Bayesian Calibration

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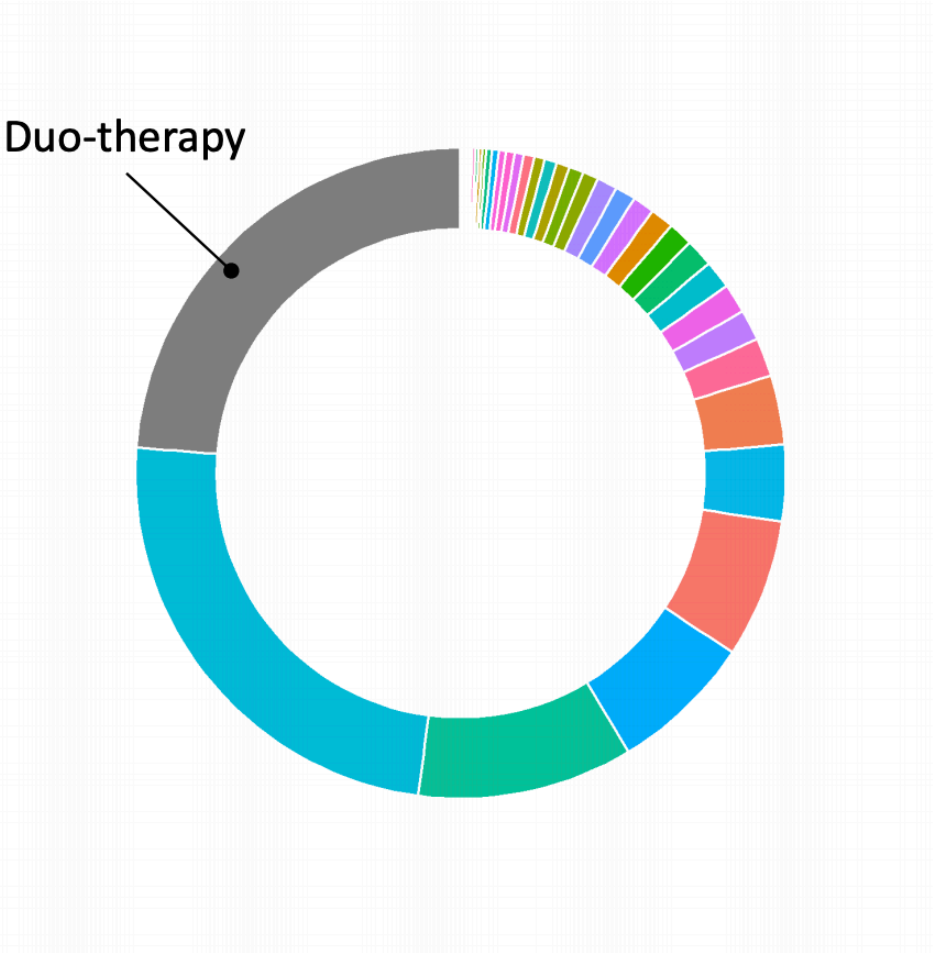
LEGEND

- Reproducible, systematized, open source approach at scale
- Negative controls
  - Drugs and outcomes “known” to have no causal association
  - Literature, product labels, spontaneous reports
  - Empirical p-values
- Positive Controls
  - Inject signals onto negative controls with known effect size
  - Calibrated confidence intervals

Hypertension mono-therapy



- Amlodipine
- Atenolol
- Azilsartan
- Benazepril
- Bisoprolol
- Candesartan
- Captopril
- Carvedilol
- Chlorthalidone
- Clonidine
- Diltiazem
- Doxazosin
- Enalapril
- Felodipine
- Fosinopril
- Furosemide
- Hydralazine
- Hydrochlorothiazide
- Indapamide
- irbesartan
- Labetalol
- Lisinopril
- Losartan
- Methyldopa
- Metoprolol
- Nadolol
- Nebivolol
- Nicardipine
- Nifedipine
- Olmesartan
- Propranolol
- Quinapril
- Ramipril
- Spironolactone
- Telmisartan
- Terazosin
- Torsemide
- Valsartan
- Verapamil

Truven Health MarketScan CCAE. Therapies > 2 ingredients not shown

58 outcomes of interest

Abdominal pain
Abnormal weight gain
Abnormal weight loss
Acute myocardial infarction
Acute pancreatitis
Acute renal failure
All-cause mortality
Anaphylactoid reaction
Anemia
Angioedema
Anxiety
Bradycardia
Cardiac arrhythmia
Cardiovascular disease
Cardiovascular-related mortality
Chest pain or angina
Chronic kidney disease
Coronary heart disease
Cough
Decreased libido
Dementia
Depression
Diarrhea
Edema
End stage renal disease
Fall
Gastrointestinal bleeding
Gout
Headache
Heart failure
Hemorrhagic stroke
Hepatic failure
Hospitalization with heart failure
Hospitalization with preinfarction syndrome
Hyperkalemia
Hypokalemia
Hypomagnesemia
Hyponatremia
Hypotension
Impotence
Ischemic stroke
Kidney disease
Malignant neoplasm
Measured renal dysfunction
Nausea
Neutropenia or agranulocytosis
Rash
Rhabdomyolysis
Stroke
Sudden cardiac death
Syncope
Thrombocytopenia
Transient ischemic attack
Type 2 diabetes mellitus
Vasculitis
Venous thromboembolic events
Vertigo
Vomiting

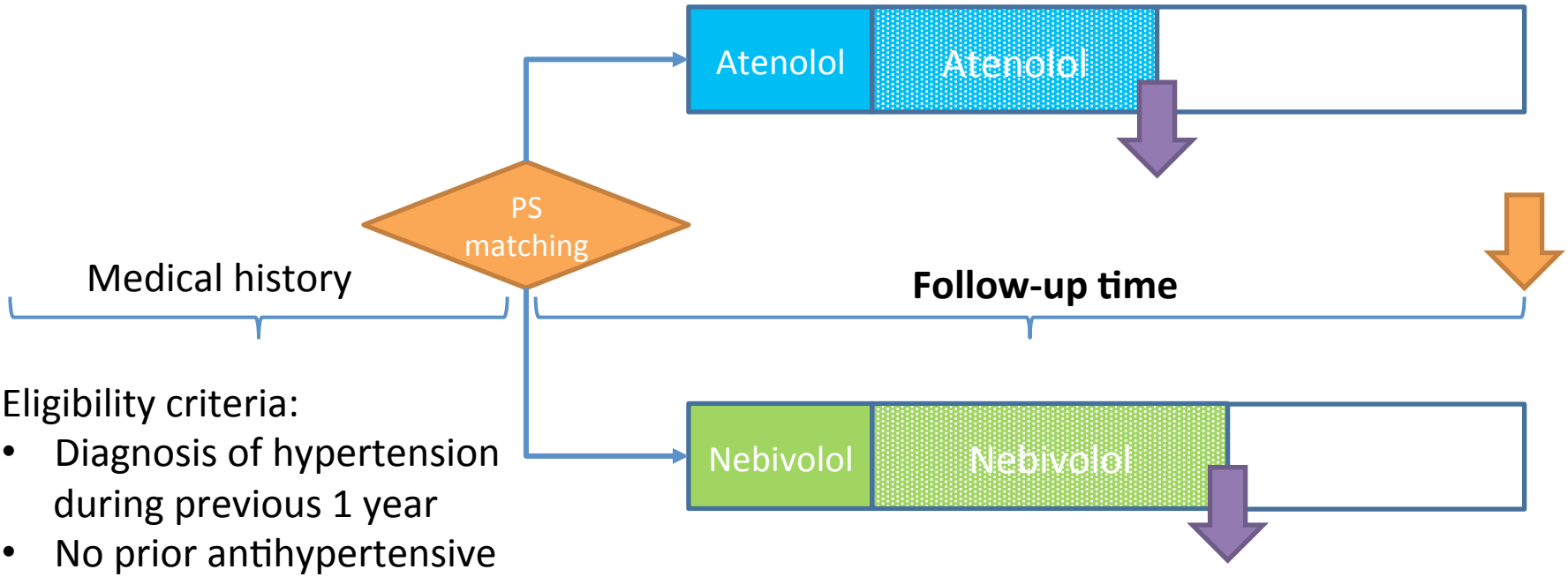
76 negative controls

Abnormal cervical smear
Abnormal pupil
Abrasion and/or friction burn of trunk without infection
Absence of breast
Absent kidney
Acid reflux
Acquired hallux valgus
Acquired keratoderma
Acquired trigger finger
Acute conjunctivitis
Amputated foot
Anal and rectal polyp
Burn of forearm
Calcaneal spur
Cannabis abuse
Cervical somatic dysfunction
Changes in skin texture
Chondromalacia of patella
Cocaine abuse
Colostomy present
Complication due to Crohn's disease
Contact dermatitis
Contusion of knee
Crohn's disease
Derangement of knee
Difficulty sleeping
Disproportion of reconstructed breast
Effects of hunger
Endometriosis
Epidermoid cyst
Feces contents abnormal
Foreign body in orifice
Ganglion cyst
Genetic predisposition
Hammer toe
Hereditary thrombophilia
Herpes zoster without complication
High risk sexual behavior
Homocystinuria
Human papilloma virus infection
Ileostomy present
Impacted cerumen
Impingement syndrome of shoulder region
Ingrowing nail
Injury of knee
Irregular periods
Kwashiorkor
Late effect of contusion
Late effect of motor vehicle accident
Leukorrhea
Macular drusen
Melena
Nicotine dependence
Noise effects on inner ear
Nonspecific tuberculin test reaction
Non-toxic multinodular goiter
Onychomycosis due to dermatophyte
Opioid abuse
Passing flatus
Postviral fatigue syndrome
Presbyopia
Problem related to lifestyle
Psychalgia
Ptotic breast
Regular astigmatism
Senile hyperkeratosis
Somatic dysfunction of lumbar region
Splinter of face, without major open wound
Sprain of ankle
Strain of rotator cuff capsule
Tear film insufficiency
Tobacco dependence syndrome
Vaginitis and vulvovaginitis
Verruca vulgaris
Wrist joint pain
Wristdrop

Method: Study design (LEGEND)

Treatment strategies:
- Atenolol
- Nebivolol

Causal contrasts of interest:
- On-treatment effect
- Intent-to-treat effect



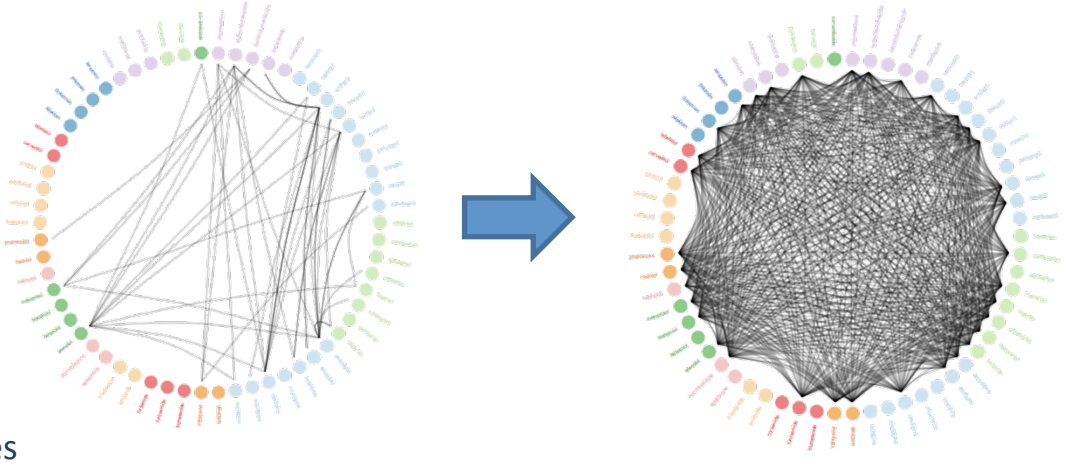
Eligibility criteria:
- Diagnosis of hypertension during previous 1 year
- No prior antihypertensive drug
- No prior cardiovascular outcome

Outcome (Major Adverse Cardio-Cerebrovascular Event):
- Hospitalized myocardial infarction, heart failure, stroke and sudden cardiac death

Method: **LEGEND** (Large-scale Evidence Generation and Evaluation in a Network of Databases

All randomized trials LEGEND

40 trials



10,278 comparisons

US Insurance databases

- **IBM® MarketScan® CCAE (Commercial Claims and Encounters)**
- IBM® MarketScan® MDCD (Multi-state Medicaid)
- IBM® MarketScan® MDCR (Medicare Supplemental Beneficiaries)
- **Optum® Clinformatics®**

Japanese insurance database

- Japan Medical Data Center (JMDC)

Korean National insurance database

- NHIS-national sample cohort (NHIS-NSC) DB

US EHR databases

- Columbia University medical Center
- **Optum® PANTHER®**

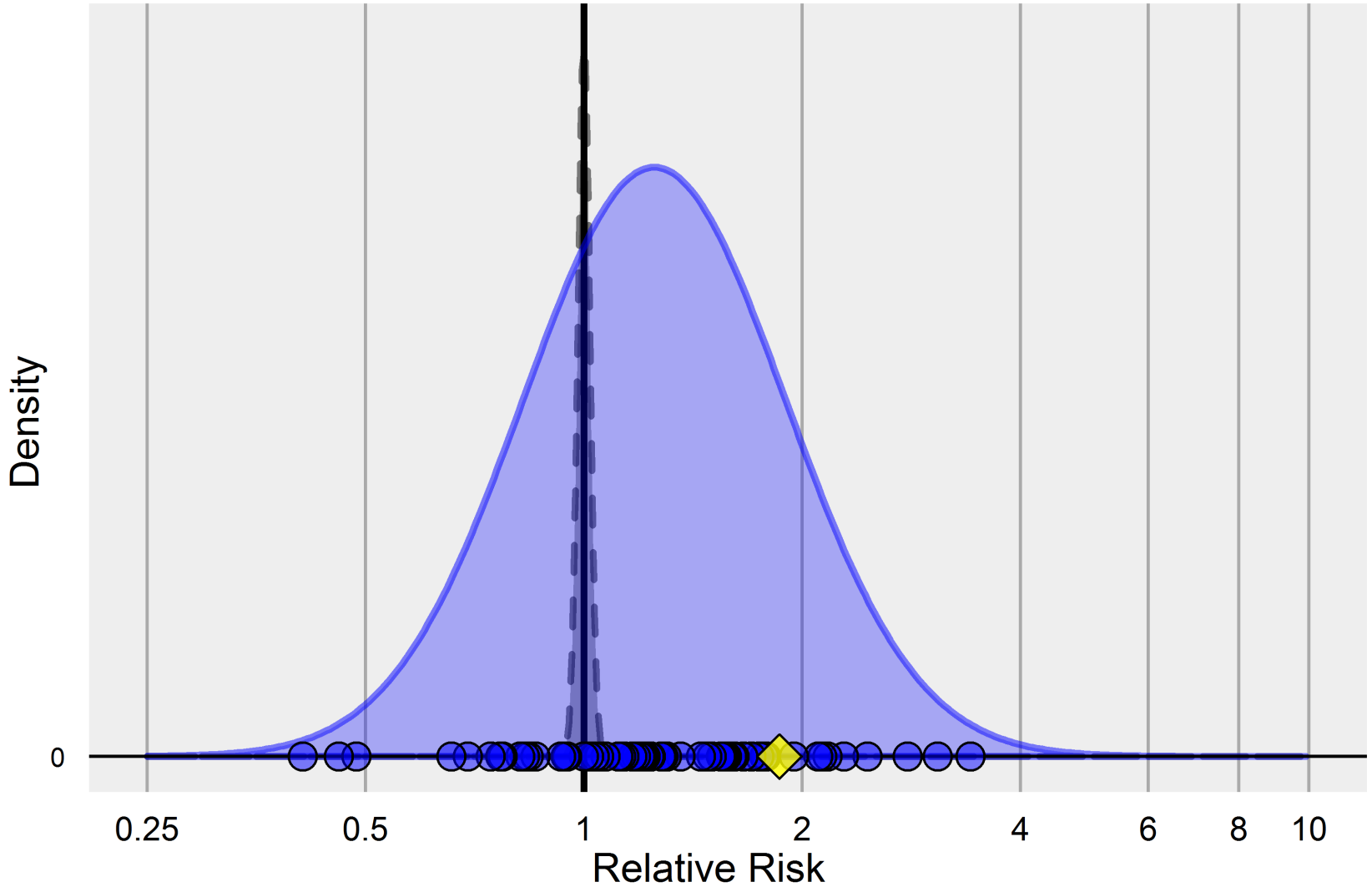
German EHR database

- QuintilesIMS Disease Analyzer (DA) Germany

https://github.com/OHDSI/LEGEND

Negative controls & the null distribution

CC: 2000314, CCAE, GI Bleed



Negative controls & the null distribution

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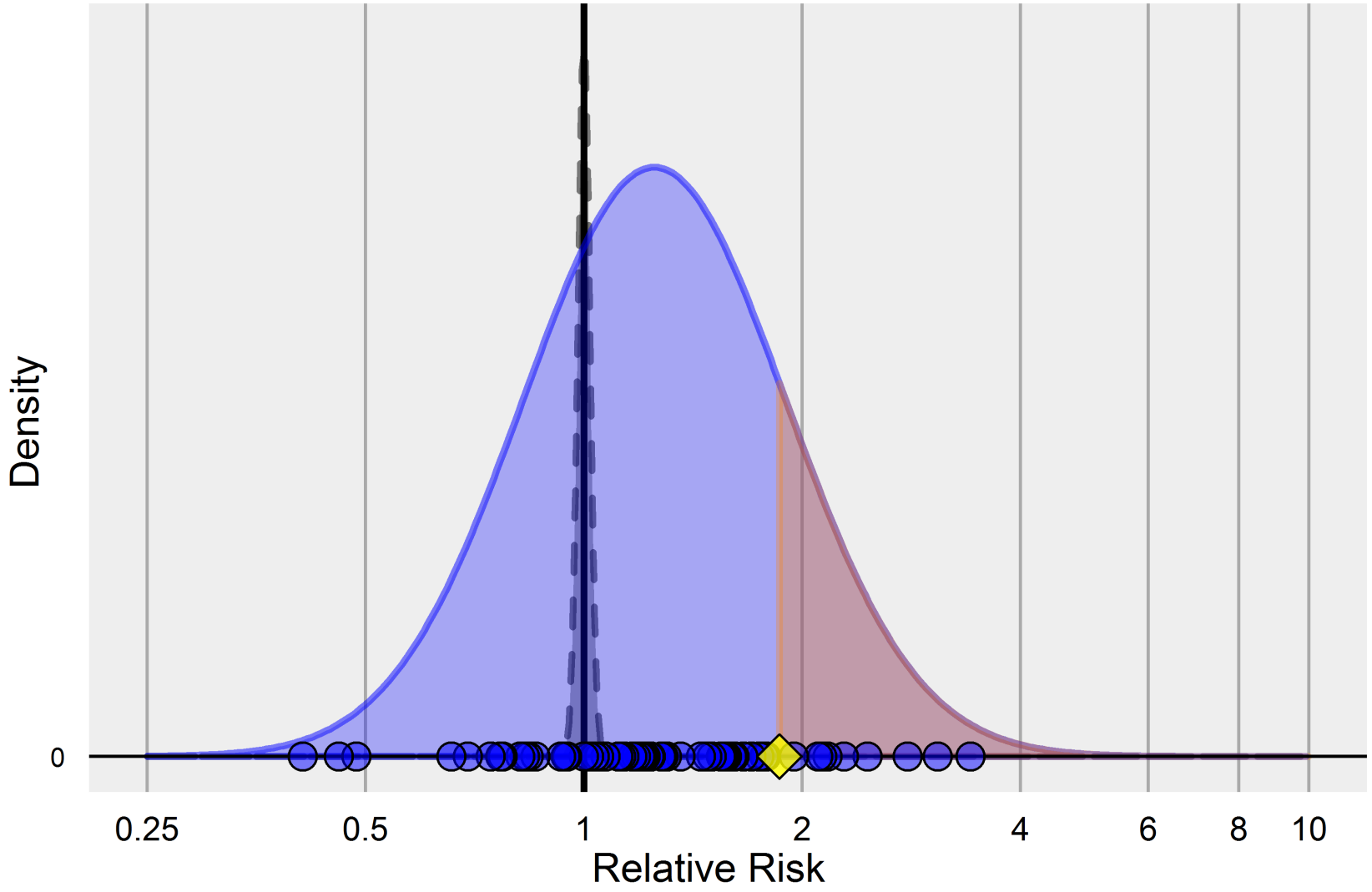


Bayesian Approach

- Compute the posterior distribution of the TCO effect of interest, conditional on:
  - Directly estimated effect for the TCO
  - Estimated effects on all negative and positive controls
  - Across all databases
  - Across all "methods" (e.g. matching versus stratification)
- MCMC

One model, one database (V1)

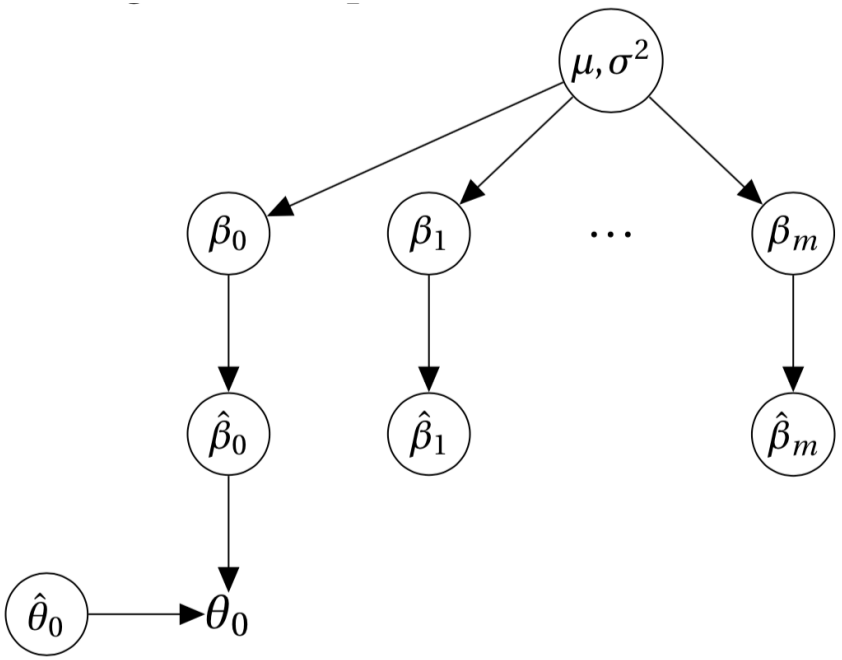
θ_0 true effect size of interest

θ_i true effect size for the controls, $i = 1, \ldots, m$

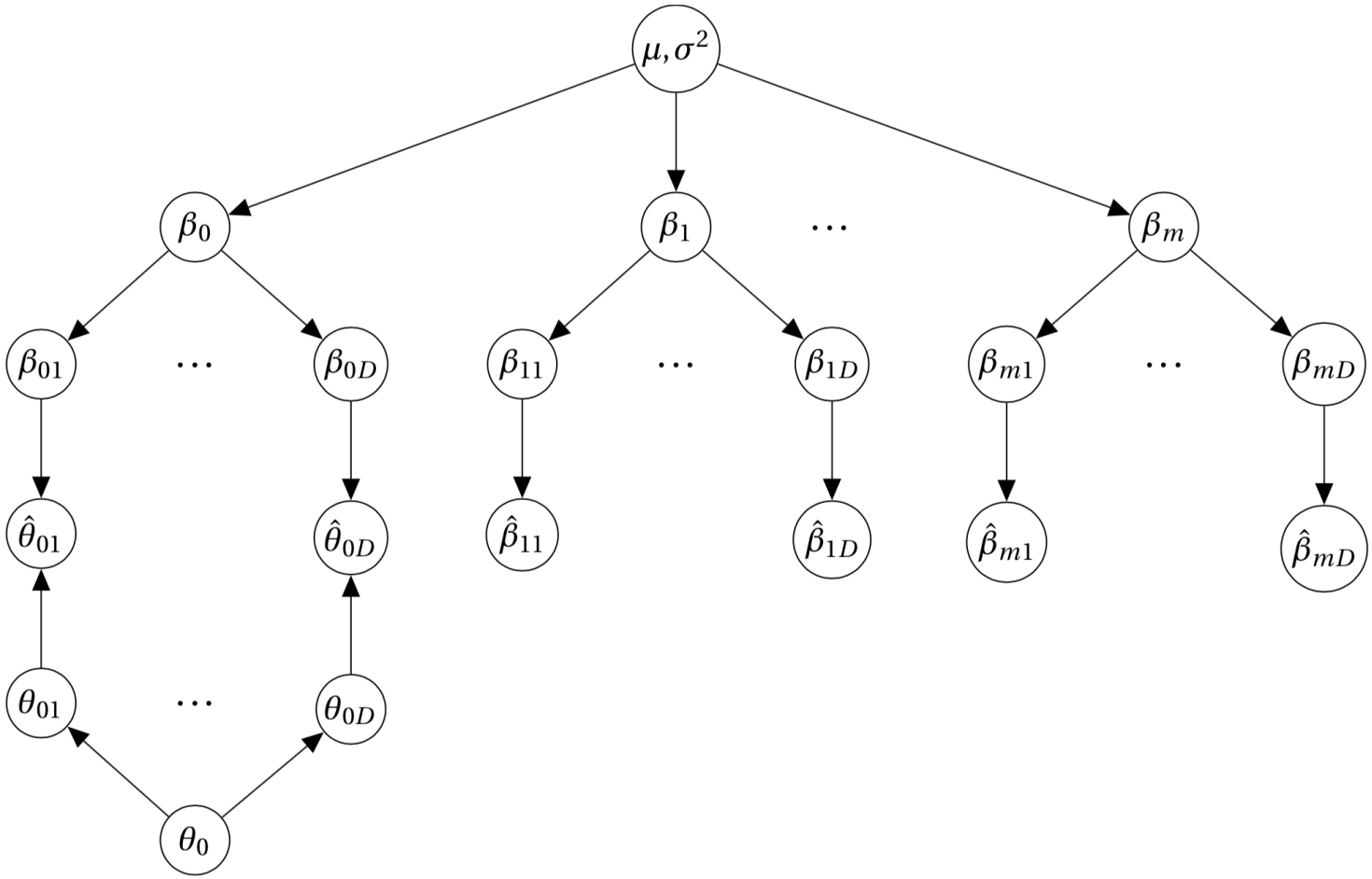
$\hat{\theta}_i$ estimated effect sizes, $i = 0, \ldots, m$

$\hat{\beta}_i = \hat{\theta}_i - \theta_i$ "estimated bias," $i = 0, \ldots, m$

$E[\hat{\beta}_i] = \beta_i$ $i = 0, \ldots, m$



One model, many databases (V2)



Combining calibration with random effects meta-analysis

Many models, many databases (V4, BMA)

$$p(\theta_0|\mathscr{D}) = \sum_k p(\theta_0|M_k,\mathscr{D})\,p(M_k|\mathscr{D})$$

where the data, $\mathscr{D}$, comprise:

$$\hat{\theta}^k_{0j}, k = 1,\ldots,M, j = 1,\ldots,D$$

$$\hat{\theta}^k_{ij}, k = 1,\ldots,M, j = 1,\ldots,D, i = 1,\ldots,Q$$

$$\theta_i, i = 1,\ldots,Q$$

can show that: $p(M_k|\mathscr{D}) \propto \prod_{i=1}^{Q}\prod_{j=1}^{D} p(\hat{\theta}^k_{ij}|\theta_i, M_k)$

Combining calibration with random effects meta-analysis and BMA

Initial results (V1)

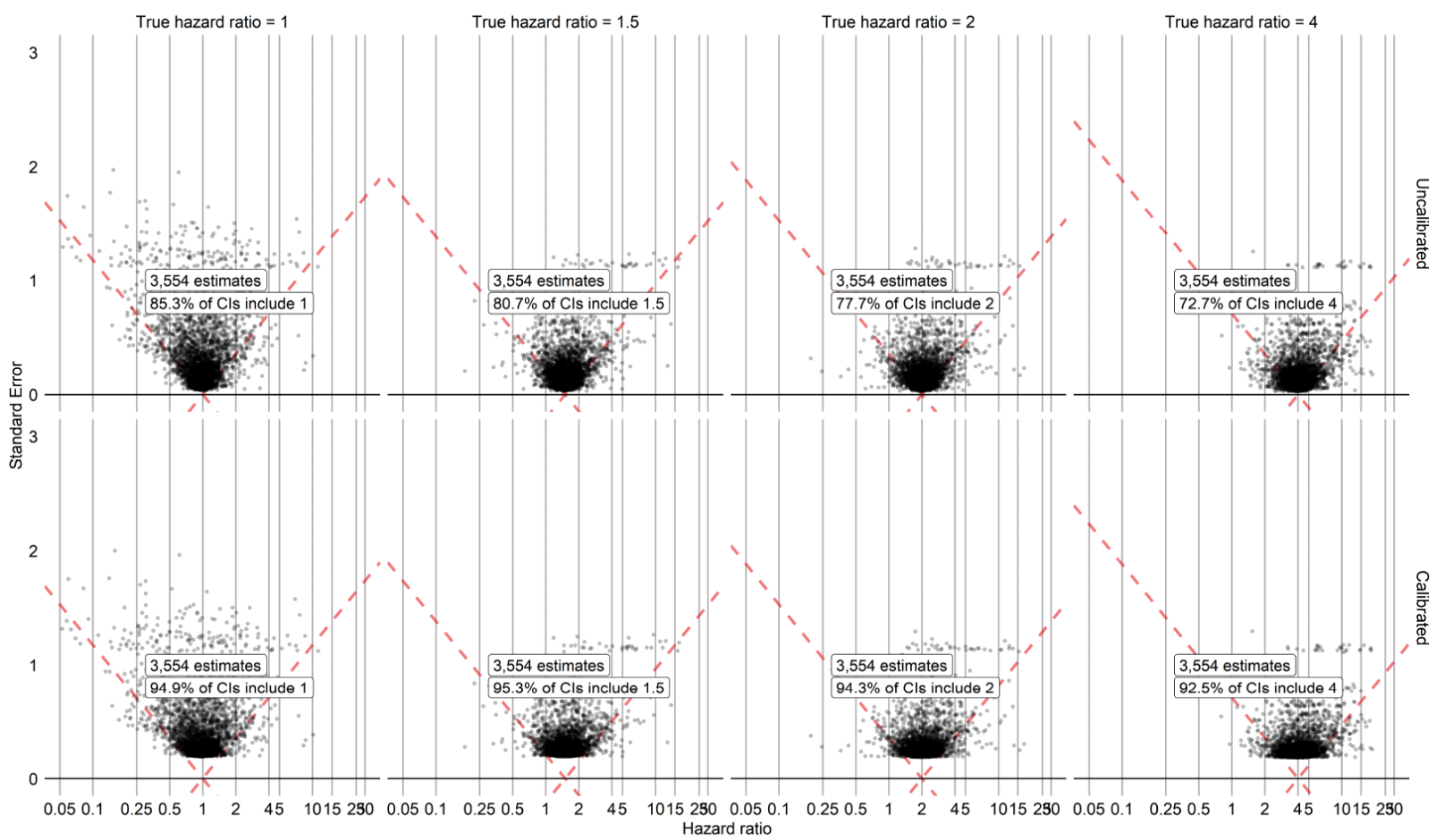
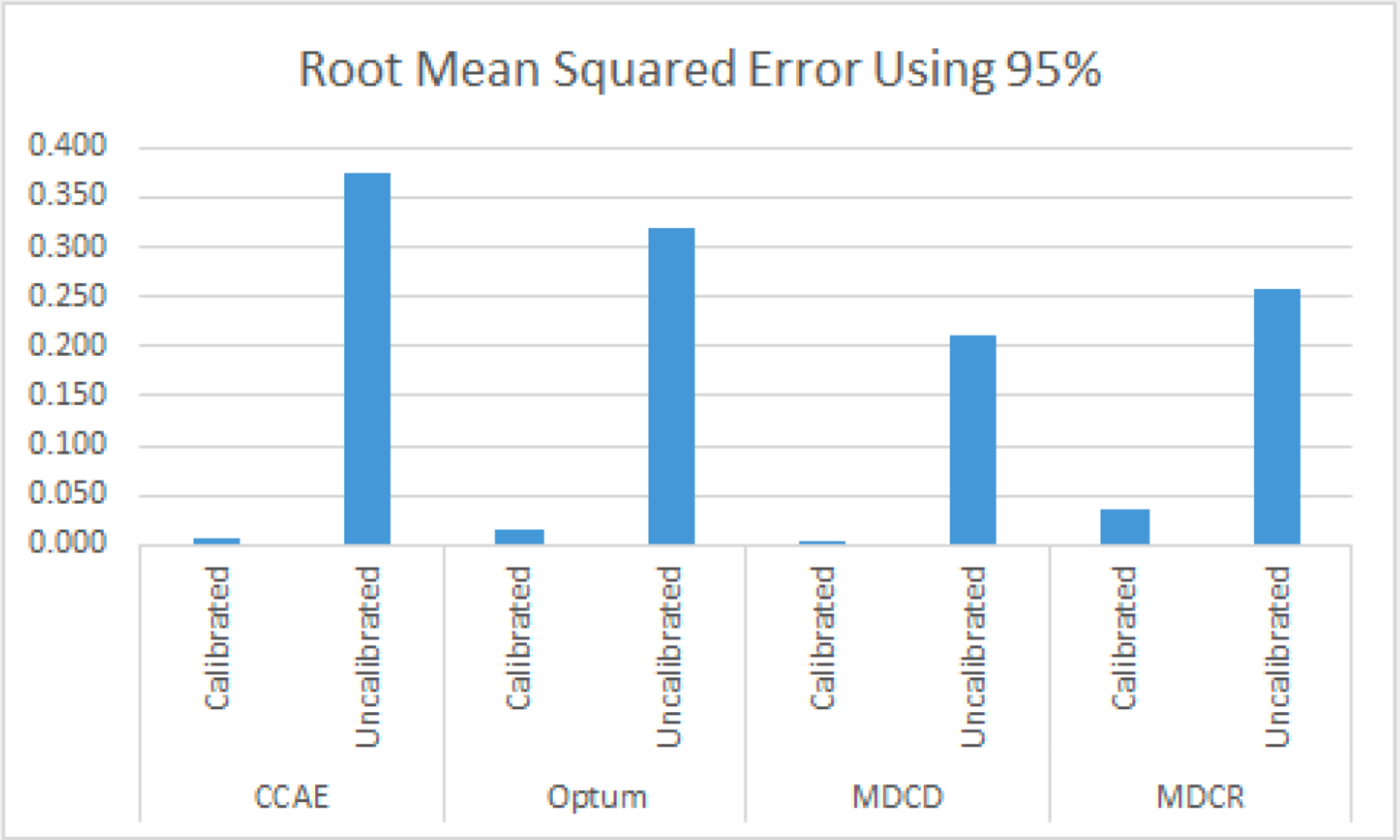


Figure: Optum Database Results


Root Mean Squared Error Using 95%
0.400
0.350
0.300
0.250
0.200
0.150
0.100
0.050
0.000
Calibrated
Uncalibrated
Calibrated
Uncalibrated
Calibrated
Uncalibrated
Calibrated
Uncalibrated
CCAE
Optum
MDCD
MDCR