EPID 765

Lesson 11: Validation Studies

1

Measurement error

- Validity depends on an accurate exposure, outcome, and covariate data
- Poorly measured data in pharmacoepidemiolgy studies may lead to misclassification of:
  - Drug exposure(s)
  - Disease/outcomes
  - Covariates
- Measurement error and misclassification (categorical variables) lead to information bias

2

PE: Mostly Misclassification

- Misclassification most problematic for exposure and outcome
- Effect of misclassification of covariates bound by confounding effect
  - Residual confounding
  - Cave: differential (e.g., look-back periods)
- Some misclassification is inevitable (cave: do not throw out the baby with the bathwater)
- Effect generally dependent on whether misclassification **differential** or **non-differential**

3

Non-differential misclassification

- When exposure (outcome) classification is incorrect for same proportion of subjects with and without the outcome (the exposure groups compared) misclassification is non-differential
- Given plausible assumptions, non-differential misclassification will tend to result in underestimation of true relative risk
- Bias towards the null
  - A "true" relative risk of 3.0 might become 2.5
  - A "true" relative risk of 0.5 might become 0.8

4

Differential misclassification

- Categorization of exposure or outcome depends on each other
  - E.g., in CC controls may underreport their past use of a medication to a greater extent than cases
  - E.g., in Cohort outcomes evaluated differently for exposed versus non-exposed individuals
- Differential misclassification can results in an overestimate or underestimate of the true RR
- Bias in any direction, including beyond the null!

5

Validation 2 x 2 table

	Disease +	Disease -	
Test +	a True Positive	b False Positive	a + b
Test -	c False Negative	d True Negative	c + d
	a + c	b + d	

Claims data (algorithms) can be conceptualized as a "test" for underlying actual treatment or disease outcome

6

Clinical Epidemiology: Se and Sp vs. PPV and NPV

- Sensitivity and specificity are mostly inherent characteristics of the test
  - Transportable, but:
  - Still dependent on database setting
  - Expected to vary over calendar time
- PPV and NPV depend on characteristics of test and population being tested
  - Not transportable!

7

PE Misclassification Examples

- First dispensed Rx not first exposure
  - Evidence for sample use (Li et al Med Care 2014)
  - Evidence for use (Young et al PDS 2016)
- Covariates
  - Short lookback -> low sensitivity (e.g., hysterectomy, cancer)
  - Varying look-back periods (Brunelli et al PDS 2013)
  - Note: also affects exclusion, i.e., study design!
- Outcomes
  - Diagnostic suspicion
  - Routine testing (e.g., liver enzymes)

8

Example: Exposure Validation

- Purpose: validate procedure codes from Medicare claims to identify use of specific chemotherapeutics
- Study goal: examine dissemination of new chemotherapy treatments
- Gold standard: abstraction of medical records and physician confirmation of treatment received
- Linkage: Unique cancer registry number allowed for direct linkage of POC with claims
- Quality of abstraction: re-abstraction and confirmation of data by cancer registries

9

Identifying Specific Chemotherapeutic Agents in Medicare Data

A Validation Study

Jennifer L. Lund, MSPH, Til Stürmer, MD, PhD,* Linda C. Harlan, PhD,† Hanna K. Sanoff, MD, MPH,‡ Robert S. Sandler, MD, MPH,§ Maurice Alan Brookhart, PhD,* and Joan L. Warren, PhD†*

TABLE 3. Comparison of Specific Chemotherapeutic Agents Identified by SEER POC Data and Medicare Claims During the 6-month Postdiagnosis Period for Selected Cancer Sites and Years*

	Source Reporting Receipt of Specific Agent							
	POC + Yes, Med + Yes	POC + No, Med + No	POC + Yes, Med + No	POC + No, Med + Yes	κ (%) (95% CI)	Se (%) (95% CI)	Sp (%) (95% CI)†	PPV (%) (95% CI)†	NPV (%) (95% CI)
Breast (2000 and 2005)									
Cyclophosphamide	39	249	13	4	83 (73, 92)	75 (61, 86)	98 (96, 100)	91 (78, 97)	95 (92, 97)
Doxorubicin	27	266	10	3	78 (67, 90)	73 (56, 86)	99 (97, 100)	90 (73, 98)	96 (93, 98)
Colorectal (2000)									
5-FU	87	62	15	5	76 (66, 86)	85 (77, 92)	93 (83, 98)	95 (88, 98)	81 (70, 89)
Colorectal (2005)									
5-FU	114	192	14	11	83 (77, 89)	89 (82, 94)	95 (91, 97)	91 (85, 96)	93 (89, 96)
Capecitabine	22	279	25	5	55 (39, 70)	47 (32, 62)	98 (96, 99)	81 (62, 94)	92 (88, 95)
Oxaliplatin	51	254	17	9	73 (63, 82)	75 (63, 85)	97 (94, 98)	85 (72, 93)	94 (90, 96)
Non-small–cell lung (2005)									
Carboplatin	77	112	4	1	95 (90, 99)	95 (88, 99)	99 (95, 100)	99 (93, 100)	97 (91, 99)
Paclitaxel	61	123	7	2	90 (83, 96)	90 (80, 96)	98 (94, 100)	97 (89, 100)	95 (89, 98)
Ovary (2002)									
Carboplatin	110	35	11	10	68 (56, 81)	91 (84, 95)	78 (63, 89)	92 (85, 96)	76 (61, 87)
Paclitaxel	100	39	13	14	62 (49, 75)	88 (81, 94)	74 (60, 85)	88 (80, 93)	75 (61, 86)

*Individuals lacking treatment data for the specific agent of interest were excluded from analysis.
†Exact binomial 95% CIs are rounded to the nearest digit. Therefore, none of the upper limits is exactly 100%.
5-FU indicates 5-fluorouracil; CI, confidence interval; Med, Medicare; NPV, negative predictive value; POC, Patterns of Care; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

Medical Care Med Care. 2013 May;51(5):e27-34.

10

Example: Outcome Validation

- Purpose: validate algorithm from Medicaid claims to identify acute myocardial infarction
- Study goal: update and improve previously published algorithm based on last century data!
- Gold standard: Endpoint adjudication in HIV cohort study
- Linkage: social security number, first, and last name (note: ease to obtain informed consent!)
- Quality of abstraction: usually excellent in typical cohort studies

11

Validation of Medicaid Claims-based Diagnosis of Myocardial Infarction Using an HIV Clinical Cohort

Emily S. Brouwer, MPH, PharmD, PhD,†‡ Sonia Napravnik, MSPH, PhD,*† Joseph J. Eron, Jr, MD,† Ross J. Simpson, Jr, MD, PhD,*§ M. Alan Brookhart, PhD,* Brant Stalzer, BS,† Michael Vinikoor, MD,† Michelle Floris-Moore, MD, MS,† and Til Stürmer, MD, PhD*‖*

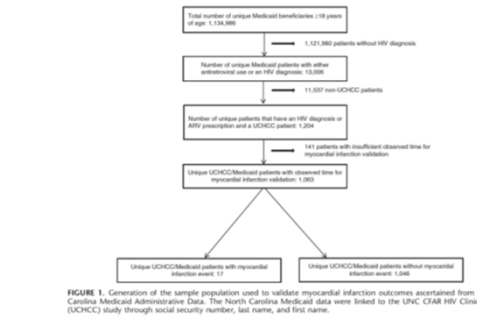


FIGURE 1. Generation of the sample population used to validate myocardial infarction outcomes ascertained from the North Carolina Medicaid Administrative Data. The North Carolina Medicaid data were linked to the UNC CFAR HIV Clinical Cohort (UCHCC) study through social security number, last name, and first name.

12

External Adjustment for Confounding

- Sensitivity analyses for single confounder
  - If possible, estimate effect of unmeasured confounder on treatment decision in validation study
  - Get estimate of the (independent or adjusted) effect of the unmeasured confounder from the literature
  - "Adjust" main study estimate for unmeasured confounding using standard formulas (Bross, J Chron Dis 66)
- Sensitivity analyses for multiple confounders
  - Separate estimates of the above for multiple confounders
  - Weighted average of expected confounding
  - Overall direction and magnitude of confounding

13

Independent Effect of BMI on Initial Insulin: External Validation Study (EMR Data)

Table 4—*Effect of BMI on channeling between initiating glargine versus initiating NPH: external validation studies*

	Glargine	NPH
MGH		
n	574	412
BMI (kg/m^2), mean ± SD*	32.7 ± 7.53	32.4 ± 8.43
BMI (kg/m^2), *n* (%)		
<19	4 (0.7)	8 (1.9)
19 to <25	77 (13.4)	67 (16.3)
25 to <30	150 (26.1)	105 (25.5)
30 to <35	146 (25.4)	104 (25.2)
35 to <40	114 (19.9)	64 (15.5)
40 to <45	45 (7.8)	36 (8.7)
≥45	38 (6.6)	28 (6.8)

14

Adjusting for Unmeasured Confounders in Pharmacoepidemiologic Claims Data Using External Information

The Example of COX2 Inhibitors and Myocardial Infarction

	No.	High School Education or Less %	Income ≤$20,000 %	Obese* %	Aspirin User %	Smoking Status: Current %	Former %	Never %
Any COX2 inhibitor†	872	69	48	24	9	8	45	46
Celecoxib only	562	69	46	24	8	9	45	46
Rofecoxib only	244	66	48	19	11	7	49	44
Nonselective NSAIDs only	1302	72	56	24	10	10	51	40
Ibuprofen	281	73	58	23	14	15	50	16
Naproxen	238	74	55	20	8	8	54	38
Other NSAIDs only	677	71	55	25	8	9	50	41
Nonusers	6611	69	53	17	9	10	50	40

Schneeweiss, Glynn, Tsai, Avorn, Solomon; Epidemiology 2005

15

Validation Studies

- Allow us to take joint distribution of multiple confounders into account
- Internal
  - Collect additional data for subset of participants
    - Random selection
    - Non-random selection:
      - 2-stage design
      - Convenience sample (cave sampling on value of covars)
- External
  - Separate study
  - Usually cross-sectional: no information on disease-outcome of interest

16

Data Structure Internal Validation Study

	Main Study	Validation Study
	Claims Data	Claims & Survey

17

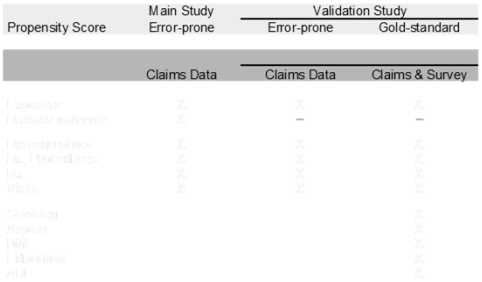
Multiple Imputation

- Impute missing values in main study based on measured values in validation study
- Linear regression model of missing covariate C on exposure, measured covariates, and outcome

  $[C \mid A, \mathbf{X}, Y] = \delta_0 + \delta_1 A + \delta_X \mathbf{X} + \delta_3 Y + \varepsilon$
- Impute values for C in e.g., 20 different datasets sampling from posterior distributions ($\boldsymbol{\delta}$ and SE)
- Analyze all 20 datasets separately
- Average results from all 20 datasets controlling for imputed values of C using variability of estimates over datasets to adjust SE for imputation

18

Propensity Score Calibration (PSC)



Propensity Score	Main Study: Error-prone	Validation Study: Error-prone	Validation Study: Gold-standard
	Claims Data	Claims Data	Claims & Survey

19

3 Steps of PSC

1. In main study
   - Estimate PS_{EP} based on observed variables
2. In validation study
   a) Estimate PS_{EP} based on same variables
   b) Estimate PS_{GS} based on variables in PS_{EP} **plus additional variables** (unobserved in main study)
   c) ME model: $E[PS_{GS} \mid A, PS_{EP}] = \delta_0 + \delta_1 A + \delta_2 PS_{EP}$
3. In main study
   - Impute missing PS_{GS} (single imputation $E[PS_{GS}]$)
   - Control (possibly imputed) for PS_{GS}

20

Conclusions PSC

- Validity of PSC dependent on direction **AND** relative magnitude of observed and unobserved confounding
- PSC bias can be predicted/corrected for 2 variable setting making assumption about unobservable RR_{CY}
- Prior data on RR_{CY} often reason for external adjustment and therefore available
- Advantage of PSC: uses external data to estimate joint distribution of confounders with exposure (unavailable from published literature)

Lunt et al., AJE 12

21

Conclusions External Adjustment for Confounding

- Implementation dependent on
  - Availability of data (rapidly increasing!)
  - Transportability of models (assumption)
- Access to EHRs offers opportunities (BMI!)
- Important part of multiple bias modeling to increase coverage of confidence intervals
- Worthwhile endeavor!

22

Conclusions Validation Studies

- Availability of linked data rapidly increasing
  - ICISS (NC cancer registry + BCBS, Medicare
  - UNChs + BCBS, Medicare coming
- Increasingly required for outcomes
- Generally not transportable over decades
  - E.g., pts with acute MI hospitalized for 3+ days
- MSs get a lot of traction
- Always consider as part of thesis!

Chun D, Lund JL, Stürmer T. Pharmacoepidemiology and Drug Safety's special issue on validation studies. PDS 2019 doi: 10.1002/pds.4694. [Epub ahead of print]

23