Impact of phenotype error adjustment on background incidence of COVID19 vaccine adverse events of special interest

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Background

Substantial background incidence rate (IR) heterogeneity has been reported across age, sex, and database for CCOVID19 vaccine adverse events of special interest (AESI)[1]. It is unclear what proportion of the observed IR heterogeneity is attributable AESI phenotype error (outcome misclassification e.g., low sensitivity). We assessed if adjusting AESI IRs for phenotype error reduced heterogeneity. We evaluated the impact of phenotype error adjustment on background IRs of 4 AESIs in 5 databases, stratified by age and by sex.

Methods

We used 5 US observational databases transformed to the OMOP CDM (4 administrative claims and 1 electronic health record) covering 3 years before the COVID19 pandemic (2017-01-01 to 2019-12-31).

We calculated background IRs as the number of outcome events divided by person time at-risk (TAR) per 100,000 person-years (100k PYs) in a target population stratified by age and by sex. The target population was persons with an observation period on 2017-01-01, 2018-01-01, or 2019-01-01 with ≥365 days of prior database observation. TAR for outcome events was 1 day after until 365 days after the target cohort entry date or end of database observation.

We assessed 4 AESI outcomes from a previous OHDSI network study[1]: Inpatient acute myocardial infarction (AMI), deep vein thrombosis (DVT), pulmonary embolism (PE), and inpatient ischemic stroke (IS). Following an event, a patient could re-enter the at-risk cohort following a 365-day clean window during which they did not contribute TAR.

We calculated outcome phenotype error metrics sensitivity (SN) and specificity (SP) in internal validation studies using a probabilistic reference standard[2, 3] where the reference standard is the probability of case status derived from a diagnostic predictive model. We stratified database-specific phenotype errors by age and by sex to make corresponding age and sex stratified IR adjustments.

We adjusted the IR numerator based on quantitative bias analysis principles[4, 5] using SN and SP point estimates: $outcomes_{adjusted} = (outcomes - (1 - SP) \times persons_{at\text{-}risk}) / (SN - (1 - SP))$. We reported patterns of IR adjustment as the number of databases for which the IR increased for AMI, DVT, PE, and IS.

We then computed pooled observed and pooled adjusted AESI IRs across databases with random-effects meta-analysis[6, 7]. We reported the pooled IR prediction interval (PI)[8, 9] before and after adjustment to quantify heterogeneity change. The pooled IR PI represents the expected range of true new estimates in subsequent similar studies. We also reported the τ^2 statistic as another measure of meta-analytic heterogeneity to compare unadjusted and adjusted pooled results.

We evaluated pooled IR adjustment with the expected absolute measurement error (EAME) metric, which is the log relative pooled IR change after adjustment compared to before and is defined as: $EAME=abs(log(IR_{adjusted}/IR))$. Lower values indicate lesser impact and higher values indicate greater adjustment impact.

We reported meta-analytic results for AMI and DVT among persons 55-64 years and among males 0-85+ years. We will report meta-analytic results for PE and IS in subsequent reports.

Results

For AMI among males 0-85+ years, sensitivity ranged from 0.582 to 0.667 and specificity ranged from 0.997 to 1.000 across databases. Among persons 55-64 years, AMI sensitivity ranged from 0.557 to 0.651 and specificity ranged from 0.997 to 0.999. For DVT among males 0-85+ years, sensitivity ranged from 0.728 to 0.889 and specificity ranged from 0.995 to 0.999 across databases. Among persons aged 55-64 years, DVT sensitivity ranged from 0.774 to 0.884 and specificity ranged from 0.995 to 0.998 (Table 1).

Table 1. AMI and DVT phenotype errors by database for [Male 0-85+] and [Male/Female 55-64] strata

Outcome	Stratum	Database	Sensitivity	Specificity
AMI	Male 0 - 85+	Clinformatics®	0.598	0.999
	Male 0 - 85+	CCAE	0.650	1.000
	Male 0 - 85+	MDCD	0.582	0.999
	Male 0 - 85+	MDCR	0.667	0.997
	Male 0 - 85+	Optum® EHR	0.621	0.999
	Male/Female 55 - 64	Clinformatics®	0.557	0.999
	Male/Female 55 - 64	CCAE	0.651	0.999
	Male/Female 55 - 64	MDCD	0.594	0.997
	Male/Female 55 - 64	MDCR	0.603	0.998
	Male/Female 55 - 64	Optum® EHR	0.615	0.999
DVT	Male 0 - 85+	Clinformatics®	0.815	0.998
	Male 0 - 85+	CCAE	0.889	0.999
	Male 0 - 85+	MDCD	0.728	0.999
	Male 0 - 85+	MDCR	0.830	0.995
	Male 0 - 85+	Optum® EHR	0.843	0.998
	Male/Female 55 - 64	Clinformatics®	0.806	0.998
	Male/Female 55 - 64	CCAE	0.884	0.998
	Male/Female 55 - 64	MDCD	0.774	0.997
	Male/Female 55 - 64	MDCR	0.832	0.995
	Male/Female 55 - 64	Optum® EHR	0.852	0.998

Key – Clinformatics®: Optum's de-identified Clinformatics® Data Mart Database, CCAE: Merative™ MarketScan® Commercial Database, MDCD: Merative™ Multi-State Medicaid Database, MDCR: Merative™ Medicare Database, Optum® EHR: Optum® de-identified Electronic Health Record Dataset

Table 2 shows that phenotype error adjustment directionally increased AMI IRs in all strata except persons 85+ years of age. Similarly, IS IRs directionally increased for all strata after adjustment. Conversely, the direction of IR adjustment was mixed across databases for DVT and PE where in no strata for either condition did all adjustments increase or decrease the IR. No statistical test informed IR increase or decrease.

Table 2: Incidence adjustment patterns

	AMI			DVT			PE			IS		
Stratum	n	IR↑	IR↓	n	IR↑	IR↓	n	IR↑	IR↓	n	IR↑	IR↓
Male/Female 0-85+	5	5	0	5	2	3	5	3	2	5	5	0
Male/Female 18-35	4	4	0	4	3	2	4	3	1	4	4	0
Male/Female 35-54	5	5	0	5	3	2	5	2	3	5	5	0
Male/Female 55-64	5	5	0	5	2	3	5	2	3	5	5	0
Male/Female 65-74	4	0	0	5	4	1	5	3	2	4	4	0
Male/Female 75-84	4	4	0	4	2	2	4	1	3	4	4	0
Male/Female 85+	4	2	2	4	2	2	3	1	2	4	4	0
Male 0-85+	5	5	0	5	2	3	5	3	2	5	5	0
Female 0-85+	5	5	0	5	2	3	5	3	2	5	5	0

Key – n: databases in which incidence adjustment was conducted, IR↑: incidence rate increased, IR↓: incidence rate decreased
AMI: inpatient acute myocardial infarction, DVT: deep vein thrombosis, IS: inpatient ischemic stroke, n: number of databases with adjusted IR, IR↑: number of databases where incidence rate increased after phenotype error adjustment, IR↓: number of databases where incidence rate decreased after phenotype error adjustment

Figure 1 and Figure 2 depict the impact of AMI IR adjustment for persons 55-64 years and males 0-85+ years, respectively. The plot component in Figure 1 and Figure 2 displays the impact patterns for the corresponding AMI strata in Table 2. Further, the figures report the unadjusted and adjusted pooled IRs and associated meta-analysis metrics for heterogeneity assessment. The plot and table values are reported on the natural logarithm scale to ease interpretation.

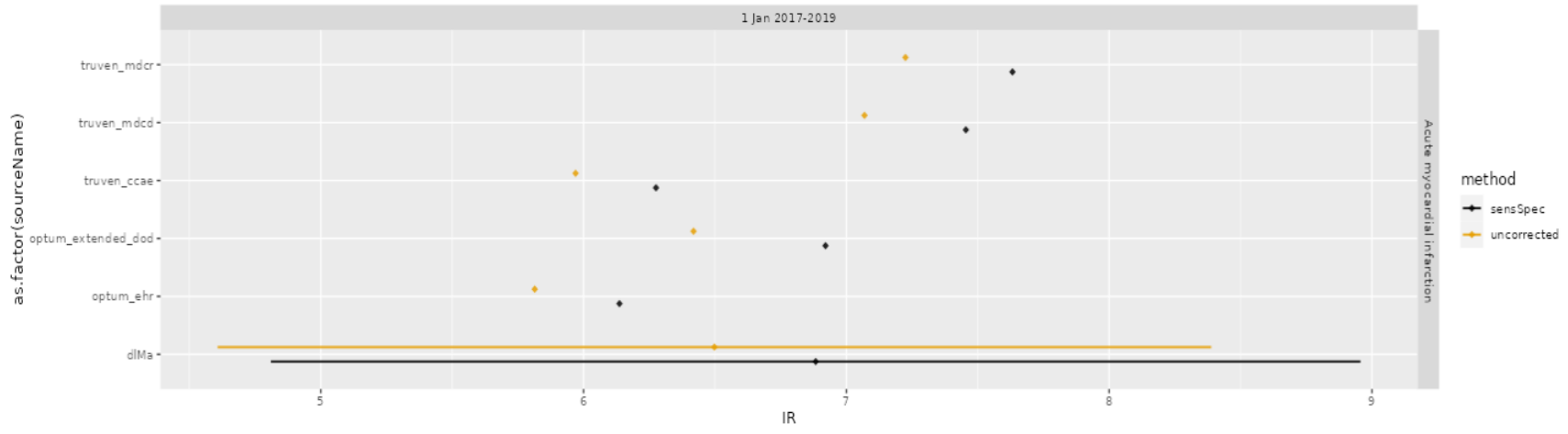
Among persons 55-64 years (Figure 1), the unadjusted AMI pooled IR was 664 events/100k PYs (95% PI: 100, 4397) with PI width=4297 and τ^2=0.294. The adjusted AMI pooled IR was 975 events/100k PYs (95% PI: 123, 7759) with PI width=7636 and τ^2=0.354. EAME was 0.35 in this stratum. Among males 0-85+ years (Figure 2), the unadjusted AMI pooled IR was 466 events/100k PYs (95% PI: 40, 5485) with PI width=5446 and τ^2=0.50. The adjusted AMI pooled IR was 656 events/100k PYs (95% PI: 51, 8470) with PI width=8419 and Tau^2=0.54. EAME was 0.13 in this stratum.

Figure 3 and Figure 4 depict the impact of DVT adjustment for persons 55-64 years and males 0-85+ years, respectively. The plot component in Figure 3 and Figure 4 displays the impact patterns for the corresponding DVT strata in Table 2. Also, unadjusted and adjusted pooled IRs and associated meta-analysis metrics are reported for heterogeneity assessment. The plot and table values are again reported on the natural logarithm scale.

Among persons 55-64 years (Figure 3), the unadjusted DVT pooled IR was 774 events/100k PYs (95% PI: 220, 2718) with PI width=2498 and τ^2=0.13. The adjusted DVT pooled IR was 779 events/100k PYs (95% PI: 156, 3894) with PI width=3738 and τ^2=0.21. Among males 0-85+ years (Figure 4), the unadjusted DVT pooled IR was 457 events/100k PYs (95% PI: 65, 3224) with PI width=3159 and τ^2 0.31. The adjusted DVT pooled IR was 461 events/100k PYs (95% PI: 56, 3805) with PI width=3749 and τ^2=0.37. EAME was 0.004 in this stratum. Meta-analysis results for other outcomes in other strata were qualitatively similar.

Figure 1: Acute myocardial infarction incidence adjustment and meta-analysis among persons 55-64 years. Incidence is on the $\log_e$ scale.

IR forest plots



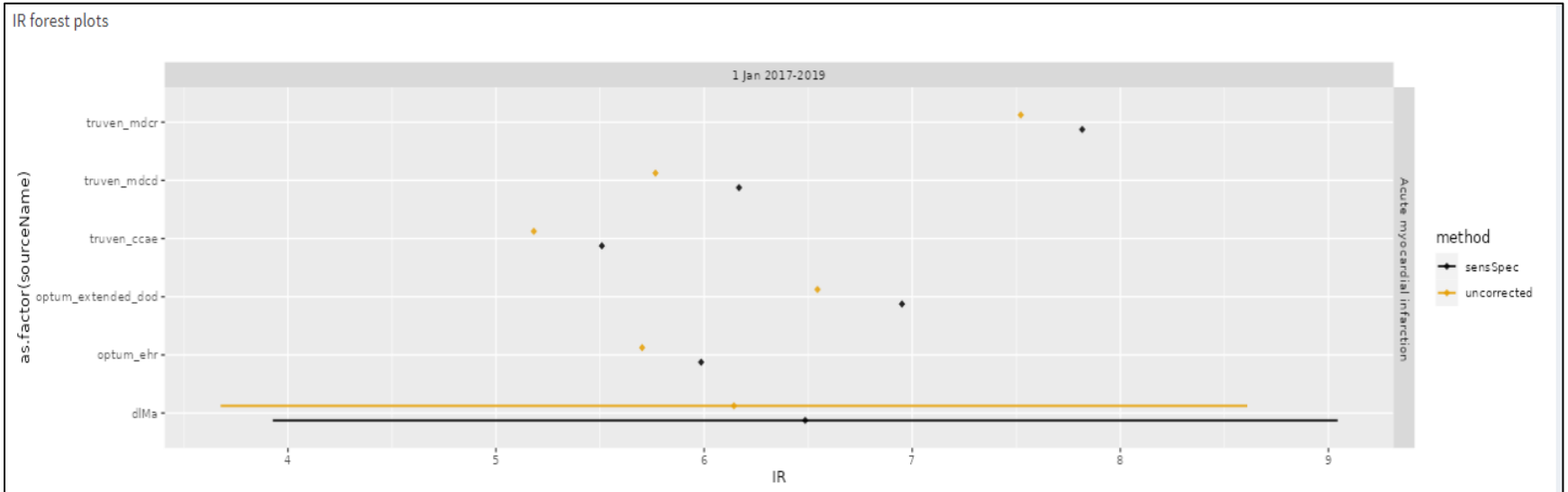
MA metrics

Show 25 entries Search:

method	source	stratum	targetName	outcomeName	ir	irLowerCi	irUpperCi	ciIntervalWidth	irLowerPredict	irUpperPredict	predictIntervalWidth	seIr	irTau2	irTau	i2	k
uncorrected	optum_extended_dod	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	6.419	6.406	6.431	2.727								
uncorrected	truven_ccae	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	5.97	5.959	5.981	2.154								
uncorrected	truven_mdcd	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	7.069	7.056	7.082	3.432								
uncorrected	truven_mdcr	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	7.225	7.128	7.322	5.588								
uncorrected	optum_ehr	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	5.814	5.806	5.822	1.714								
uncorrected	dlMa	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	6.498	6.022	6.974	6.486	4.607	8.389	0.599	0.243	0.294	0.542	1	5
sensSpec	optum_extended_dod	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	6.921	6.911	6.93	2.976								
sensSpec	truven_ccae	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	6.276	6.266	6.285	2.307								
sensSpec	truven_mdcd	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	7.455	7.444	7.466	3.622								
sensSpec	truven_mdcr	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	7.632	7.553	7.711	5.789								
sensSpec	optum_ehr	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	6.137	6.13	6.144	1.874								
sensSpec	dlMa	Male/Female 55 - 64	1 Jan 2017-2019	Acute myocardial infarction	6.883	6.362	7.405	6.97	4.81	8.957	0.622	0.266	0.354	0.595	1	5

Key – optum_extended_dod: Optum's de-identified Clinformatics® Data Mart Database, truven_ccae: Merative™ MarketScan® Commercial Database, truven_mdcd: Merative™ Multi-State Medicaid Database, truven_mdcr: Merative™ Medicare Database, optum_ehr: Optum® de-identified Electronic Health Record Dataset

Figure 2: Acute myocardial infarction incidence adjustment and meta-analysis among males 0-85+ years. Incidence on $\log_e$ scale.



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method	source	stratum	targetName	outcomeName	ir	irLowerCi	irUpperCi	ciIntervalWidth	irLowerPredict	irUpperPredict	predictIntervalWidth	seIr	irTau2	irTau	i2	k
uncorrected	optum_extended_dod	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	6.545	6.539	6.551	2.117								
uncorrected	truven_ccae	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	5.182	5.171	5.192	1.289								
uncorrected	truven_mdcd	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	5.766	5.755	5.777	1.945								
uncorrected	truven_mdcr	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	7.522	7.508	7.535	3.924								
uncorrected	optum_ehr	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	5.702	5.697	5.707	1.152								
uncorrected	dlMa	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	6.143	5.523	6.763	6.422	3.677	8.61	0.851	0.316	0.501	0.708	1	5
sensSpec	optum_extended_dod	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	6.951	6.946	6.956	2.318								
sensSpec	truven_ccae	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	5.509	5.5	5.517	1.452								
sensSpec	truven_mdcd	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	6.167	6.159	6.176	2.145								
sensSpec	truven_mdcr	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	7.817	7.805	7.829	4.068								
sensSpec	optum_ehr	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	5.986	5.981	5.99	1.293								
sensSpec	dlMa	Male 0 - 85+	1 Jan 2017-2019	Acute myocardial infarction	6.486	5.843	7.129	6.806	3.928	9.044	0.834	0.328	0.539	0.734	1	5

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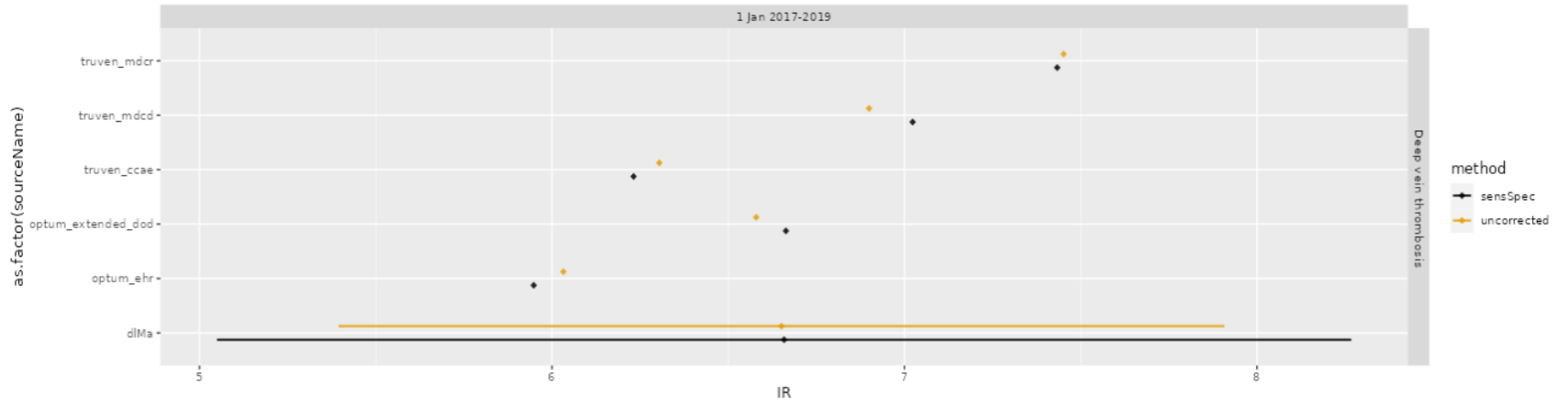
Figure 3. Deep vein thrombosis incidence adjustment and meta-analysis among persons 55-64 years. Incidence on $\log_e$ scale.

IR forest plots



MA metrics

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method	source	stratum	targetName	outcomeName	ir	irLowerCi	irUpperCi	ciIntervalWidth	irLowerPredict	irUpperPredict	predictIntervalWidth	seIr	irTau2	irTau	i2	k
uncorrected	optum_extended_dod	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	6.579	6.568	6.591	2.809								
uncorrected	truven_ccae	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	6.304	6.295	6.314	2.323								
uncorrected	truven_mdcd	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	6.9	6.885	6.914	3.348								
uncorrected	truven_mdcr	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	7.452	7.364	7.539	5.707								
uncorrected	optum_ehr	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	6.032	6.025	6.04	1.824								
uncorrected	dlMa	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	6.651	6.335	6.967	6.21	5.394	7.908	0.382	0.161	0.13	0.36	1	5
sensSpec	optum_extended_dod	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	6.664	6.653	6.675	2.851								
sensSpec	truven_ccae	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	6.231	6.222	6.241	2.287								
sensSpec	truven_mdcd	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	7.023	7.01	7.037	3.409								
sensSpec	truven_mdcr	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	7.433	7.345	7.521	5.698								
sensSpec	optum_ehr	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	5.948	5.94	5.956	1.782								
sensSpec	dlMa	Male/Female 55 - 64	1 Jan 2017-2019	Deep vein thrombosis	6.658	6.254	7.063	6.474	5.05	8.267	0.493	0.207	0.213	0.461	1	5

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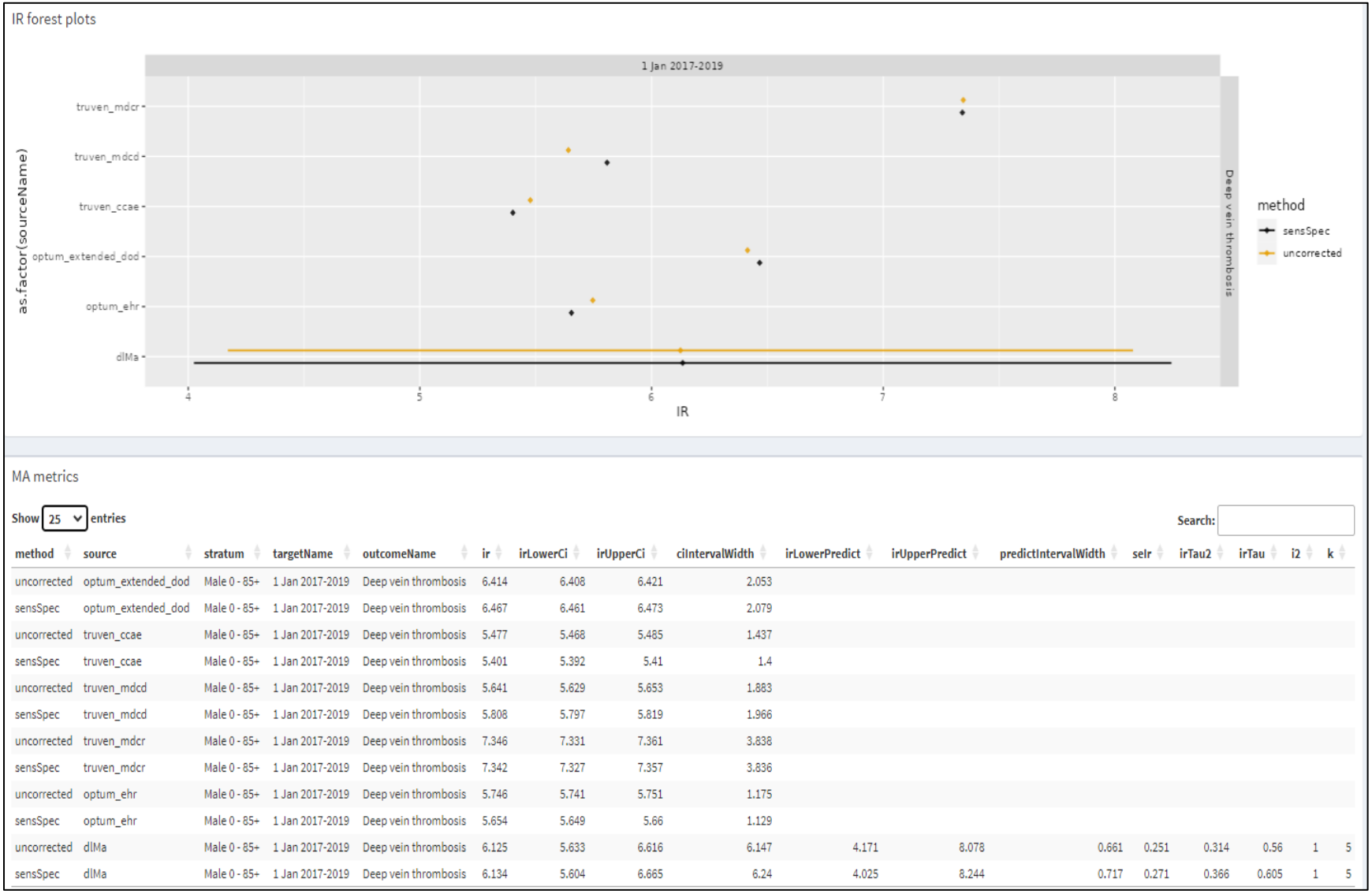
Figure 4. Deep vein thrombosis incidence adjustment and meta-analysis among males 0-85+ years. Incidence on $\log_e$ scale.



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method	source	stratum	targetName	outcomeName	ir	irLowerCi	irUpperCi	ciIntervalWidth	irLowerPredict	irUpperPredict	predictIntervalWidth	seIr	irTau2	irTau	i2	k
uncorrected	optum_extended_dod	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	6.414	6.408	6.421	2.053								
sensSpec	optum_extended_dod	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	6.467	6.461	6.473	2.079								
uncorrected	truven_ccae	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	5.477	5.468	5.485	1.437								
sensSpec	truven_ccae	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	5.401	5.392	5.41	1.4								
uncorrected	truven_mdcd	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	5.641	5.629	5.653	1.883								
sensSpec	truven_mdcd	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	5.808	5.797	5.819	1.966								
uncorrected	truven_mdcr	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	7.346	7.331	7.361	3.838								
sensSpec	truven_mdcr	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	7.342	7.327	7.357	3.836								
uncorrected	optum_ehr	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	5.746	5.741	5.751	1.175								
sensSpec	optum_ehr	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	5.654	5.649	5.66	1.129								
uncorrected	dlMa	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	6.125	5.633	6.616	6.147	4.171	8.078	0.661	0.251	0.314	0.56	1	5
sensSpec	dlMa	Male 0 - 85+	1 Jan 2017-2019	Deep vein thrombosis	6.134	5.604	6.665	6.24	4.025	8.244	0.717	0.271	0.366	0.605	1	5

Key – optum_extended_dod: Optum's de-identified Clinformatics® Data Mart Database, truven_ccae: Merative™ MarketScan® Commercial Database, truven_mdcd: Merative™ Multi-State Medicaid Database, truven_mdcr: Merative™ Medicare Database, optum_ehr: Optum® de-identified Electronic Health Record Dataset

Conclusion

Contrary to a qualitative hypothesis, adjusting two COVID19 AESI IRs for phenotype error did not reduce IR heterogeneity across 5 data sources. However, it is unclear how much phenotype error adjustment is expected given there is little phenotype error heterogeneity across these few US data sources. Adjustment predominantly increased IRs for AMI and IS, although IR adjustment direction was mixed for DVT and PE.

For AMI and IS, sensitivity was low among persons 55-64 and among males 0-85+ years. Given similar sensitivity values and near perfect specificity across databases, it followed that adjusted IRs increased roughly proportionally after adjustment across strata. This did not reduce heterogeneity as shown by similar PI widths and Tau^2 values between unadjusted and adjusted pooled estimates.

For DVT and PE, sensitivity was higher among persons 55-64 years and among males 0-85+ years compared to AMI and IS in the same strata. Although these sensitivity values were higher, they were unevenly distributed by database. Given this finding with near perfect specificity across databases, it followed that adjusted IRs both increased and decreased across strata. Like AMI and IS, this did not reduce heterogeneity as shown by similar PI widths and Tau^2 values between unadjusted and adjusted pooled estimates.

The greater and consistent AMI and IS IR increases across databases compared to that of DVT and PE was reflected by larger EASE values for the former conditions than the latter.

Limitations of this work include our use of five US databases, 4 of which are administrative claims, so there is little prior expectation that phenotype errors would be substantially different. We also used simple rather than multidimensional or probabilistic quantitative bias analysis methods[10]. Probabilistic bias analysis may reduce the impact of inaccurate or biased phenotype error point estimates, which is common to validation studies. We note our pooled results had wide PIs, which is a function of including few databases in the meta-analysis. PI width can be reduced by including more sources in future studies. Lastly, we reported and interpreted a subset of results that did not include age × sex strata. It is likely that IR heterogeneity within age × sex strata may be reduced by phenotype error correction.

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