Post-Authorization Safety Studies of Acute Liver Injury and Severe Complications of Urinary Tract Infection in Patients With Type 2 Diabetes Exposed to Dapagliflozin in a Real-World Setting

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Heather E. Danysh, PhD[1] (0000-0003-3014-7508); Catherine B. Johannes, PhD[1] (0000-0002-0586-9886); Daniel C. Beachler, PhD[2] (0000-0003-2788-3061); J. Bradley Layton, PhD[3] (0000-0003-0994-5820); Ryan Ziemiecki, MS[4] (0000-0002-1774-7034); Alejandro Arana, MD[5] (0000-0002-1593-3124); Jade Dinh, MPH[6] (0000-0003-0386-2776); Ling Li, MSPH[2]; Brian Calingaert, MS[3] (0000-0001-8177-6326); Manel Pladevall-Vila, MD[5,7] (0000-0002-9359-6055); Phillip R. Hunt, ScD[8] (0000-0002-9559-175X); Hungta Chen, PhD[8]; Cecilia Karlsson, MD[9] (0000-0002-4299-8775); Kristina Johnsson, MD[9]; Alicia Gilsenan, PhD (0000-0002-9266-1417)[3]

[1] Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, Waltham, MA, USA

[2] Department of Safety and Epidemiology, HealthCore, Inc., Wilmington, DE, USA

[3] Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, Research Triangle Park, NC, USA

[4] Department of Biostatistics, RTI Health Solutions, Research Triangle Park, NC, USA

[5] Department of Pharmacoepidemiology and Risk Management, RTI Health Solutions, Barcelona, Spain

[6] Department of Research Operations, HealthCore, Inc., Wilmington, DE, USA

[7] The Center for Health Policy and Health Services Research, Henry Ford Health System, Detroit, MI, USA

[8] BioPharmaceuticals Business Unit, AstraZeneca, Gaithersburg, MD, USA

[9] BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden

Corresponding Author:

Heather E. Danysh

Department of Pharmacoepidemiology and Risk Management

RTI Health Solutions

307 Waverley Oaks Road, Suite 101

Waltham, MA 02452-8413

Telephone: +1.781.434.1772

Email: hdanysh@rti.org

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Table S1. Results of the Cohort Selection Process to Assess Hospitalization for Acute Liver Injury: Counts of Treatment Episodes After Exclusions and Final Matched Cohorts

	CPRD		HIRD		Medicare	
Type of exclusion	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD
Total number of potential treatment episodes during the study period	14,881	114,639	46,581	1,014,001	50,262	2,424,555
CPRD-only exclusions:						
Prior to practice up-to-standard date	0	0	NA	NA	NA	NA
Aged < 18 years	0	25	NA	NA	NA	NA
< 180 days of lookback	893	14,343	NA	NA	NA	NA
HIRD-only exclusions:						
Aged < 18 or ≥ 65 years	NA	NA	4,663	215,794	NA	NA
< 180 days of lookback	NA	NA	7,963	269,275	NA	NA
Medicare-only exclusions:						
Aged < 65 years	NA	NA	NA	NA	1,178	47,798
Enrolled because of disability or end-stage renal disease	NA	NA	NA	NA	~ 20[a]	9,661
Not a resident of a US state or District of Columbia at the index date	NA	NA	NA	NA	41	4,992
< 6 months of enrollment	NA	NA	NA	NA	15,554	828,088
Index date coincided with the last date meeting Medicare enrollment criteria (i.e., patient had no follow-up time)	NA	NA	NA	NA	< 11[b]	394
Potential treatment episodes meeting the inclusion criteria after applying the data source–specific exclusions	13,988	100,271	33,955	528,932	33,470	1,533,622

Type of exclusion	CPRD		HIRD		Medicare	
	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD
Diagnosis of type 1 diabetes mellitus on or before the index date	677	3,411	3,347	40,925	2,941	141,937
Dapagliflozin use before the study period	0	0	0	0	0	0
Other SGLT2 inhibitor medication use on or before the index date	174	12,039	6,952	142,609	5,132	215,909
Comparator GLD use starts during dapagliflozin exposure period	0	11	NA	7,207	0	5,713
Potential treatment episodes meeting the inclusion criteria after applying the diabetes-related exclusions	13,137	84,810	23,656	337,226	25,397	1,170,063
Acute liver injury	712	4,744	512	7,516	1,245	50,783
Chronic liver disease or alcoholism	898	5,725	4,494	65,767	7,084	365,527
Chronic or acute hepatitis	~ 95[a]	508	109	1,907	219	7,906
Chronic or acute disease of the gallbladder or pancreas	725	4,968	770	11,353	1,333	76,687
Hepatic, biliary or pancreatic cancer	< 5[c]	69	NR	146	29	1,556
Heart failure	223	3,792	580	10,570	2,207	130,233
Final number of treatment episodes eligible for cohort selection	10,478	65,004	17,187	239,967	13,280	537,371
Final number of treatment episodes selected into the cohort[d]	10,466	39,173	17,187	195,393	13,280	199,193

CMS = Center for Medicare and Medicaid Services; GLD = glucose lowering drug; NA = not applicable; SGLT2 = sodium-glucose cotransporter 2; US = United States.

[a] Approximate value reported to prevent the derivation of unreportable values in other cells.

[b] According to CMS policy, any cell with a value of 1 to 10 cannot be reported.

[c] According to CPRD policy, any cell with a value of 1 to 4 cannot be reported.

[d] Final number of treatment episodes selected after matching and before propensity score trimming.

Table S2. Drugs With Known Association With Liver Injury, Included as Covariate Medications in Analysis to Assess Hospitalization for Acute Liver Injury

Acarbose	Enalapril	Phenobarbital
Acetaminophen (prescription)	Erythromycins	Phenothiazines
Allopurinol	Estrogens	Phenytoin
Amiodarone	Fluoxetine	Pyrazinamide
Amitriptyline	Flutamide	Rifampicin
Amoxicillin + clavulanic acid	HAART drugs	Risperidone
Anabolic steroids	Irbesartan	Sertraline
Aripiprazole	Isoniazid	Statins
Azathioprine	Ketoconazole	Sulfonamides
Baclofen	Lamotrigine	Terbinafine
Bupropion	Lisinopril	Tetracyclines
Captopril	Losartan	Trazodone
Carbamazepine	Methotrexate	Tricyclics
Chlorpromazine	Mirtazapine	Trimethoprim-sulfamethoxazole
Ciprofloxacin	Nitrofurantoin	Valproic acid
Clindamycin	NSAIDs	Verapamil
Clopidogrel	Omeprazole	
Cyproheptadine	Oral contraceptives	
Duloxetine	Paroxetine	

HAART = highly active antiretroviral therapy; NSAID = nonsteroidal anti-inflammatory drug.

Table S3. Selected Baseline Characteristics of Cohorts to Assess Hospitalization for Acute Liver Injury, After Propensity Score Trimming

	CPRD		HIRD		Medicare	
	Dapagliflozin (n = 9,027)	Comparator GLD (n = 32,455)	Dapagliflozin (n = 15,217)	Comparator GLD (n = 175,107)	Dapagliflozin (n = 11,332)	Comparator GLD (n = 172,986)
Age, mean (SD),[a] years	57.6 (10.6)	58.5 (10.9)	51.5 (8.7)	51.6 (8.8)	69.8 (4.4)	69.8 (4.5)
Female sex, n (%)	3,663 (40.6)	13,073 (40.3)	6,747 (44.3)	77,963 (44.5)	5,350 (47.2)	81,418 (47.1)
Race/ethnicity,[b] n (%)						
Asian	NA	NA	NA	NA	462 (4.1)	6,914 (4.0)
Black	NA	NA	NA	NA	781 (6.9)	13,828 (8.0)
Hispanic	NA	NA	NA	NA	448 (4.0)	6,704 (3.9)
White	NA	NA	NA	NA	9,041 (79.8)	135,881 (78.6)
Other[c]	NA	NA	NA	NA	274 (2.4)	4,709 (2.7)
Unknown	NA	NA	NA	NA	326 (2.9)	4,950 (2.9)
Insulin use at the index date, n (%)	954 (10.6)	1,706 (5.3)	2,053 (13.5)	19,462 (11.1)	1,840 (16.2)	23,290 (13.5)
One or more drugs with a known association with liver injury,[d] n (%)	8,275 (91.7)	29,316 (90.3)	13,306 (87.4)	151,279 (86.4)	9,226 (81.4)	143,614 (83.0)
Indicators of diabetes severity, n (%)						
Diabetic nephropathy or renal insufficiency	88 (1.0)	310 (1.0)	280 (1.8)	3,745 (2.1)	729 (6.4)	14,874 (8.6)
Retinopathy	2,566 (28.4)	8,329 (25.7)	3,516 (23.1)	36,845 (21.0)	3,845 (33.9)	52,059 (30.1)
Peripheral neuropathy	256 (2.8)	832 (2.6)	250 (1.6)	2,647 (1.5)	462 (4.1)	7,147 (4.1)
Peripheral vascular disease[e]	292 (3.2)	1,067 (3.3)	3,317 (21.8)	35,228 (20.1)	3,560 (31.4)	50,341 (29.1)
Coronary heart disease	1,043 (11.6)	3,969 (12.2)	1,082 (7.1)	12,753 (7.3)	2,516 (22.2)	37,311 (21.6)
Cerebrovascular disease	391 (4.3)	1,714 (5.3)	196 (1.3)	2,583 (1.5)	991 (8.7)	15,150 (8.8)
Amputation	70 (0.8)	280 (0.9)	42 (0.3)	702 (0.4)	45 (0.4)	1,129 (0.7)
Body mass index (kg/m^2),[f] n (%)						
< 20 (underweight)	16 (0.2)	101 (0.3)	NA	NA	NA	NA

	CPRD		HIRD		Medicare	
	Dapagliflozin (n = 9,027)	Comparator GLD (n = 32,455)	Dapagliflozin (n = 15,217)	Comparator GLD (n = 175,107)	Dapagliflozin (n = 11,332)	Comparator GLD (n = 172,986)
20 to < 25 (normal)	299 (3.3)	1,624 (5.0)	NA	NA	NA	NA
25 to < 30 (overweight)	1,982 (22.0)	8,560 (26.4)	NA	NA	NA	NA
30 to < 40 (obese)	4,932 (54.6)	16,576 (51.1)	NA	NA	NA	NA
≥ 40 (severely obese)	1,648 (18.3)	4,861 (15.0)	NA	NA	NA	NA
Unknown	150 (1.7)	733 (2.3)	NA	NA	NA	NA
Healthcare utilization in the 180 days before the index date						
No. of outpatient visits,[g] n (%)						
0	407 (4.5)	1,297 (4.0)	249 (1.6)	4,282 (2.4)	681 (6.0)	11,624 (6.7)
1	791 (8.8)	2,777 (8.6)	646 (4.2)	8,571 (4.9)	809 (7.1)	13,600 (7.9)
2 or more	7,829 (86.7)	28,381 (87.4)	14,322 (94.1)	162,254 (92.7)	9,842 (86.9)	147,762 (85.4)
No. of hospitalizations, n (%)						
0	8,275 (91.7)	29,497 (90.9)	14,852 (97.6)	169,744 (96.9)	10,980 (96.9)	166,156 (96.1)
1	565 (6.3)	2,118 (6.5)	333 (2.2)	4,872 (2.8)	290 (2.6)	5,447 (3.1)
2 or more	187 (2.1)	840 (2.6)	32 (0.2)	491 (0.3)	62 (0.5)	1,383 (0.8)
No. of GLD classes[h] used within 12 months[i] before the index date, n (%)						
0	73 (0.8)	486 (1.5)	2,227 (14.6)	31,885 (18.2)	757 (6.7)	15,181 (8.8)
1-2	6,100 (67.6)*	27,969 (86.2)*	11,016 (72.4)	131,099 (74.9)	7,220 (63.7)*	127,377 (73.6)*
3-4	2,825 (31.3)*	3,956 (12.2)*	1,965 (12.9)	12,105 (6.9)	3,342 (29.5)*	30,263 (17.5)*
5-8	29 (0.3)	44 (0.1)	NR	18 (< 0.1)	13 (0.1)	165 (0.1)
Type of index therapy,[j] n (%)						
Index monotherapy with no prior treatment	184 (2.0)	566 (1.7)	1,276 (8.4)	15,622 (8.9)	1,175 (10.4)	12,930 (7.5)
Combined index therapy with no prior treatment	129 (1.4)	860 (2.6)	1,188 (7.8)	18,303 (10.5)	606 (5.3)	18,360 (10.6)

	CPRD		HIRD		Medicare	
	Dapagliflozin (n = 9,027)	Comparator GLD (n = 32,455)	Dapagliflozin (n = 15,217)	Comparator GLD (n = 175,107)	Dapagliflozin (n = 11,332)	Comparator GLD (n = 172,986)
Add-on index therapy	5,591 (61.9)	23,021 (70.9)	10,162 (66.8)	110,058 (62.9)	6,417 (56.6)	92,689 (53.6)
Switched-to index therapy	354 (3.9)	2,153 (6.6)	330 (2.2)	3,379 (1.9)	817 (7.2)	15,383 (8.9)
Add-on and switched-to index therapy	2,451 (27.2)*	4,783 (14.7)*	1,208 (7.9)	9,229 (5.3)	1,719 (15.2)	24,663 (14.3)
Nonevaluable[k]	318 (3.5)	1,072 (3.3)	1,053 (6.9)	18,516 (10.6)	598 (5.3)	8,961 (5.2)

CPRD = Clinical Practice Research Datalink; GLD = glucose-lowering drug; HIRD = HealthCore Integrated Research Database; NA = not applicable; SD = standard deviation.

* Absolute standardized difference (StDiff) > 0.20.

[a] Patients were aged 18 years or older in CPRD, 18-64 years in the HIRD, and 65 years or older in Medicare.

[b] Data on race/ethnicity were available only in Medicare.

[c] Includes patients categorized as Other or North American Native in Medicare.

[d] Drugs with a known association with liver injury are listed in Table S2.

[e] Includes peripheral artery disease.

[f] Data on body mass index were available only in CPRD.

[g] Outpatient visits included general practitioner and outpatient hospital visits.

[h] Glucose-lowering drug classes that were considered were insulin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, biguanides (metformin), alpha glucosidase inhibitors, and meglitinides.

[i] Those with at least 180 days of available lookback data before the index date were eligible for inclusion in the study, and therefore some patients had less than 12 months of available lookback data.

[j] Detailed definitions for the index therapy type categories are provided in Section 1.5.

[k] Patients who did not have sufficient follow-up time to assess the 90-day add-on/switch requirement.

Table S4. Results of the Cohort Selection Process to Assess Severe Complications of Urinary Tract Infection: Counts of Treatment Episodes After Exclusions and Final Matched Cohorts

	CPRD		HIRD		Medicare	
Type of exclusion	**Dapagliflozin**	**Comparator GLD**	**Dapagliflozin**	**Comparator GLD**	**Dapagliflozin**	**Comparator GLD**
Total number of potential treatment episodes during the study period	14,881	114,639	46,581	1,014,001	50,262	2,424,555
CPRD-only exclusions:						
Prior to practice up-to-standard date	0	0	NA	NA	NA	NA
Aged < 18 years	0	25	NA	NA	NA	NA
< 180 days of lookback	893	14,343	NA	NA	NA	NA
HIRD-only exclusions:						
Aged < 18 or ≥ 65 years	NA	NA	4,663	215,794	NA	NA
< 180 days of lookback	NA	NA	7,963	269,275	NA	NA
Medicare-only exclusions:						
Aged < 65 years	NA	NA	NA	NA	1,178	47,798
Enrolled because of disability or end-stage renal disease	NA	NA	NA	NA	~ 20[a]	9,661
Not a resident of a US state or District of Columbia at the index date	NA	NA	NA	NA	41	4,992
< 6 months of enrollment	NA	NA	NA	NA	15,554	828,088
Index date coincided with the last date meeting Medicare enrollment criteria (i.e., patient has no follow-up time)	NA	NA	NA	NA	< 11[b]	394
Potential treatment episodes meeting the inclusion criteria after applying the data source–specific exclusions	13,988	100,271	33,955	528,932	33,470	1,533,622
Diagnosis of type 1 diabetes mellitus on or before the index date	677	3,411	3,347	40,925	2,941	141,937

Type of exclusion	CPRD		HIRD		Medicare	
	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD
Dapagliflozin use before the study period	0	0	0	0	0	0
Other SGLT2 inhibitor medication use on or before the index date	174	12,039	6,952	142,609	5,132	215,909
Comparator GLD use starts during dapagliflozin exposure period	0	11	0	7,207	0	5,713
Potential treatment episodes meeting the inclusion criteria after applying the diabetes-related exclusions	13,137	84,810	23,656	337,226	25,397	1,170,063
Chronic pyelonephritis	10	92	< 11[c]	295	53	2,944
Females						
Final number of treatment episodes eligible for cohort selection	5,510	36,276	10,551	158,833	12,561	618,885
Final number of treatment episodes selected into the cohort[d]	5,508	20,807	10,544	124,755	12,561	188,415
Males						
Final number of treatment episodes eligible for cohort selection	7,617	48,442	13,095	178,098	12,783	548,234
Final number of treatment episodes selected into the cohort[d]	7,610	29,195	13,091	147,737	12,783	191,736

CMS = Center for Medicare and Medicaid Services; CPRD = Clinical Practice Research Datalink; GLD = glucose-lowering drug; HIRD = HealthCore Integrated Research Database; NA = not applicable; SGLT2 = sodium-glucose cotransporter 2; US = United States.

[a] Approximate value reported to prevent the derivation of unreportable values in other cells.

[b] According to CMS policy, any cell with a value of 1 to 10 cannot be reported.

[c] According to HIRD policy, any cell with a value of 1 to 10 cannot be reported.

[d] Final number of treatment episodes selected into the cohort after matching and before propensity score trimming.

Table S5. Selected Baseline Characteristics of Cohorts to Assess Severe Complications of Urinary Tract Infection, After Propensity Score Trimming

	CPRD		HIRD		Medicare	
	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD
Females	**n = 4,764**	**n = 17,901**	**n = 9,413**	**n = 111,587**	**n = 10,653**	**n = 163,262**
Age, mean (SD),[a] years	57.0 (11.1)	58.4 (11.3)	51.6 (8.8)	51.5 (9.1)	71.7 (5.8)	71.7 (5.8)
Race/ethnicity,[b] n (%)						
Asian	NA	NA	NA	NA	725 (6.8)	8,458 (5.2)
Black	NA	NA	NA	NA	930 (8.7)	17,401 (10.7)
Hispanic	NA	NA	NA	NA	554 (5.2)	7,596 (4.7)
White	NA	NA	NA	NA	8,003 (75.1)	122,314 (74.9)
Other[c]	NA	NA	NA	NA	263 (2.5)	5,052 (3.1)
Unknown	NA	NA	NA	NA	178 (1.7)	2,441 (1.5)
Insulin use at the index date, n (%)	535 (11.2)	1,072 (6.0)	1,355 (14.4)	13,472 (12.1)	1,899 (17.8)	25,000 (15.3)
Kidney diseases, all types, acute and chronic, n (%)	406 (8.5)	2,166 (12.1)	418 (4.4)	5,579 (5.0)	1,849 (17.4)	34,065 (20.9)
Urinary infections (chronic or recurring), n (%)	217 (4.6)	833 (4.7)	1,051 (11.2)	12,944 (11.6)	2,706 (25.4)	42,013 (25.7)
Indicators of diabetes severity, n (%)						
Diabetic nephropathy or renal insufficiency	33 (0.7)	108 (0.6)	179 (1.9)	2,337 (2.1)	963 (9.0)	17,292 (10.6)
Retinopathy	1,205 (25.3)	4,070 (22.7)	2,316 (24.6)	24,583 (22.0)	4,294 (40.3)	59,751 (36.6)
Peripheral neuropathy	137 (2.9)	485 (2.7)	204 (2.2)	2,197 (2.0)	768 (7.2)	12,172 (7.5)
Peripheral vascular disease[d]	97 (2.0)	469 (2.6)	2,174 (23.1)	23,449 (21.0)	4,305 (40.4)	62,327 (38.2)
Coronary heart disease	357 (7.5)	1,549 (8.7)	667 (7.1)	8,009 (7.2)	3,171 (29.8)	46,806 (28.7)
Cerebrovascular disease	202 (4.2)	957 (5.3)	168 (1.8)	2,286 (2.0)	1,700 (16.0)	25,432 (15.6)
Amputation	14 (0.3)	85 (0.5)	13 (0.1)	186 (0.2)	43 (0.4)	1,083 (0.7)

	CPRD		HIRD		Medicare	
	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD
Body mass index (kg/m^2),[e] n (%)						
< 20 (underweight)	11 (0.2)	119 (0.7)	NA	NA	NA	NA
20 to < 25 (normal)	154 (3.2)	1,272 (7.1)	NA	NA	NA	NA
25 to < 30 (overweight)	794 (16.7)	3,748 (20.9)	NA	NA	NA	NA
30 to < 40 (obese)	2,462 (51.7)	8,553 (47.8)	NA	NA	NA	NA
≥ 40 (severely obese)	1,271 (26.7)	3,641 (20.3)	NA	NA	NA	NA
Unknown	72 (1.5)	568 (3.2)	NA	NA	NA	NA
Healthcare utilization in the 180 days before the index date						
No. of outpatient visits,[f] n (%)						
0	173 (3.6)	573 (3.2)	90 (1.0)	1,737 (1.6)	467 (4.4)	8,864 (5.4)
1	303 (6.4)	1,113 (6.2)	249 (2.6)	3,381 (3.0)	568 (5.3)	9,936 (6.1)
2 or more	4,288 (90.0)	16,215 (90.6)	9,074 (96.4)	106,469 (95.4)	9,618 (90.3)	144,462 (88.5)
No. of hospitalizations, n (%)						
0	4,272 (89.7)	15,871 (88.7)	9,103 (96.7)	106,866 (95.8)	10,001 (93.9)	149,512 (91.6)
1	352 (7.4)	1,366 (7.6)	272 (2.9)	4,135 (3.7)	443 (4.2)	8,998 (5.5)
2 or more	140 (2.9)	664 (3.7)	38 (0.4)	586 (0.5)	209 (2.0)	4,752 (2.9)
No. of GLD classes[g] used within 12 months[h] before the index date, n (%)						
0	42 (0.9)	382 (2.1)	1,398 (14.9)	21,299 (19.1)	700 (6.6)	13,435 (8.2)
1-2	3,427 (71.9)*	15,442 (86.3)*	6,962 (74.0)	83,046 (74.4)	6,949 (65.2)	121,122 (74.2)
3-4	1,285 (27.0)*	2,056 (11.5)*	1,049 (11.1)*	7,230 (6.5)*	2,983 (28.0)*	28,522 (17.5)*
5-8	10 (0.2)	21 (0.1)	NR	12 (< 0.1)	21 (0.2)	183 (0.1)
Type of index therapy,[i] n (%)						

	CPRD		HIRD		Medicare	
	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD
Index monotherapy with no prior treatment	122 (2.6)	401 (2.2)	910 (9.7)	14,113 (12.6)	1,147 (10.8)	14,545 (8.9)
Combined index therapy with no prior treatment	62 (1.3)	536 (3.0)	638 (6.8)	8,532 (7.6)	547 (5.1)	14,103 (8.6)
Add-on index therapy	2,938 (61.7)	12,204 (68.2)	6,192 (65.8)	67,774 (60.7)	5,843 (54.8)	82,551 (50.6)
Switched-to index therapy	271 (5.7)	1,591 (8.9)	261 (2.8)	2,975 (2.7)	912 (8.6)	18,773 (11.5)
Add-on and switched-to index therapy	1,204 (25.3)*	2,553 (14.3)*	807 (8.6)	6,692 (6.0)	1,625 (15.3)	24,070 (14.7)
Nonevaluable[j]	167 (3.5)	616 (3.4)	605 (6.4)	11,501 (10.3)	579 (5.4)	9,220 (5.6)
Males	**n = 6,411**	**n = 23,768**	**n = 11,550**	**n = 132,196**	**n = 10,744**	**n = 164,580**
Age, mean (SD),[a] years	58.0 (10.1)	58.5 (10.4)	52.0 (8.3)	52.1 (8.3)	71.3 (5.3)	71.3 (5.3)
Race/ethnicity,[b] n (%)						
Asian	NA	NA	NA	NA	521 (4.8)	6,584 (4.0)
Black	NA	NA	NA	NA	520 (4.8)	11,184 (6.8)
Hispanic	NA	NA	NA	NA	317 (3.0)	4,963 (3.0)
White	NA	NA	NA	NA	8,750 (81.4)	131,270 (79.8)
Other[c]	NA	NA	NA	NA	308 (2.9)	5,556 (3.4)
Unknown	NA	NA	NA	NA	328 (3.1)	5,023 (3.1)
Insulin use at the index date, n (%)	683 (10.7)	1,314 (5.5)	1,592 (13.8)	15,261 (11.5)	1,799 (16.7)	23,446 (14.2)
Kidney diseases, all types, acute and chronic, n (%)	433 (6.8)	2,010 (8.5)	583 (5.0)	7,978 (6.0)	2,098 (19.5)	37,611 (22.9)
Urinary infections (chronic or recurring), n (%)	85 (1.3)	331 (1.4)	298 (2.6)	3,525 (2.7)	1,089 (10.1)	16,151 (9.8)
Indicators of diabetes severity, n (%)						
Diabetic nephropathy or renal insufficiency	75 (1.2)	254 (1.1)	247 (2.1)	3,381 (2.6)	1,089 (10.1)	19,392 (11.8)
Retinopathy	1,862 (29.0)	6,291 (26.5)	2,816 (24.4)	30,317 (22.9)	3,936 (36.6)	54,684 (33.2)

	CPRD		HIRD		Medicare	
	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD
Peripheral neuropathy	230 (3.6)	718 (3.0)	216 (1.9)	2,496 (1.9)	749 (7.0)	10,866 (6.6)
Peripheral vascular disease[d]	272 (4.2)	974 (4.1)	2,724 (23.6)	30,004 (22.7)	4,194 (39.0)	60,905 (37.0)
Coronary heart disease	1,053 (16.4)	3,819 (16.1)	1,412 (12.2)	16,542 (12.5)	4,394 (40.9)	65,775 (40.0)
Cerebrovascular disease	316 (4.9)	1,312 (5.5)	215 (1.9)	2,773 (2.1)	1,622 (15.1)	25,146 (15.3)
Amputation	71 (1.1)	276 (1.2)	47 (0.4)	638 (0.5)	110 (1.0)	1,966 (1.2)
Body mass index (kg/m^2),[e] n (%)						
< 20 (underweight)	8 (0.1)	39 (0.2)	NA	NA	NA	NA
20 to < 25 (normal)	255 (4.0)	1,446 (6.1)	NA	NA	NA	NA
25 to < 30 (overweight)	1,518 (23.7)	6,827 (28.7)	NA	NA	NA	NA
30 to < 40 (obese)	3,603 (56.2)	12,169 (51.2)	NA	NA	NA	NA
≥ 40 (severely obese)	908 (14.2)	2,678 (11.3)	NA	NA	NA	NA
Unknown	119 (1.9)	609 (2.6)	NA	NA	NA	NA
Healthcare utilization in the 180 days before the index date						
No. of outpatient visits,[f] n (%)						
0	293 (4.6)	981 (4.1)	210 (1.8)	3,694 (2.8)	454 (4.2)	8,156 (5.0)
1	620 (9.7)	2,231 (9.4)	531 (4.6)	6,931 (5.2)	607 (5.6)	10,205 (6.2)
2 or more	5,498 (85.8)	20,556 (86.5)	10,809 (93.6)	121,571 (92.0)	9,683 (90.1)	146,219 (88.8)
No. of hospitalizations, n (%)						
0	5,839 (91.1)	21,373 (89.9)	11,150 (96.5)	126,280 (95.5)	10,035 (93.4)	150,481 (91.4)
1	410 (6.4)	1,621 (6.8)	360 (3.1)	5,325 (4.0)	511 (4.8)	9,730 (5.9)
2 or more	162 (2.5)	774 (3.3)	40 (0.3)	591 (0.4)	198 (1.8)	4,369 (2.7)
No. of GLD classes[g] used within 12 months[h] before the index date, n (%)						
0	63 (1.0)	438 (1.8)	1,542 (13.4)	21,550 (16.3)	678 (6.3)	13,440 (8.2)

	CPRD		HIRD		Medicare	
	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD	Dapagliflozin	Comparator GLD
1-2	4,253 (66.3)*	20,316 (85.5)*	8,228 (71.2)	100,001 (75.6)	6,766 (63.0)*	120,763 (73.4)*
3-4	2,070 (32.3)*	2,983 (12.6)*	1,777 (15.4)*	10,636 (8.0)*	3,267 (30.4)*	30,124 (18.3)*
5-8	25 (0.4)	31 (0.1)	NR	NR	33 (0.3)	253 (0.2)
Type of index therapy,[i] n (%)						
Index monotherapy with no prior treatment	117 (1.8)	409 (1.7)	808 (7.0)	7,652 (5.8)	1,039 (9.7)	12,009 (7.3)
Combined index therapy with no prior treatment	97 (1.5)	679 (2.9)	900 (7.8)	15,115 (11.4)	532 (5.0)	15,997 (9.7)
Add-on index therapy	4,039 (63.0)	17,033 (71.7)	7,927 (68.6)	86,106 (65.1)	6,171 (57.4)	87,377 (53.1)
Switched-to index therapy	198 (3.1)	1,325 (5.6)	208 (1.8)	1,963 (1.5)	758 (7.1)	15,319 (9.3)
Add-on and switched-to index therapy	1,729 (27.0)*	3,489 (14.7)*	865 (7.5)	6,966 (5.3)	1,671 (15.6)	24,800 (15.1)
Nonevaluable[j]	231 (3.6)	833 (3.5)	842 (7.3)	14,394 (10.9)	573 (5.3)	9,078 (5.5)

CPRD = Clinical Practice Research Datalink; GLD = glucose-lowering drug; HIRD = HealthCore Integrated Research Database; NA = not applicable; SD = standard deviation.

* Absolute standardized difference (StDiff) > 0.20.

[a] Patients were aged 18 years or older in CPRD, 18-64 years in the HIRD, and 65 years or older in Medicare.

[b] Data on race/ethnicity were available only in Medicare.

[c] Includes patients categorized as Other or North American Native in Medicare.

[d] Includes peripheral artery disease.

[e] Data on body mass index were available only in CPRD.

[f] Outpatient visits included general practitioner and outpatient hospital visits.

[g] Glucose-lowering drug classes that were considered were insulin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, biguanides (metformin), alpha glucosidase inhibitors, and meglitinides.

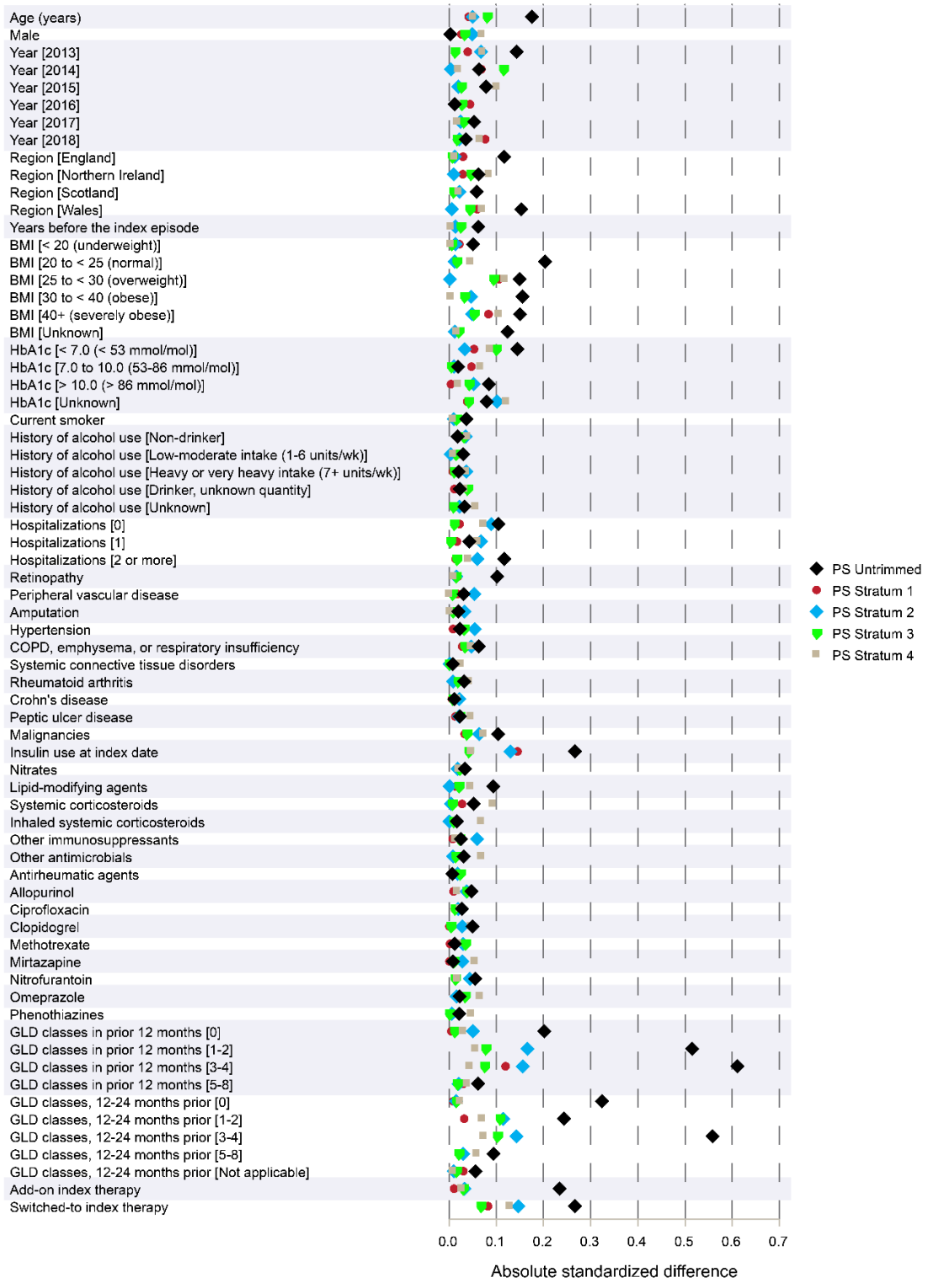
[h] Those with at least 180 days of available lookback data before the index date were eligible for inclusion in the study, and therefore some patients had less than 12 months of available lookback data.

[i] Detailed definitions for the index therapy type categories are provided in Section 1.5.

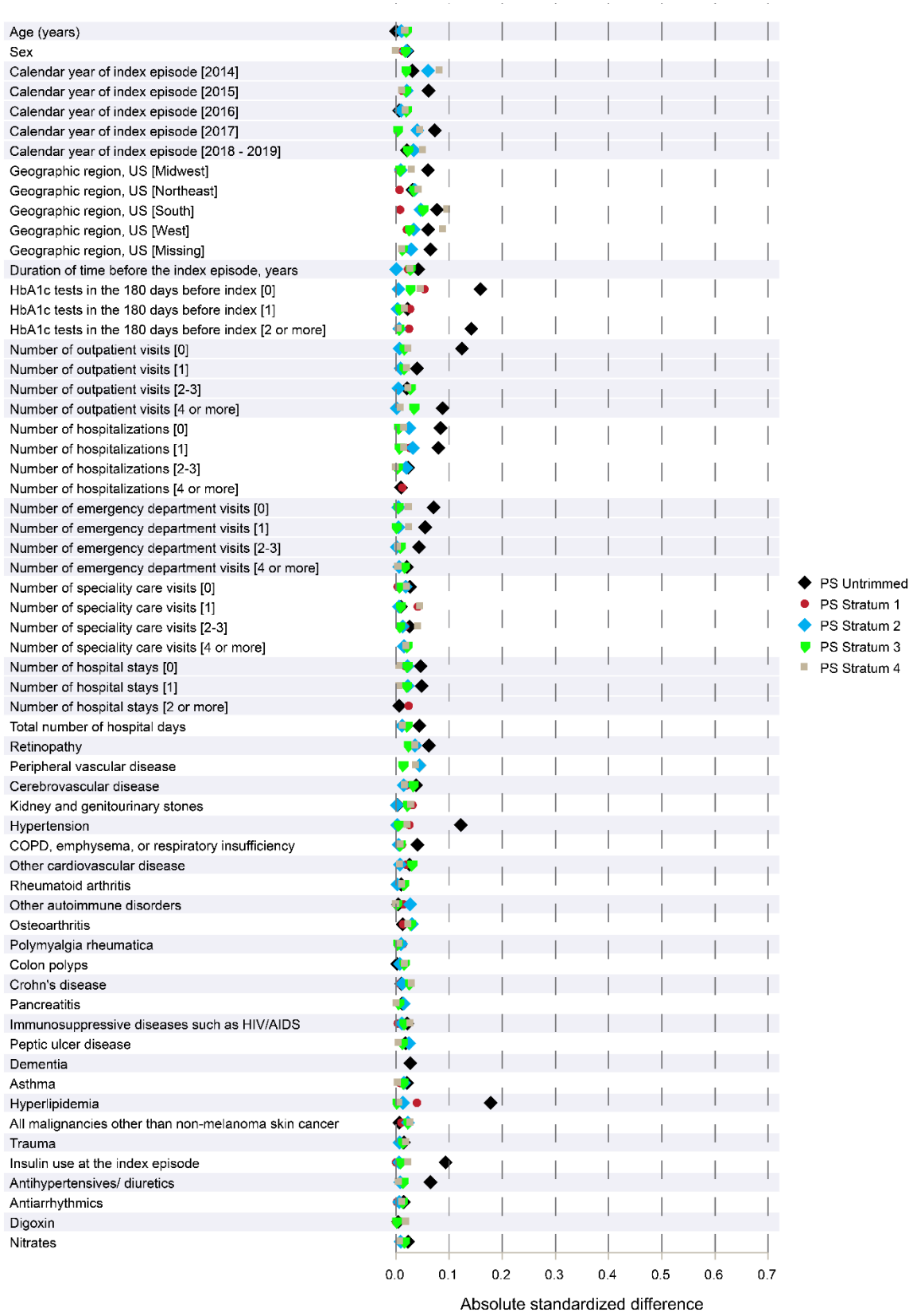
[j] Patients who did not have sufficient follow-up time to assess the 90-day add-on/switch requirement.

Figure S1. Balance of Covariates[a] in the Cohorts to Assess Hospitalization for Acute Liver Injury, Full Cohort Before Propensity Score Trimming and Within Propensity Score Strata After Trimming, by Data Source

CPRD



HIRD



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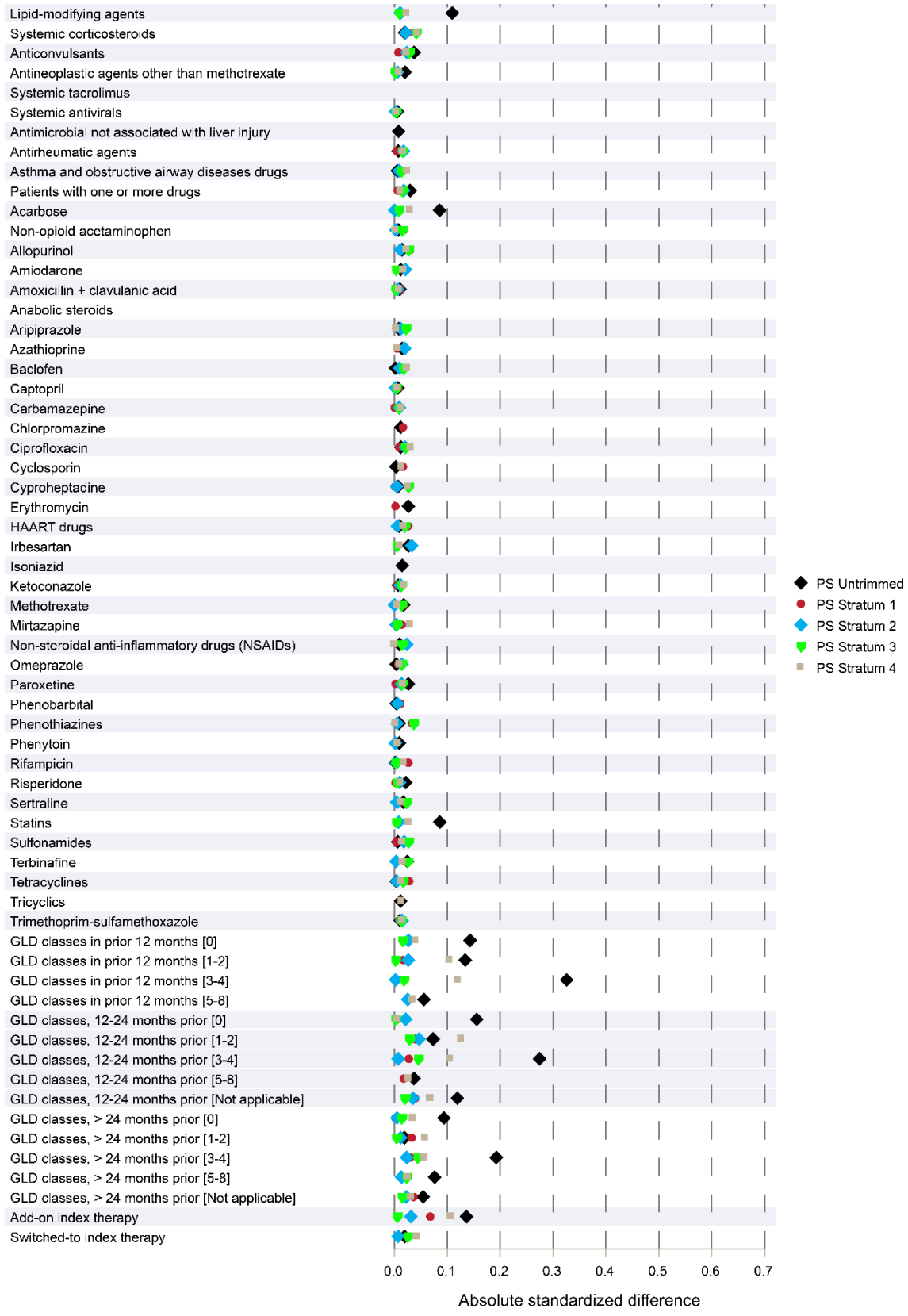
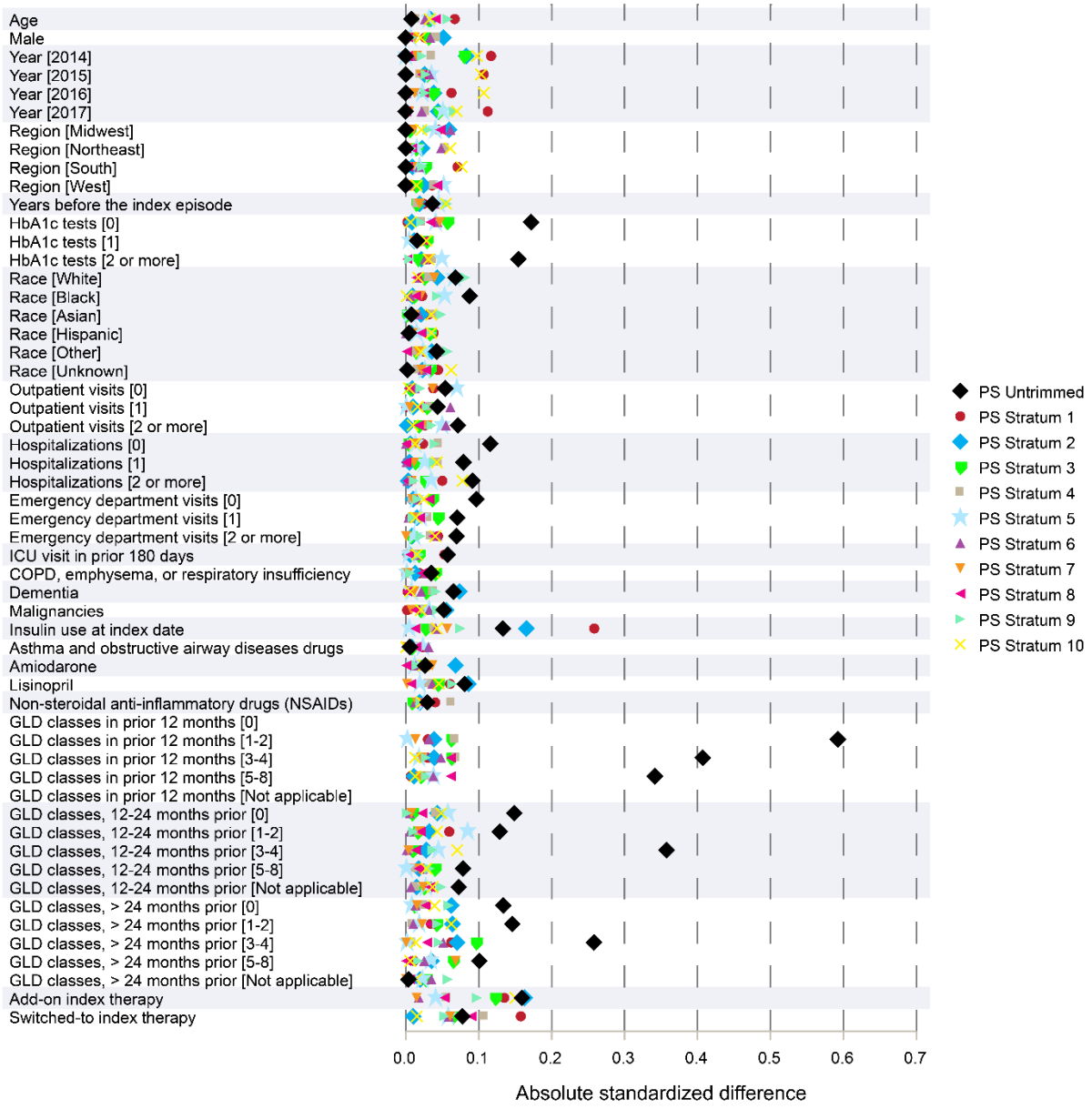


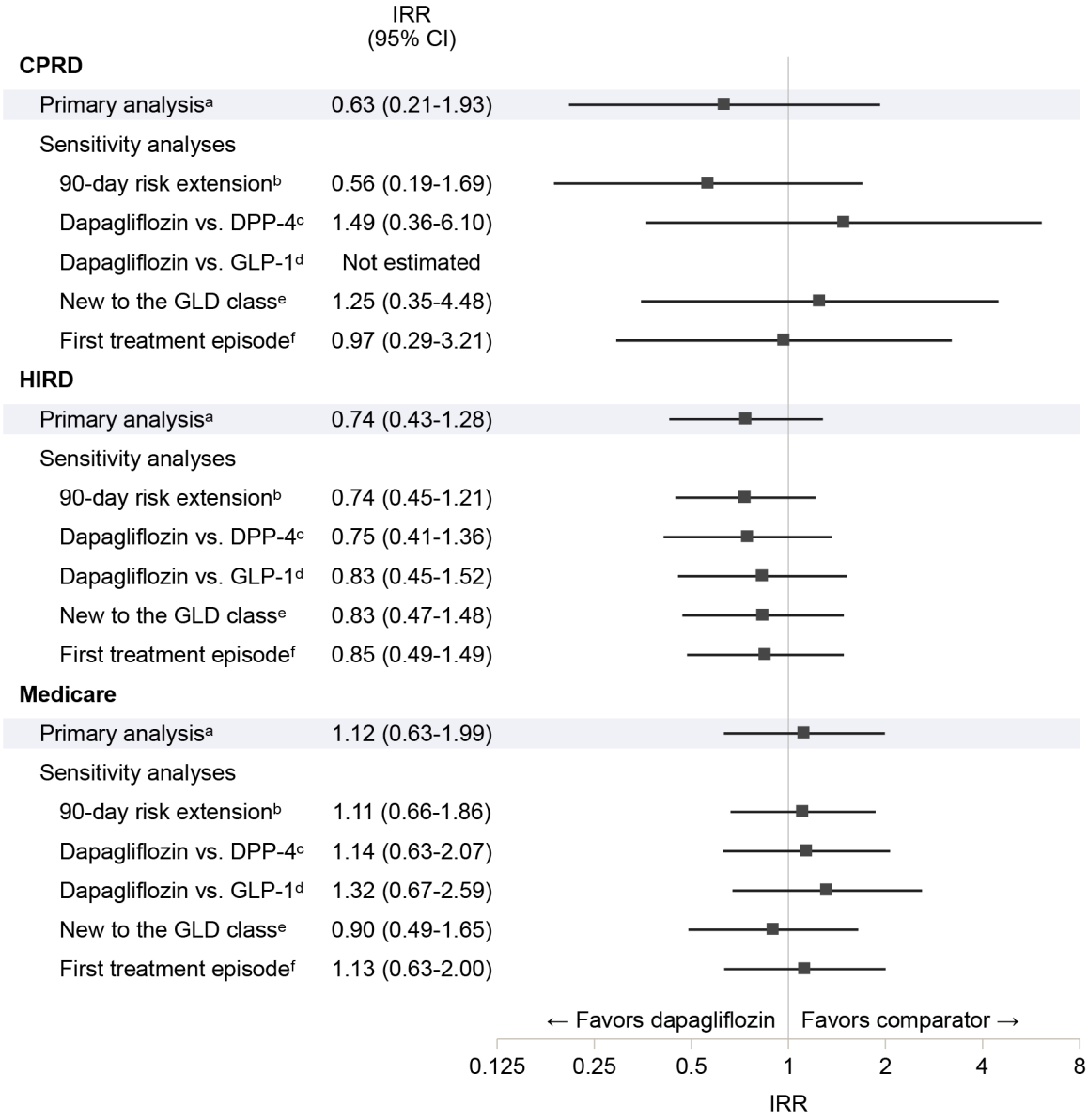
Medicare



BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPRD = Clinical Practice Research Datalink; GLD = glucose-lowering drug; HAART = highly active antiretroviral therapy; HbA1c = glycated hemoglobin; HIRD = HealthCore Integrated Research Database HIV = human immunodeficiency virus; ICU = intensive care unit; PS = propensity score; US = United States.

[a] Each data source−specific plot presents only the variables that were included as covariates in the propensity score model for each respective data source.

Figure S2. Adjusted Incidence Rate Ratios for Hospitalization for Acute Liver Injury, Sensitivity Analyses Compared With the Primary Results



CI = confidence interval; CPRD = Clinical Practice Research Datalink; GLD = glucose-lowering drug; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HIRD = HealthCore Integrated Research Database; IRR = incidence rate ratio.

[a] The primary analysis was the overall analysis.

[b] The risk extension window was increased from 30 days to 90 days.

[c] Compared dapagliflozin treatment episodes with treatment episodes of DPP-4 inhibitors as an alternative comparator GLD cohort. Propensity scores were calculated on the overall sample.

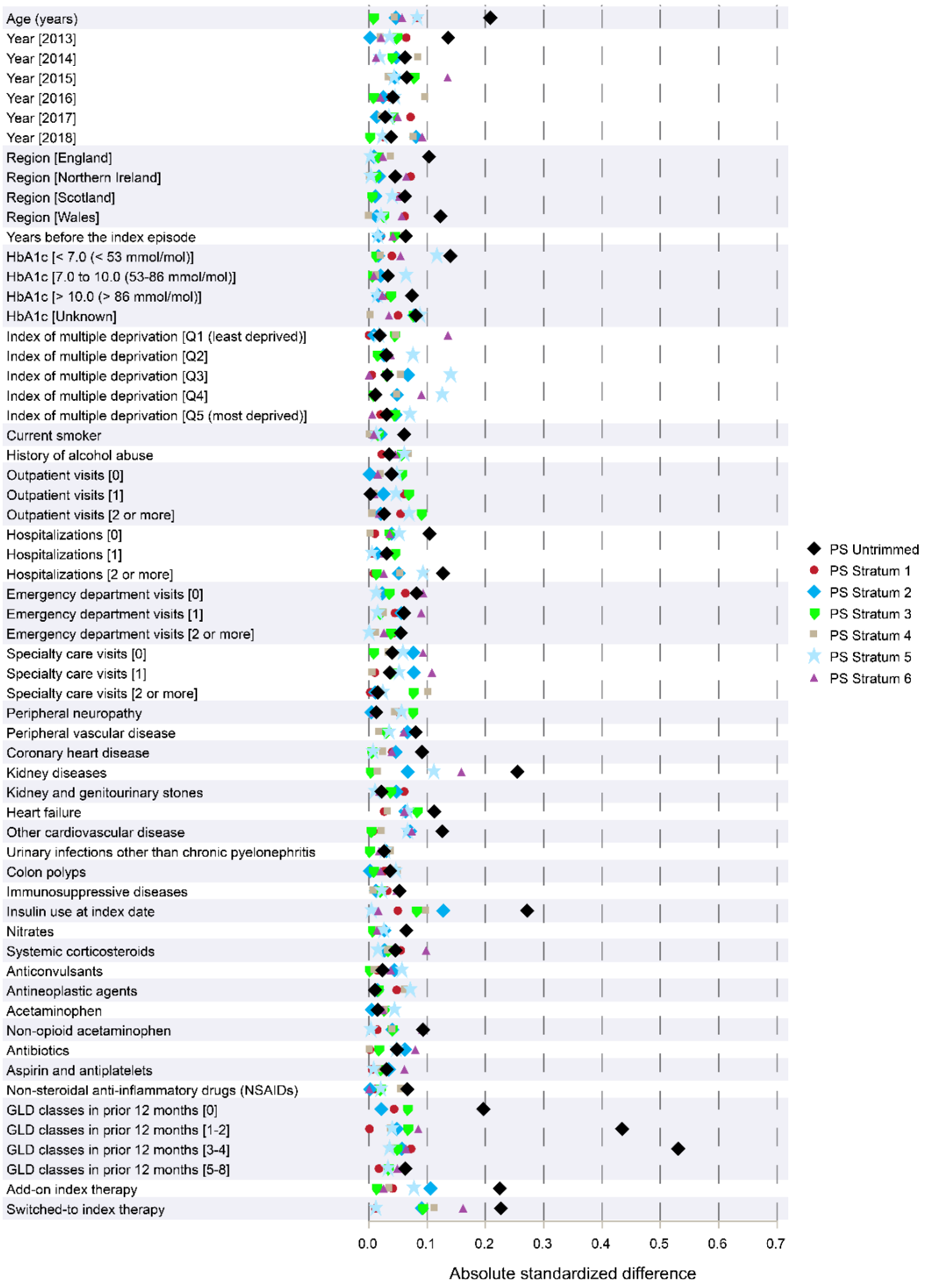
[d] Compared dapagliflozin treatment episodes with treatment episodes of GLP-1 receptor agonists as an alternative comparator GLD cohort. Propensity scores were calculated on the overall sample.

[e] Included only comparator GLD treatment episodes in which the patient was new to the index GLD class. The propensity score model was calculated after removing patients not new to the index GLD class.

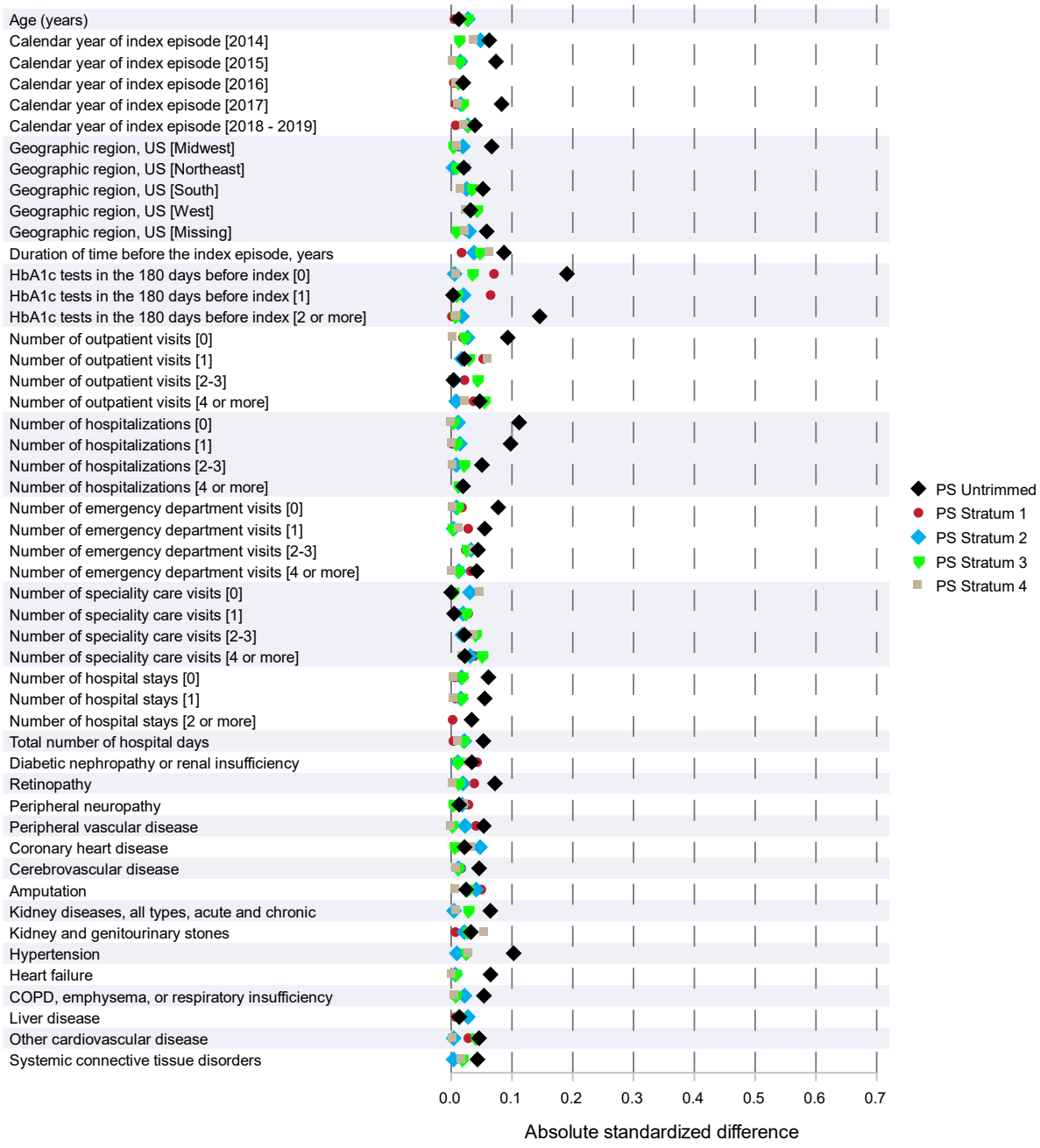
[f] Conducted using only the first treatment episode for each person in each treatment group in the primary analysis sample.

Figure S3. Balance of Covariates[a] in the Cohorts to Assess Severe Complications of Urinary Tract Infection, Full Cohort Before Propensity Score Trimming and Within Propensity Score Strata After Trimming, by Sex and Data Source

Females – CPRD



Females – HIRD



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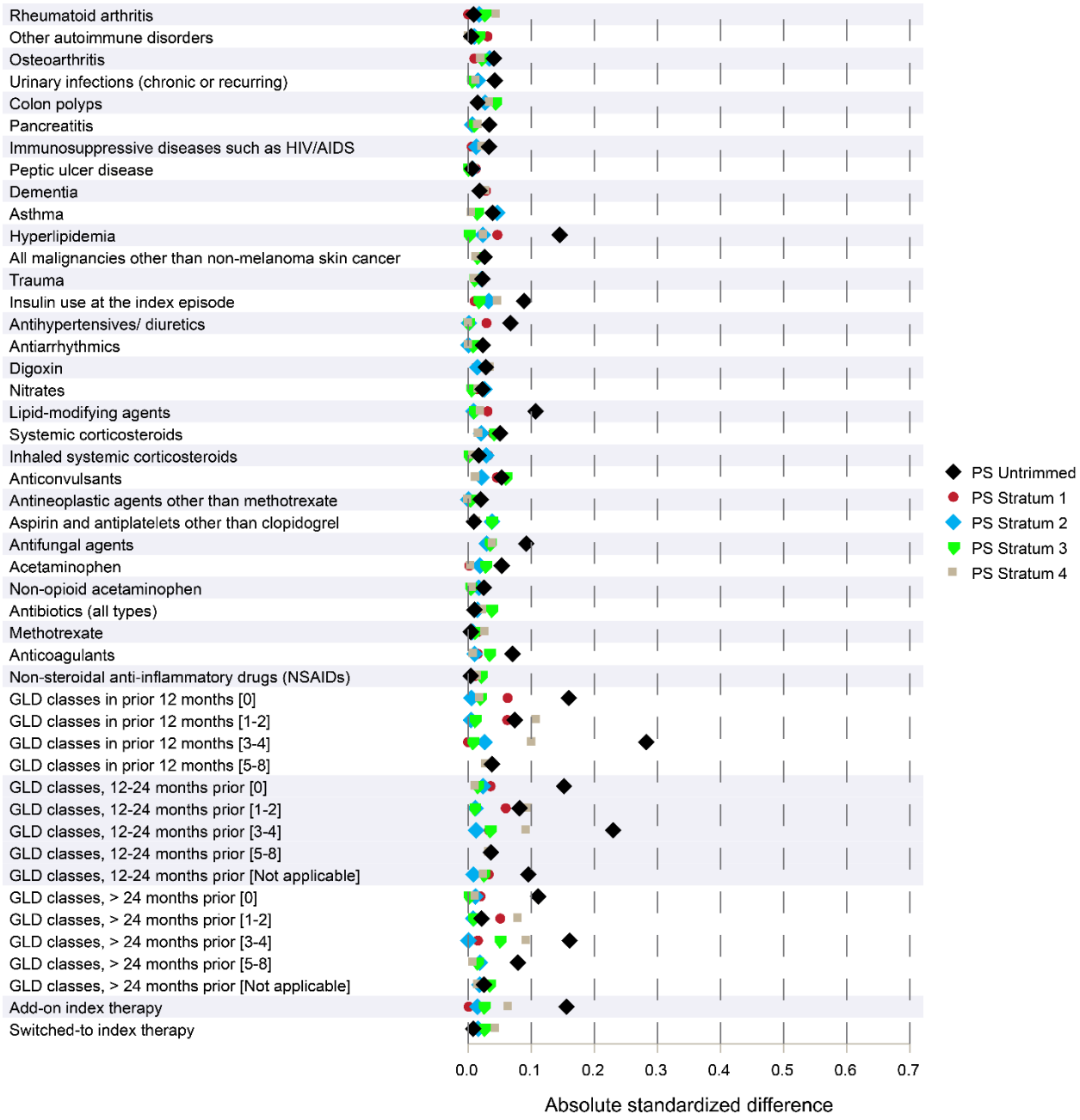
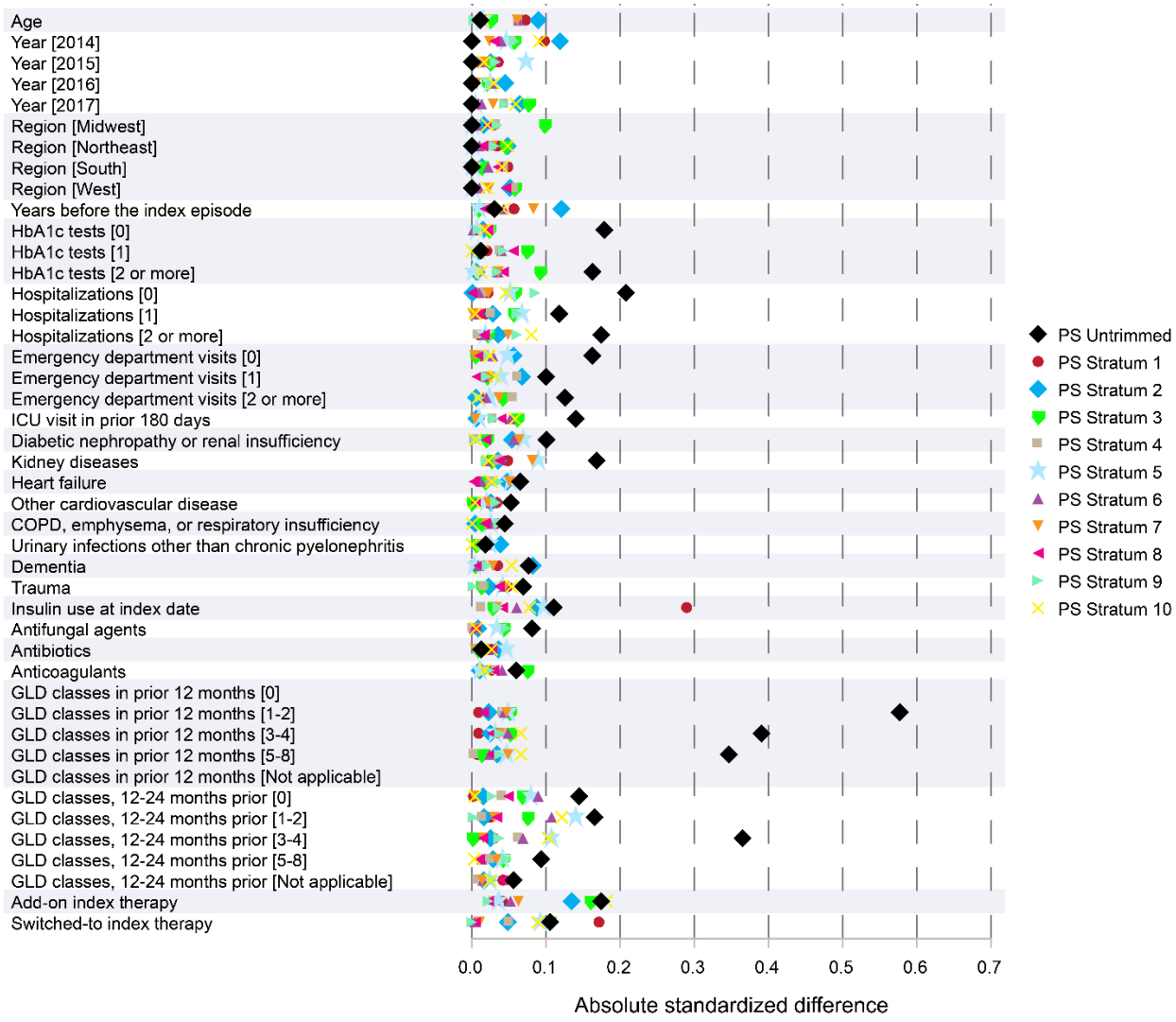
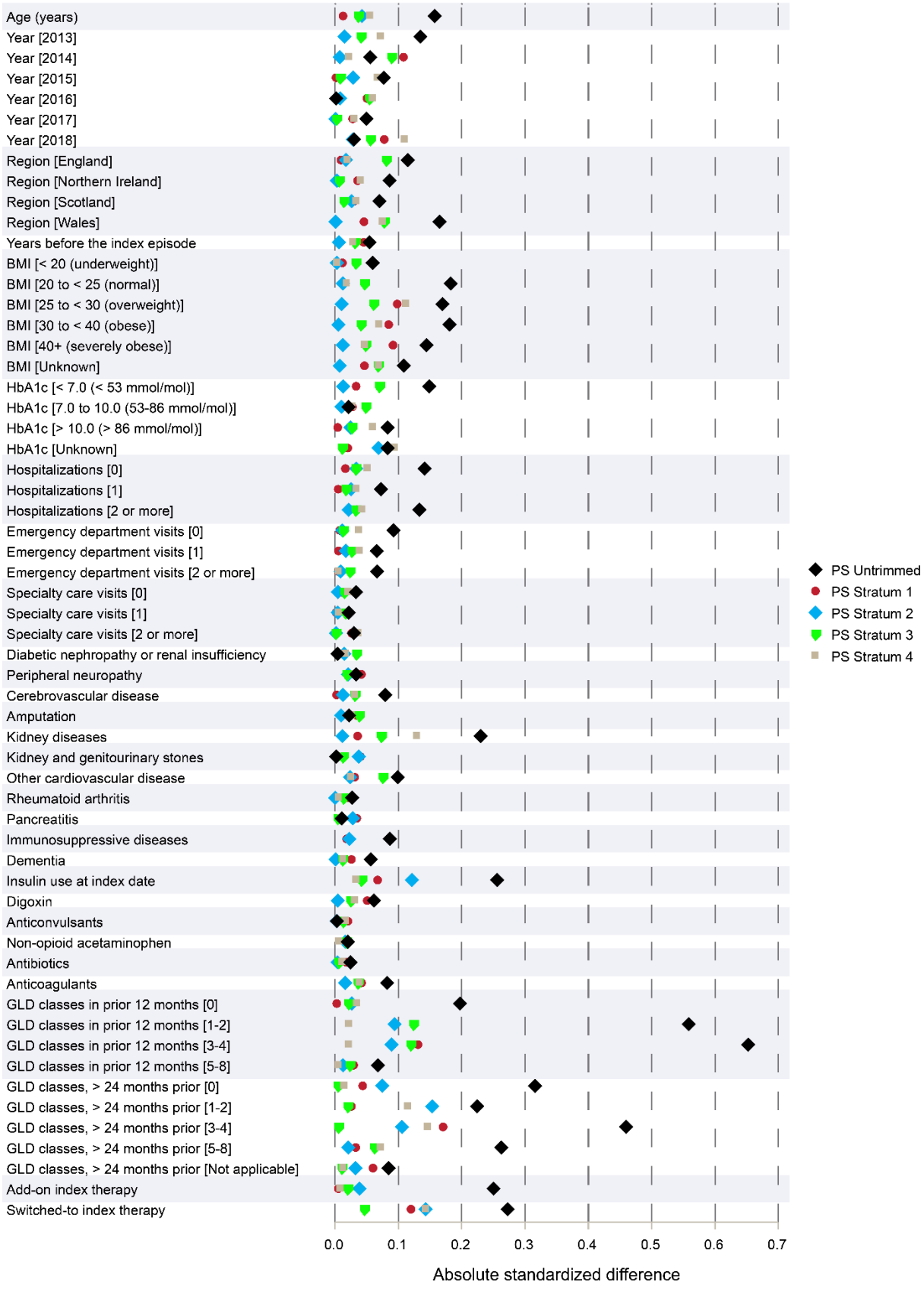


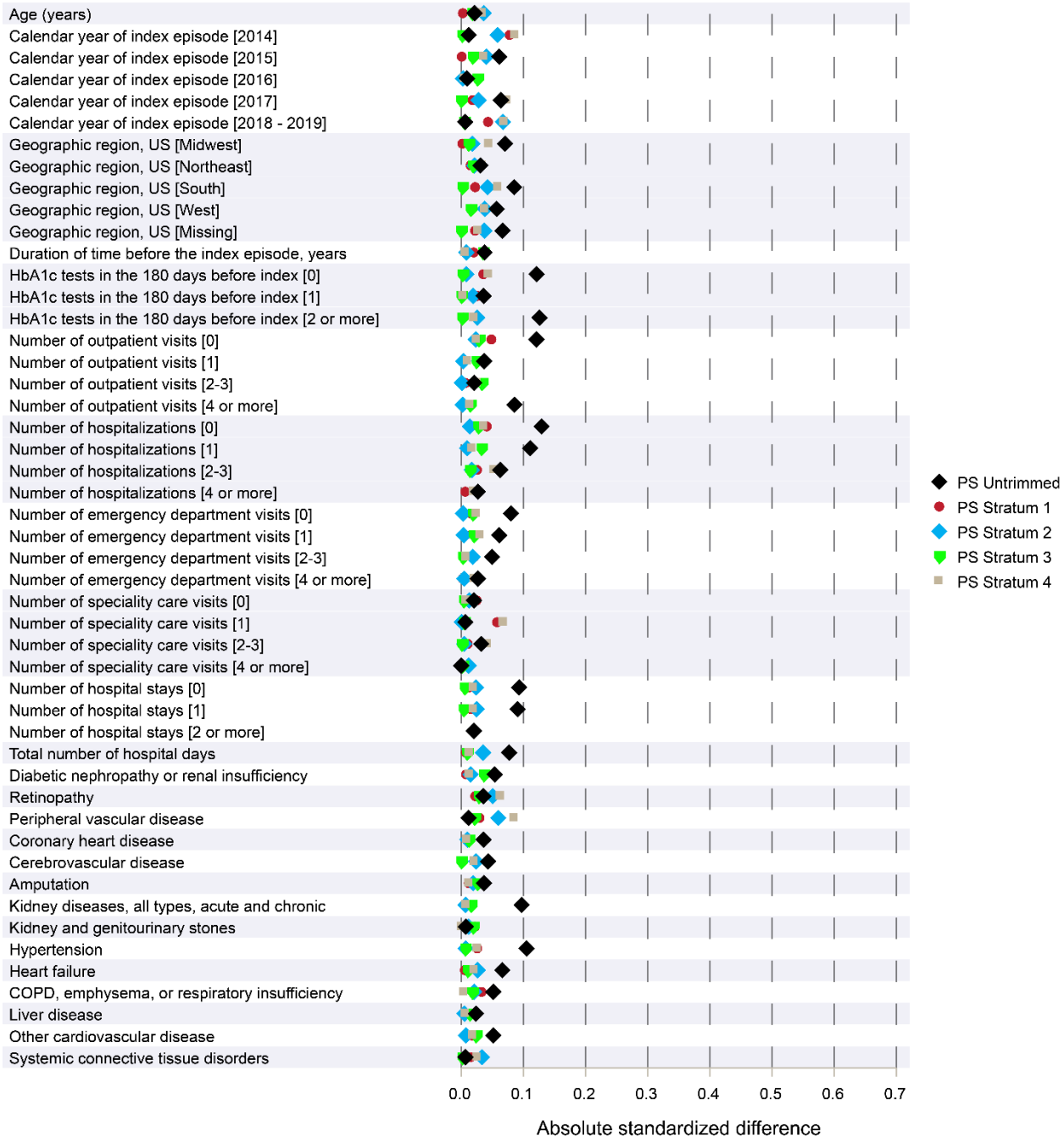
Females – Medicare



Males – CPRD


Age (years)
Year [2013]
Year [2014]
Year [2015]
Year [2016]
Year [2017]
Year [2018]
Region [England]
Region [Northern Ireland]
Region [Scotland]
Region [Wales]
Years before the index episode
BMI [< 20 (underweight)]
BMI [20 to < 25 (normal)]
BMI [25 to < 30 (overweight)]
BMI [30 to < 40 (obese)]
BMI [40+ (severely obese)]
BMI [Unknown]
HbA1c [< 7.0 (< 53 mmol/mol)]
HbA1c [7.0 to 10.0 (53-86 mmol/mol)]
HbA1c [> 10.0 (> 86 mmol/mol)]
HbA1c [Unknown]
Hospitalizations [0]
Hospitalizations [1]
Hospitalizations [2 or more]
Emergency department visits [0]
Emergency department visits [1]
Emergency department visits [2 or more]
Specialty care visits [0]
Specialty care visits [1]
Specialty care visits [2 or more]
Diabetic nephropathy or renal insufficiency
Peripheral neuropathy
Cerebrovascular disease
Amputation
Kidney diseases
Kidney and genitourinary stones
Other cardiovascular disease
Rheumatoid arthritis
Pancreatitis
Immunosuppressive diseases
Dementia
Insulin use at index date
Digoxin
Anticonvulsants
Non-opioid acetaminophen
Antibiotics
Anticoagulants
GLD classes in prior 12 months [0]
GLD classes in prior 12 months [1-2]
GLD classes in prior 12 months [3-4]
GLD classes in prior 12 months [5-8]
GLD classes, > 24 months prior [0]
GLD classes, > 24 months prior [1-2]
GLD classes, > 24 months prior [3-4]
GLD classes, > 24 months prior [5-8]
GLD classes, > 24 months prior [Not applicable]
Add-on index therapy
Switched-to index therapy
PS Untrimmed
PS Stratum 1
PS Stratum 2
PS Stratum 3
PS Stratum 4
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
Absolute standardized difference

Males – HIRD



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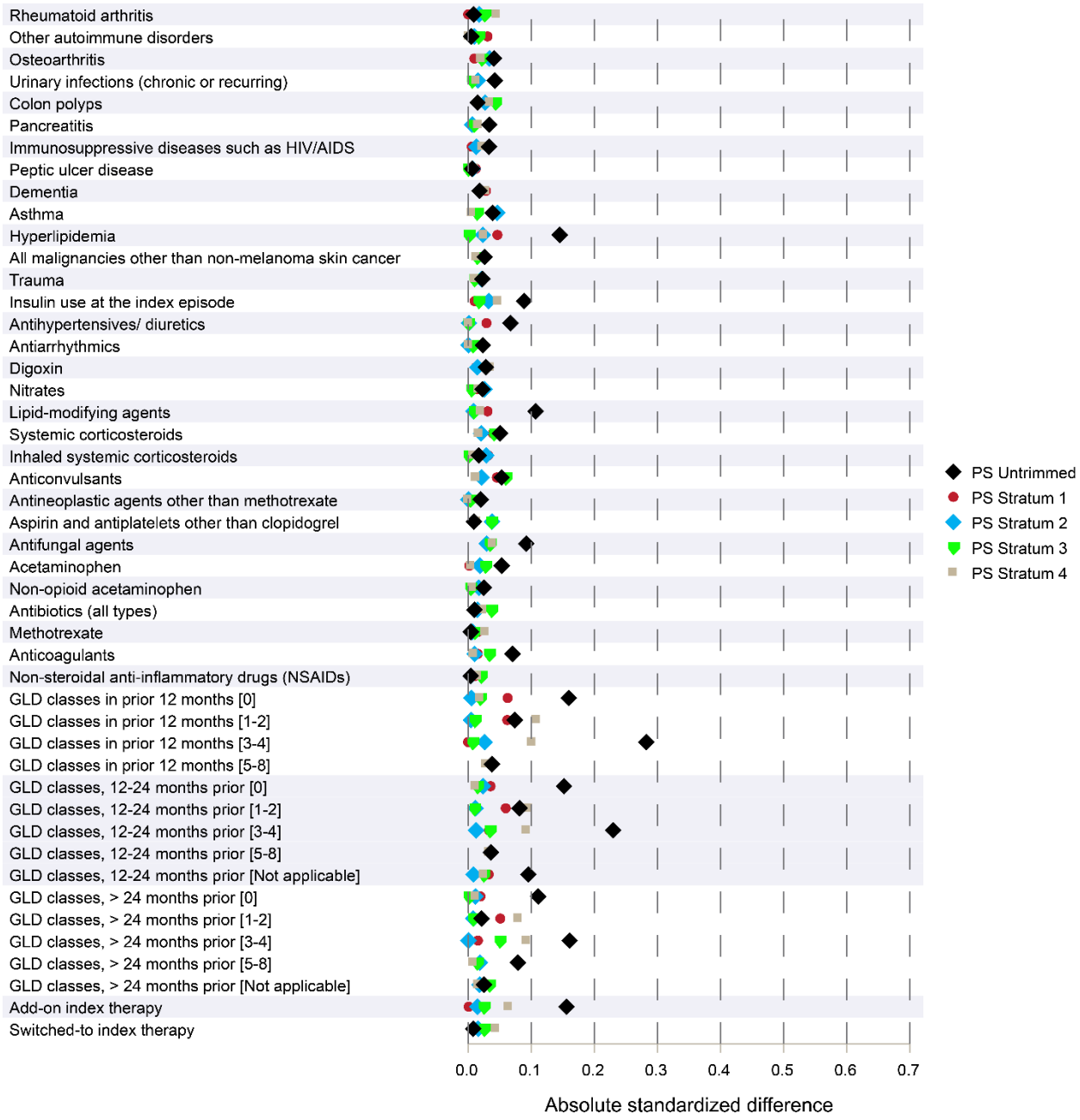
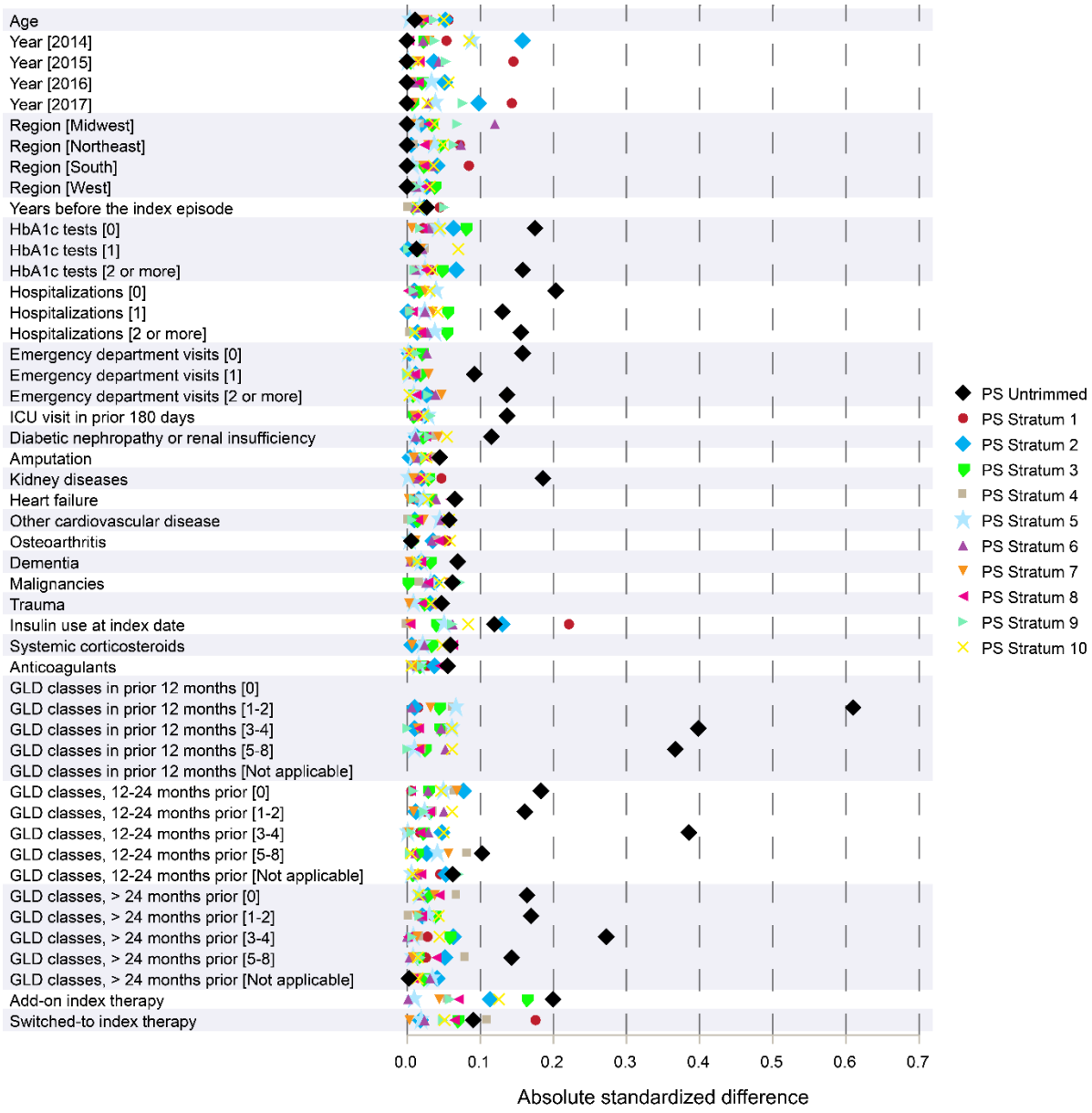


Males – Medicare

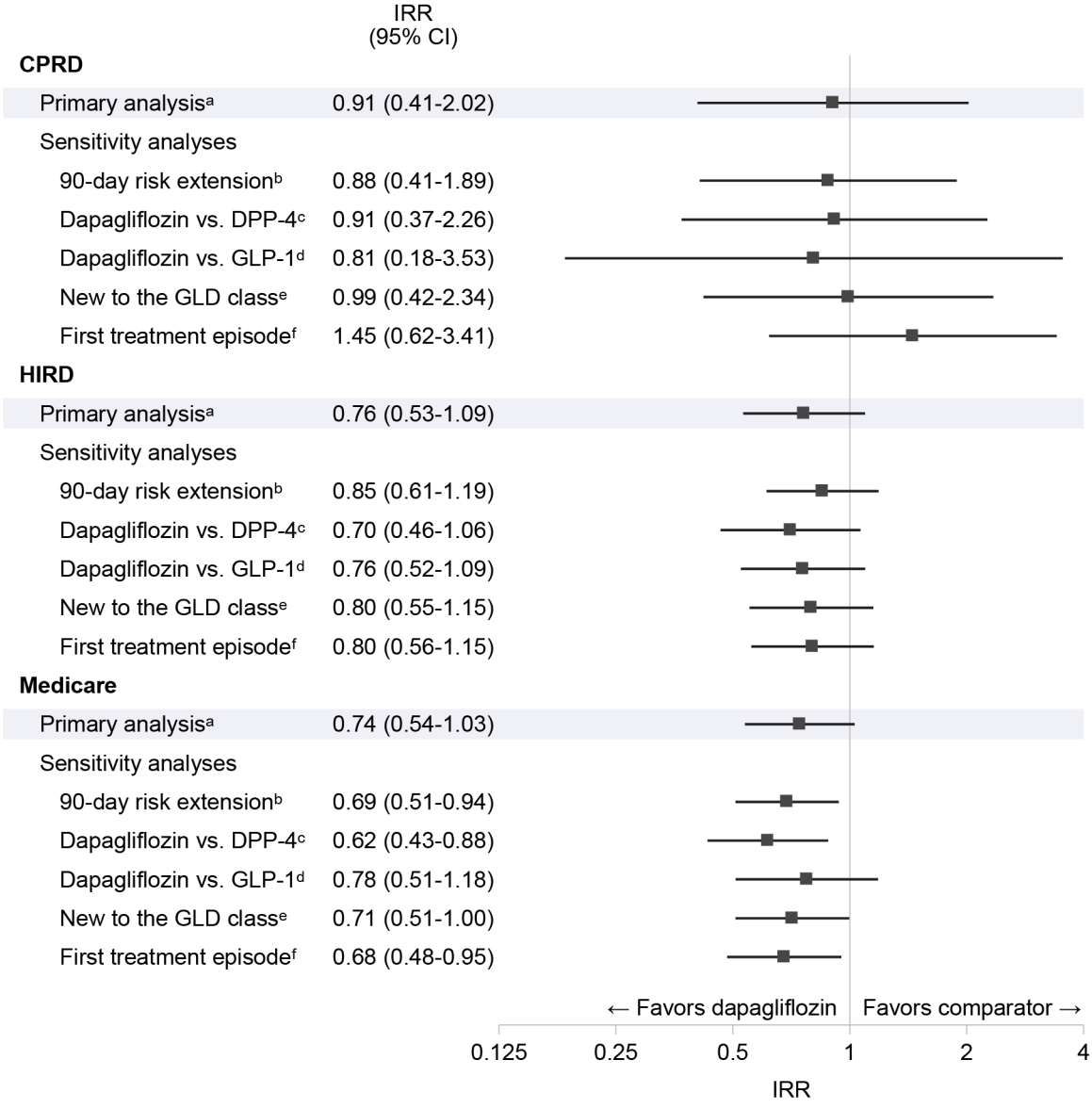


BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPRD = Clinical Practice Research Datalink; GLD = glucose-lowering drug; HbA1c = glycated hemoglobin; HIRD = HealthCore Integrated Research Database; HIV = human immunodeficiency virus; ICU = intensive care unit; Q*n* = quintile; PS = propensity score; US = United States.

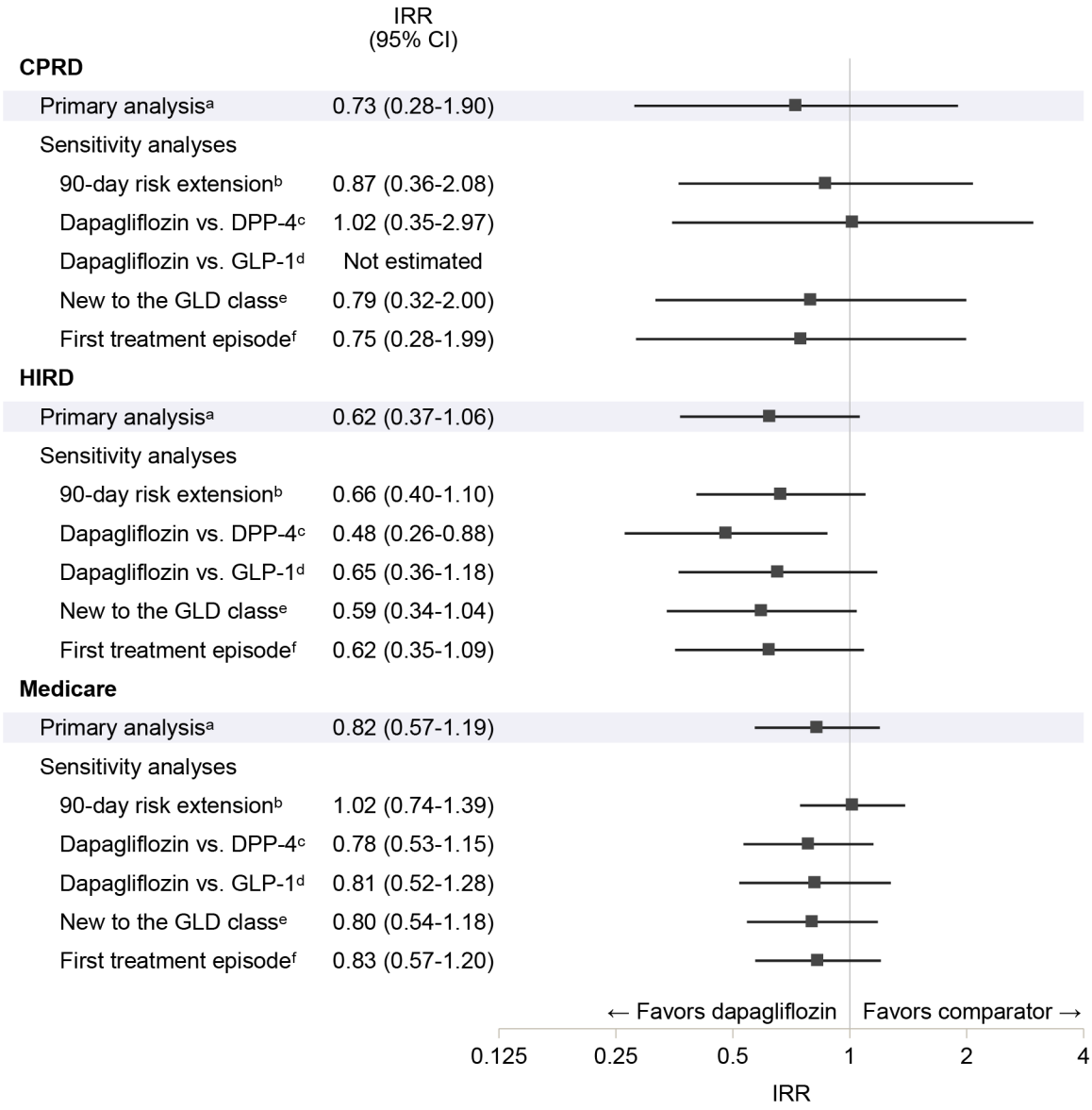
[a] Each data source−specific plot presents only the variables that were included as covariates in the propensity score model for each respective data source.

Figure S4. Adjusted Incidence Rate Ratios for Severe Complications of Urinary Tract Infection, Sensitivity Analyses Compared With the Primary Results, by Sex

Females



Males



CI = confidence interval; CPRD = Clinical Practice Research Datalink; GLD = glucose-lowering drug; DPP-4 = dipeptidyl peptidase-4; GLD = glucose-lowering drug; GLP-1 = glucagon-like peptide-1; HIRD = HealthCore Integrated Research Database; IRR = incidence rate ratio.

[a] The primary analysis was the overall analysis.

[b] The risk extension window was increased from 30 days to 90 days.

[c] Compared dapagliflozin treatment episodes with treatment episodes of DPP-4 inhibitors as an alternative comparator GLD cohort. Propensity scores were calculated on the overall sample.

[d] Compared dapagliflozin treatment episodes with treatment episodes of GLP-1 receptor agonists as an alternative comparator GLD cohort. Propensity scores were calculated on the overall sample.

[e] Included only comparator GLD treatment episodes in which the patient was new to the index GLD class. The propensity score model was calculated after removing patients not new to the index GLD class.

[f] Conducted using only the first treatment episode for each person in each treatment group in the primary analysis sample.

PART B. SUPPLEMENTAL METHODS AND RESULTS

1 Methods and Results

1.1 Treatment Episodes

The *index date* for a treatment episode was defined as the date a patient received a new prescription or dispensing of either dapagliflozin (single-entity dapagliflozin or the fixed-dose combination of dapagliflozin and another GLD) or an eligible comparator GLD on or after the beginning of the study period if all inclusion criteria have been met. To identify the index treatment episodes, the first use of dapagliflozin or each potential comparator GLD was identified in the patient's entire available history, and treatment episodes occurring within the study period were eligible for selection into the study analysis.

1.1.1 Primary Exposure

The primary exposure of interest was newly initiated dapagliflozin use during the study period by eligible patients with or without concomitant use of any other GLD. Dapagliflozin could be prescribed or dispensed either as a single agent, as part of a fixed-dose combination with metformin or other GLDs, or as part of free-form combinations with other blood glucose–lowering drugs, including insulin.

All eligible dapagliflozin new-use treatment episodes were evaluated first and included in the analysis if at least one eligible new-use comparator GLD episode could be matched to the dapagliflozin treatment episode. If dapagliflozin and an eligible comparator GLD were initiated by an individual patient on the same day, the dapagliflozin treatment episode was selected as the index treatment episode in the study analysis.

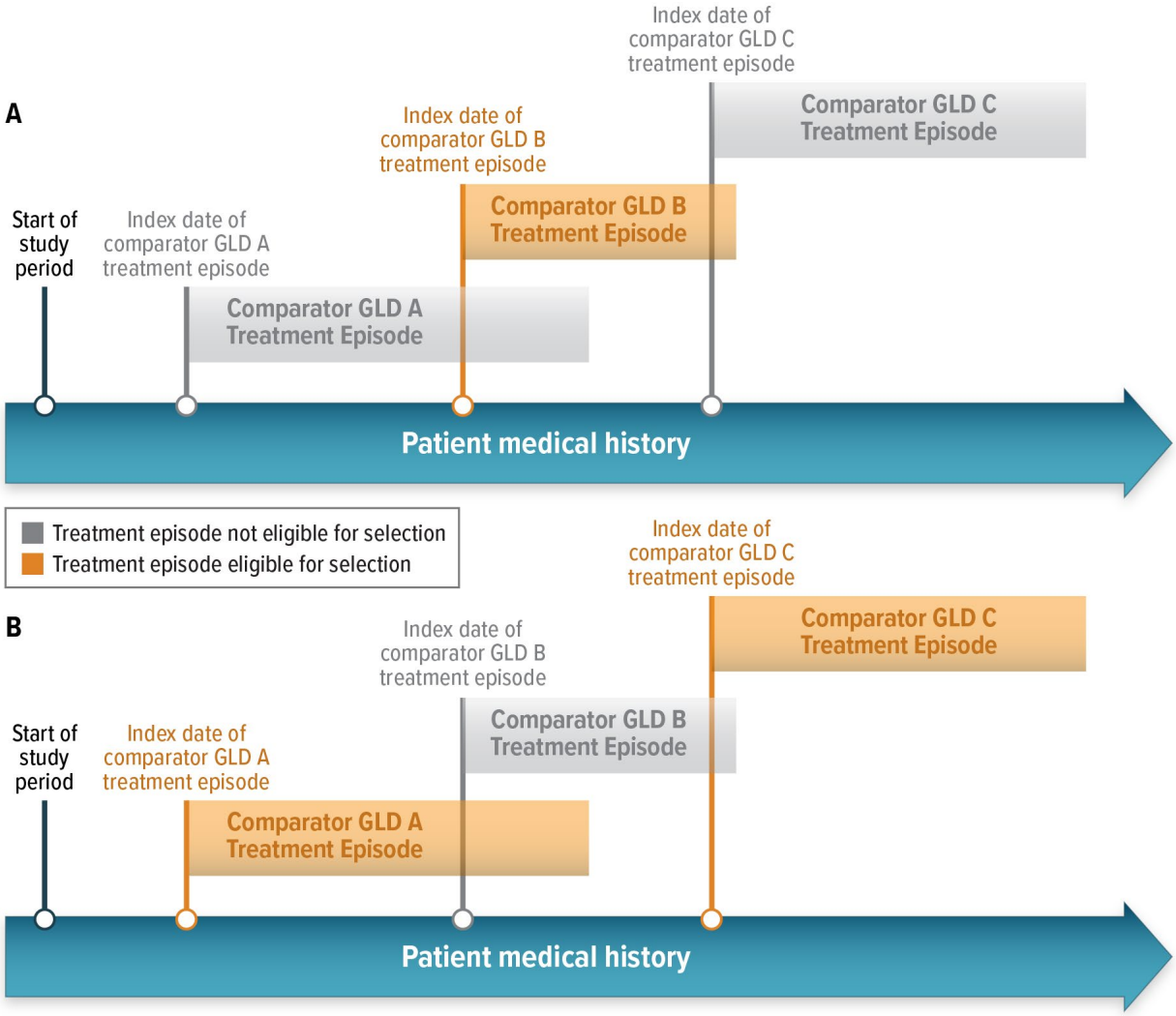
1.1.2 Comparator Exposure

Comparator GLD exposure was defined as new use of any eligible GLD with or without concomitant use of any other GLD on the index date. Comparator GLD exposure did not include insulin monotherapy, metformin monotherapy, or sulfonylurea monotherapy, but the combination of metformin plus sulfonylurea was considered as an eligible comparator GLD. Initial new-use dates for comparator GLD exposure was selected based on individual drug substances, not by drug class.

If metformin or a sulfonylurea medication (not as a preparation combined with another GLD) was initiated during a comparator GLD treatment episode (before the 30-day extension period) it was considered as part of the treatment episode. Metformin or sulfonylurea monotherapy, if added as monotherapy during the 30-day risk extension window, did not extend a continuous comparator GLD treatment episode.

Multiple treatment episodes for a patient could be selected as comparator GLD exposures during the matching process if a qualifying drug substance was initiated at a point in time after the first eligible treatment episode ended and was a different drug substance than the first. Potential comparator GLDs were eligible to enter the pool of treatment episodes from which comparator episodes could be selected multiple times (i.e., if they qualified with drug substance A and then later switched to drug substance B, which also qualified as a new comparator drug, they could enter both times). In Figure S5, all three comparator GLD treatment episodes are eligible to be matched to a dapagliflozin treatment episode and enter in the analysis. However, given that overlapping person-time of treatment episodes is not allowed, if the comparator GLD B treatment episode is selected into analysis by being matched to a dapagliflozin episode (Panel A), then the treatment episodes for both comparator GLD A and comparator GLD C would then not be eligible to also be selected because they overlap with the comparator GLD B treatment episode. Likewise, the treatment episodes for both comparator GLD A and comparator GLD C could be selected into the analysis (Panel B), but the treatment episode for comparator GLD B would not be eligible to also selected because it overlaps with both.

Figure S5. Eligible Comparator GLD Treatment Episodes Available for Selection into the Study Analysis



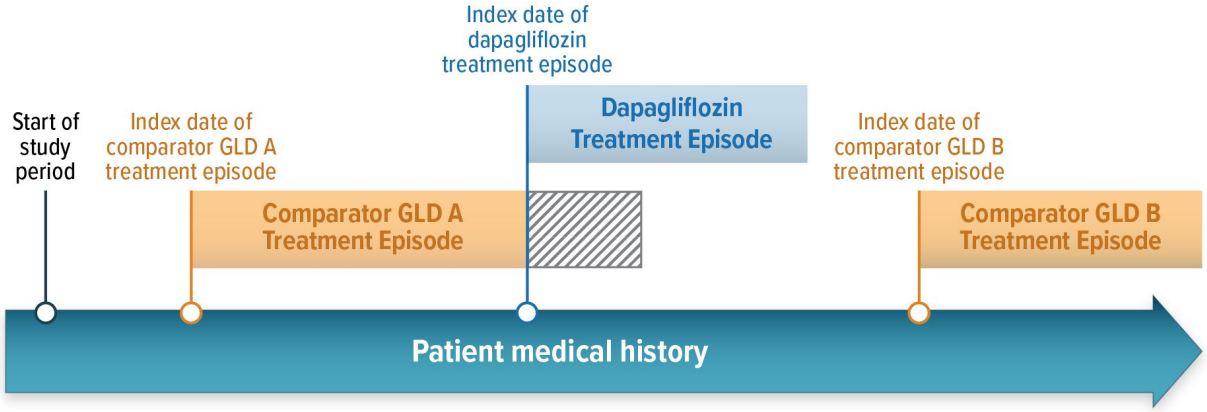
GLD = glucose-lowering drug.

Note: The orange treatment episodes represent comparator GLD treatment episodes that are selected (i.e., matched to a dapagliflozin treatment episode) or eligible for selection based on other comparator GLD treatment episodes that are selected. The gray comparator GLD treatment episodes represent treatment episodes that are not eligible to be selected due to overlap with other selected comparator GLD treatment episodes.

Figure S6 illustrates a scenario where a patient contributes person-time to both the comparator GLD group and the dapagliflozin group. Patients selected as new users of dapagliflozin and who later switched to an eligible comparator GLD, after the dapagliflozin exposure period terminated, were also eligible to be selected as a comparator GLD. Separate non-overlapping treatment episodes for the same patient were assumed to be independent. Therefore, a given patient could have more than one index date for different eligible medications. Follow-up was not censored with the addition of another GLD during the treatment episode, unless dapagliflozin or another SGLT2 inhibitor was initiated during a comparator GLD treatment episode. This is illustrated in

Figure S6, where the comparator GLD A treatment episode is censored at the index date of the dapagliflozin treatment episode.

Figure S6. Example of Patient Contributing Person-time to the Comparator GLD Group and the Dapagliflozin Group



GLD = glucose-lowering drug.

Note: The hatched gray represents comparator GLD A person-time that is not counted in the analysis due to censoring at the initiation of dapagliflozin.

1.2 Propensity Score Modeling Approach

Propensity score models were built separately in each data source for each of the outcomes, hospitalization for acute liver injury (hALI) and severe complications of urinary tract infection (sUTI), to estimate the probability of an individual receiving dapagliflozin versus a comparator glucose-lowering drug (GLD). For the sUTI outcome, separate propensity score models were built for females and males. Covariates were selected for the propensity score models from a list of preidentified potential confounders. First, we evaluated each individual covariate's influence on the association of dapagliflozin exposure with hALI or sUTI using separate Cox proportional hazards regression models with a base set of covariates that was the same in all data sources: age at the index date, sex, duration of lookback time, primary care practice or geographic region, whether the index medication was "added on" or "switched to" (yes/no; detailed definitions for the index therapy type are described in Section 1.5), insulin use at the index date (yes/no), and calendar year of the index date. Second, each of the remaining potential candidate variables were included in separate base models, and if the resulting treatment-related hazard ratio (HR) met one of two conditions—(1) change in the absolute value of the HR estimate of more than 0.005 or (2) change in the value of the HR estimate of more than 0.05%—the variable was selected for inclusion in the final propensity score model. Lastly, we calculated propensity scores for each treatment episode by fitting a multivariate logistic regression model with exposure as the dependent variable (0 = comparator GLD initiator, 1 = dapagliflozin initiator) and including as independent variables the base set of covariates and all other data source–specific covariates identified in the variable selection process. The standardized differences plots presented in

Figure S1 (hALI) and Figure S3 (sUTI) show the variables included in each data source−specific propensity score model.

1.3 Estimation of Pooled Adjusted Incidence Rate Ratio

For each study outcome in each data source, the adjusted data source–specific incidence rate ratio (IRR) estimates were pooled across the data sources to generate an overall (i.e., pooled) adjusted IRR estimate. Before pooling, we evaluated homogeneity among the data source–specific IRRs by examining the value and direction of the IRRs and their corresponding 95% confidence intervals (CIs).
Within each data source, separately for each outcome, event counts and person-time were aggregated by exposure category and propensity score stratum. The stratum-specific estimates were pooled across all data sources using Mantel-Haenszel methods [1].

Statistical heterogeneity between the data source–specific estimates was assessed using the I^2 index [2]. This index measures the amount of between-study variation in the IRRs and thus the appropriateness of pooling estimates from the data sources. If the calculated I^2 index was below 50%, the pooled Mantel-Haenszel–adjusted IRR was reported.

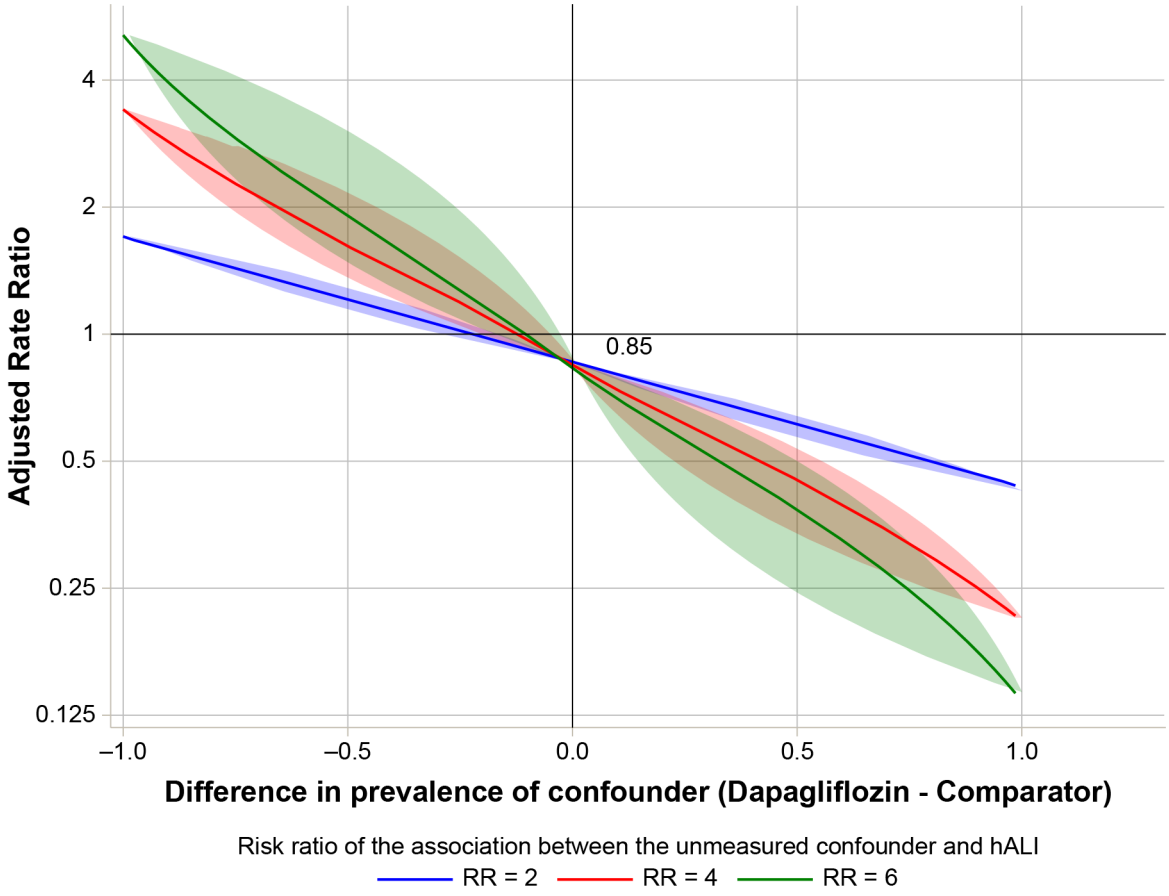
1.4 Assessment of the Potential Effect of Unmeasured Confounders (Quantitative Bias Analysis Methods, Results, and Interpretation)

In this sensitivity analysis, the potential impact of a hypothetical unmeasured confounder on the observed pooled IRRs for each of the study outcomes, hALI and sUTI, was evaluated using quantitative bias analysis. We used the method described by Lash et al. [3].

A series of IRRs associating dapagliflozin exposure with the outcome, adjusted for a hypothetical unmeasured confounder, were plotted under varying assumptions of unmeasured confounding compared with the observed IRR estimate from the pooled analysis. Figure S7 (hALI) and Figure S8 (sUTI) each present three scenarios of the association of a hypothetical unmeasured confounder with the study outcome—relative risk (RR) = 1.5 (moderate association, blue), RR = 3.0 (strong association, red), and RR = 4.5 (very strong association, green)—with a series of potential imbalances of the prevalence of the hypothetical unmeasured confounder in the two treatment groups. The series of prevalence imbalances range from -100% (i.e., the hypothetical unmeasured confounder is present in every comparator GLD patient and not present in any dapagliflozin patient) to 100% (i.e., the hypothetical unmeasured confounder is present in every dapagliflozin patient and not present in any comparator GLD patient). The colored bands for each confounding scenario represent the minimum and maximum possible corrected IRR (i.e., corrected for hypothetical unmeasured confounder strength) at each level of prevalence imbalance, and the solid line represents the mean corrected IRR at each imbalance level.

1.4.1 Hospitalization for Acute Liver Injury

Figure S7. Sensitivity Analysis, Adjusted Incidence Rate Ratios for hALI Under Varying Assumptions of Unmeasured Confounding Compared With the Observed Incidence Rate Ratio Estimate From the Pooled Analysis



hALI = hospitalization for acute liver injury (the study outcome); RR = risk ratio.

For hALI, the observed IRR estimate in the pooled analysis was 0.85. In the worst-case scenario of having a hypothetical confounder moderately associated with the outcome (risk ratio [RR] = 1.5) in which the treatment groups would be completely imbalanced (i.e., 0% prevalence in the dapagliflozin group and 100% prevalence in the comparator GLD group), the maximum true hALI IRR would be 1.28; any imbalance less extreme would result in IRRs lower than 1.28. A hypothetical moderate confounder (RR = 1.5) would require an imbalance of at least approximately −40% (i.e., higher prevalence in the comparator GLD group) to mask a true IRR greater than 1.0. If the hypothetical unmeasured confounder had a stronger independent relationship with the outcome, RR = 3.0 or 4.5, then a smaller imbalance would be required to mask a true hALI IRR greater than 1.0.

For context, in the overall CPRD population, current smoker status has an imbalance of only −1.3% (15.6% in dapagliflozin users, 16.9% in comparator GLD users) in the full sample (i.e.,

before propensity score trimming). Although smoking status was not measured in the HIRD or Medicare, related variables such as chronic obstructive pulmonary disease (COPD), which may be correlated with smoking status, were included. Smoking is a risk factor for liver disease among patients with type 2 diabetes mellitus (T2DM), with a reported adjusted HR with severe liver disease of 1.58 (95% CI, 1.35-1.86) [4]. Similarly, male sex and hypertension have been reported to be associated with increased acute liver injury risk in patients with T2DM, but adjusted HRs for both are below 1.50 [4]. However, in all three data sources, the imbalance of sex was approximately 1% or less in the present study, and hypertension had an imbalance of less than 6% in all databases in the full sample.

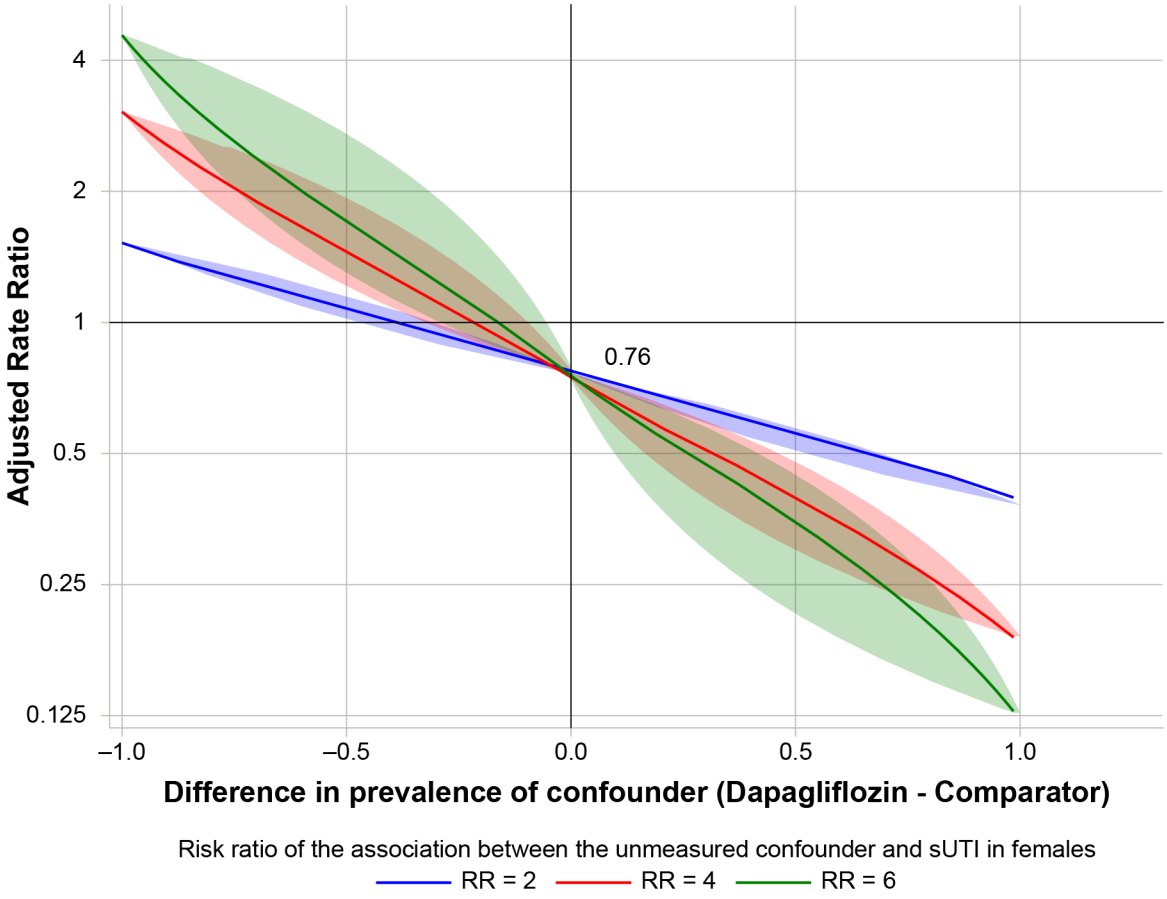
Some individual medications are highly associated with drug-induced liver injury. However, the use of many of the medications with known associations with acute liver injury collected in this study was generally very low (except for the notable exceptions of acetaminophen, NSAIDs [nonsteroidal anti-inflammatory drugs], omeprazole, and statins), and the balance of these variables was very good between treatment groups in the full sample. In all data sources, imbalances in the dapagliflozin group versus the comparator GLD group were generally less than 2% for all medications except for statins in the HIRD (57.3% vs. 53.0%) and lisinopril in Medicare (30.2% vs. 34.0%).

It is not anticipated that a common, moderate or strong confounder would be unmeasured and imbalanced enough and uncorrelated with measured, included covariates to mask a true harmful association of hALI with dapagliflozin.

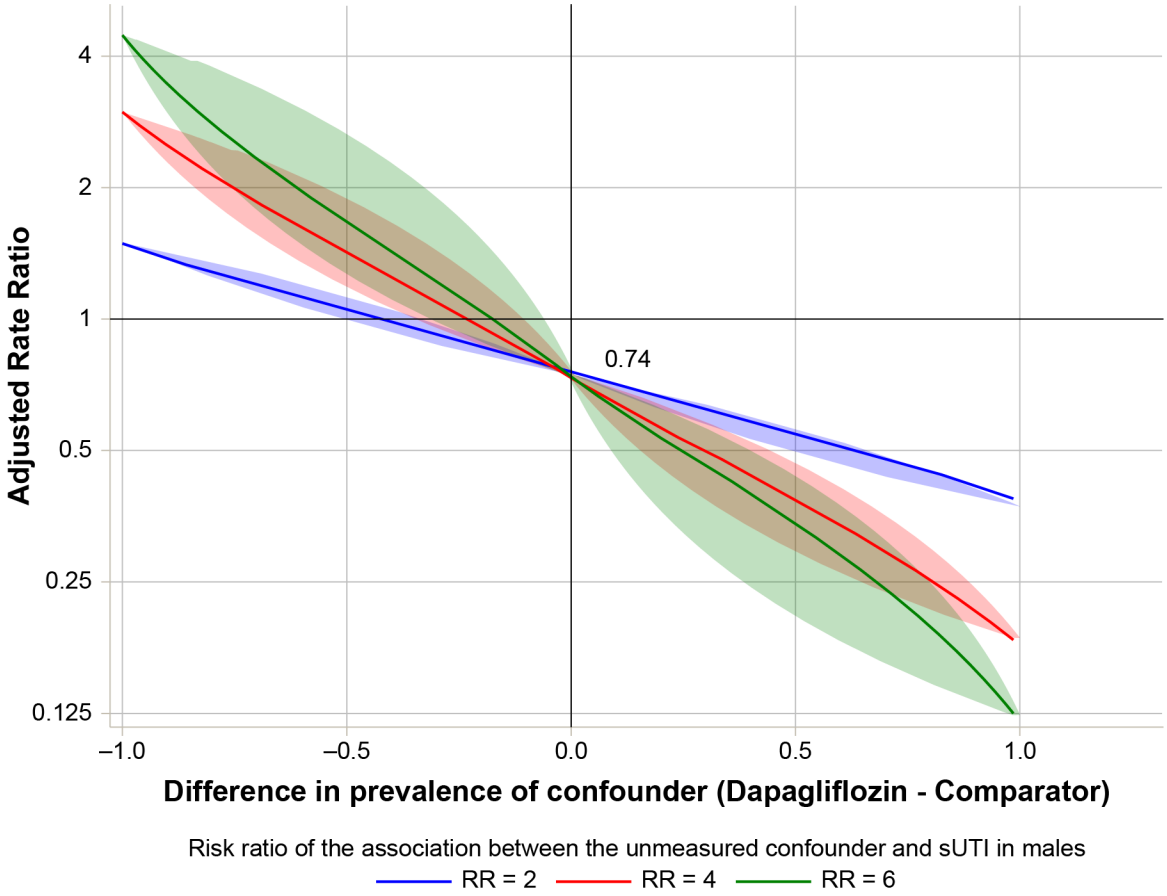
1.4.2 Severe Complications of Urinary Tract Infection

Figure S8. Sensitivity Analysis, Adjusted Incidence Rate Ratios for sUTI Under Varying Assumptions of Unmeasured Confounding Compared With the Observed Incidence Rate Ratio Estimate From the Pooled Analysis, by Sex

Females



Males



RR = risk ratio; sUTI = hospitalization or emergency department visit for severe complications of urinary tract infection.

For sUTI, the observed IRR estimates in the pooled analyses were 0.76 for females and 0.74 for males. In the worst-case scenario of having a hypothetical confounder moderately associated with the outcome (RR = 1.5) in which groups would be completely imbalanced (0% prevalence in the dapagliflozin group and 100% prevalence in the comparator GLD group), the maximum true sUTI IRR would be 1.05; any imbalance less extreme would result in IRRs lower than 1.05. A hypothetical moderate confounder (RR = 1.5) would require an imbalance of at least approximately -70% (i.e., higher prevalence in the comparator GLD group) among males or females to mask a true sUTI IRR greater than 1.0. If the hypothetical unmeasured confounder had a stronger, independent relationship with the outcome, RR = 3.0 or 4.5, then a smaller imbalance would be required.

For context, an unrelated study reported risk factors associated with pyelonephritis in a population of otherwise healthy women; risk factors included use of antibiotics in the past 30 days, with an odds ratio of 2.1 (95% CI, 1.3-3.4), and current smoking, with an odds ratio of 1.8 (95% CI, 1.3-2.4) [5]. In the current study, antibiotic use had an imbalance of -2.3% in CPRD, -0.5% in the HIRD, and 0.6% in Medicare in the full samples. Similarly, in CPRD, current smoker status had an imbalance of -2.3%. Hypertension, body mass index greater than

30 kg/m^2, and nephropathy have been reported as risk factors for urinary tract infection (not necessarily severe complications) among patients with T2DM, although all with RRs of 1.42 or less [6]. Some specific factors may be much more strongly associated with sUTI; among females, some sexual behaviors were associated with pyelonephritis, with odds ratios as high as 7.6 for ever versus never having sexual intercourse [5], and among patients admitted to an emergency department, use of an indwelling catheter was associated with bacteremic urinary tract infection (RR = 3.3) [7].

It is not anticipated that a common, moderate or strong confounder would be unmeasured and imbalanced enough and uncorrelated with measured, included covariates to mask a true harmful association of sUTI with dapagliflozin.

1.5 Definitions for Index Therapy Type Categories

The frequency distributions of the index therapy type in the full samples (i.e., before propensity score trimming) and in the propensity score-trimmed samples are presented, respectively, in Table 3 (main manuscript) and Table S3 for hALI and in Table 5 (main manuscript) and Table S5 for sUTI. The index medication could be initiated as monotherapy, added to another GLD, switched from another GLD to the index medication, or initiated as index combined therapy (more than one drug was initiated on the index date). For creation of the index therapy type categories, three intervals of time were considered: *interval 1* = the 90 days before (and not including) the index date; *interval 2* = study drug index date; *interval 3* = the 90 days after (and not including) the index date.

The following categories of index medication exposure were created based on individual drugs (i.e., the drug substance), not by drug class:

Index monotherapy with no prior treatment. Only a single index drug substance was prescribed or dispensed on the index date (interval 2), and there was no prescription or dispensing for a GLD or insulin in interval 1. Note that interval 3 could be less than 90 days and the definition of index monotherapy would still apply.

Index combined therapy with no prior treatment. Multiple drug substances were prescribed or dispensed at interval 2, and there was no prescription or dispensing for any GLD or insulin in interval 1. Note that interval 3 could be less than 90 days and the definition of index combined therapy would still apply.

Add-on index therapy. A GLD or insulin other than the index medication was prescribed or dispensed during interval 1, and then a subsequent prescription or dispensing for the same drug substance was identified during interval 2 or 3. If multiple drug substances were identified during interval 1, then *all* these drug substances would need a new prescription or dispensing during interval 2 or 3 to fit this category.

Switched-to index therapy. A drug substance(s) other than the index GLD was prescribed or dispensed during interval 1 and had no subsequent prescriptions or dispensings during intervals 2 and 3. If multiple drug substances were identified in interval 1, no additional prescriptions or dispensings for any of these substances could occur in intervals 2 and 3.

Add-on and switched-to index therapy. A patient had multiple drug substances with a reported prescription or dispensing in interval 1 and the following two criteria were met:

- At least one drug substance had a prescription or dispensing during interval 2 or interval 3.
- At least one drug substance had no prescription or dispensing during interval 2 and interval 3.

Non-evaluable index treatment. A drug substance(s) was prescribed or dispensed during interval 1 and the patient had less than 90 days of follow-up; therefore, it could not be determined if there was an add-on or a switch or both. Note that an outcome of interest was not allowed to truncate the patient's record for the assignment of medication type.

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