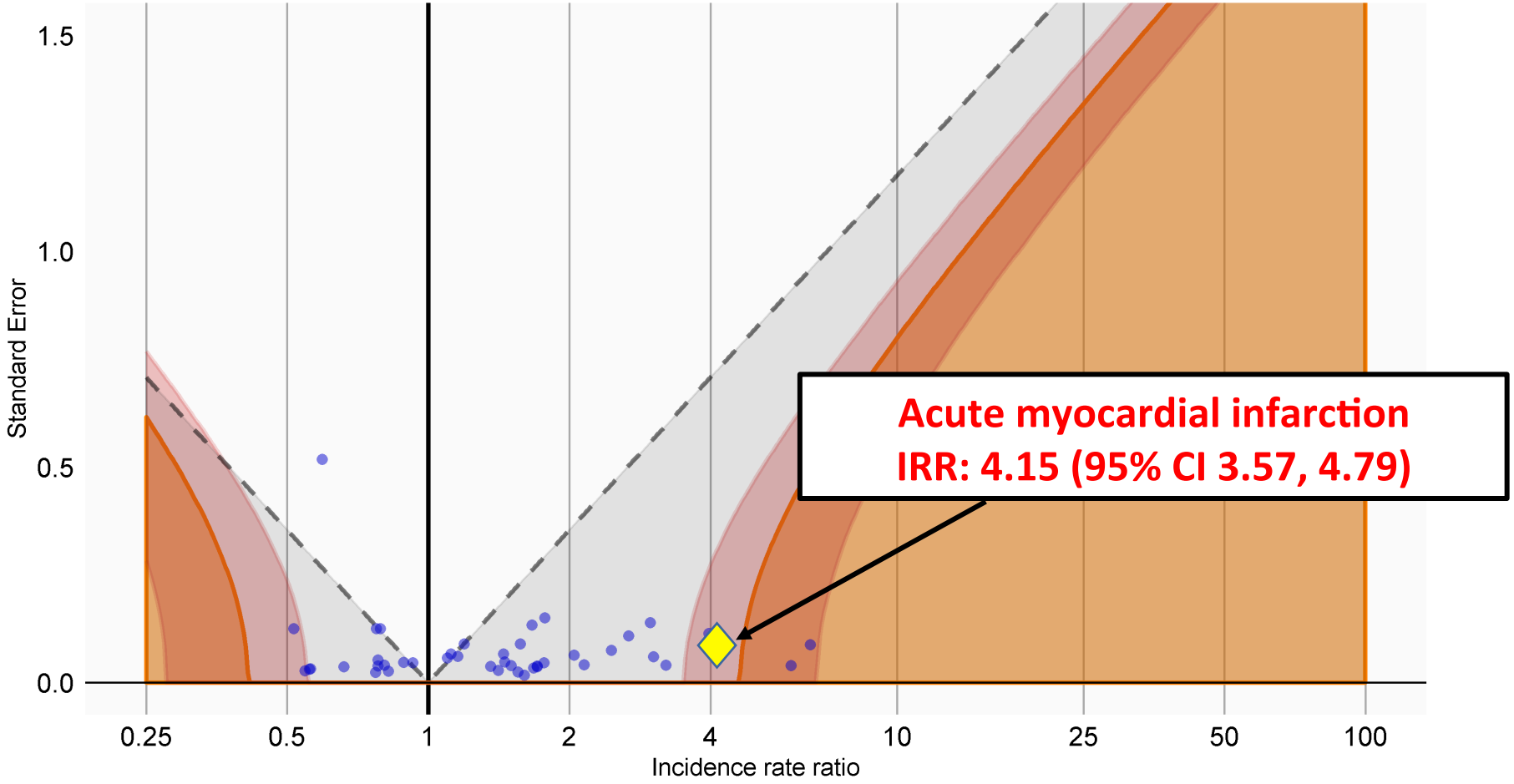
Replication results

Influenza diagnosis code (any visit), outcome (IP)



Replication results

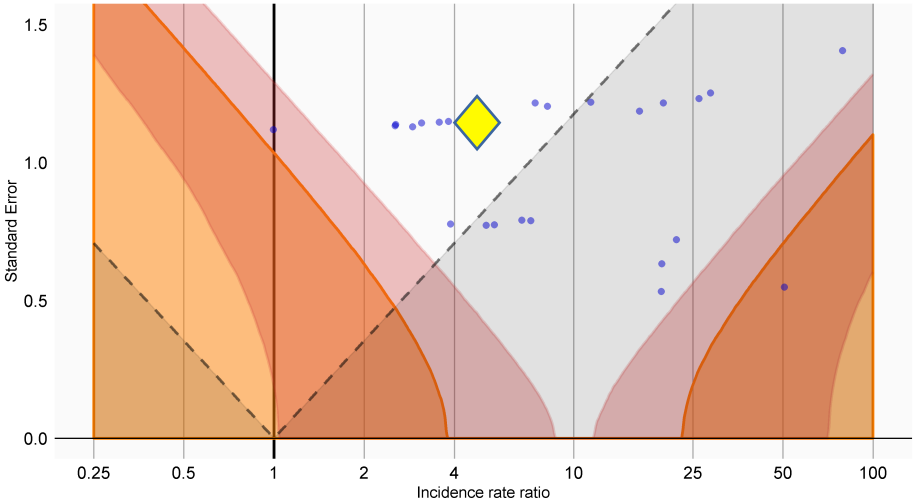
Influenza diagnosis code (any visit), outcome (any visit)

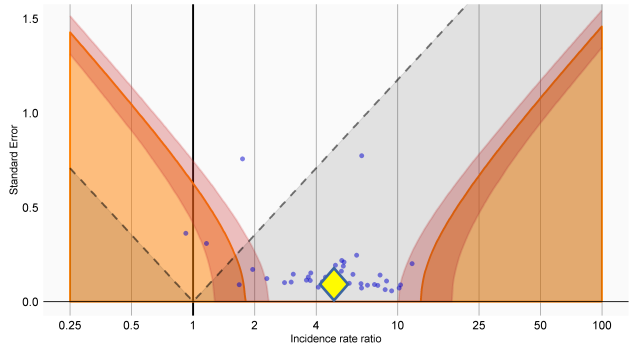


Replication results

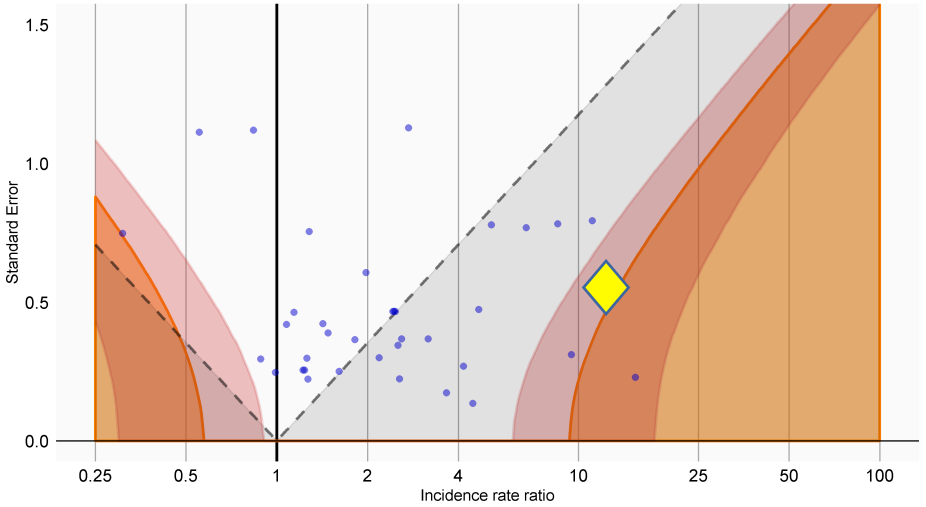
Influenza +lab result (any visit)

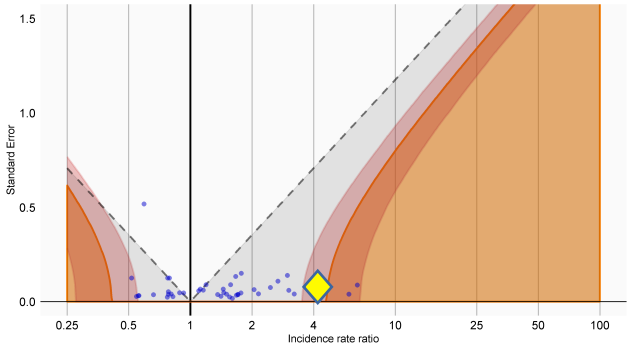
Outcome (IP)





Outcome (any visit)





Discussion

- **Negative controls are an important diagnostic to understand the validity of study findings**
- Negative controls **CAN**:
  - Identify problems, quantify error, test hypotheses, and compare alternative methods
- Negative controls **CANNOT**:
  - Solve the problem they help identify, generate hypotheses

Thank you!

- Contact:
  - Jamie Weaver: jweave17@its.jnj.com
- Collaborators:
  - Patrick Ryan (Janssen, Columbia, OHDSI)
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  - Jeff Kwong et al. (ICES)