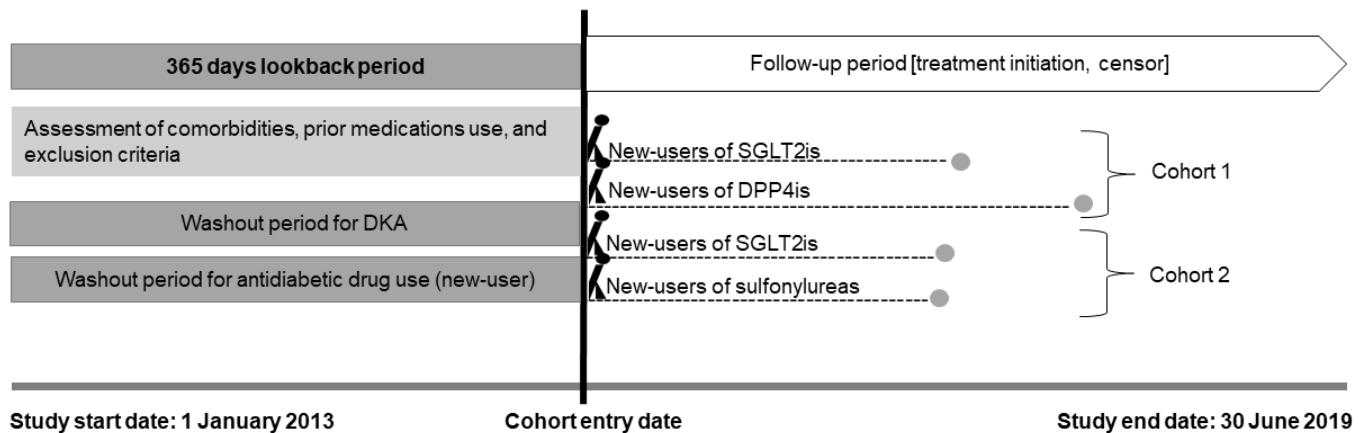


# **Appendix**

## Appendix Figure S1. Study design



### Exclusion criteria:

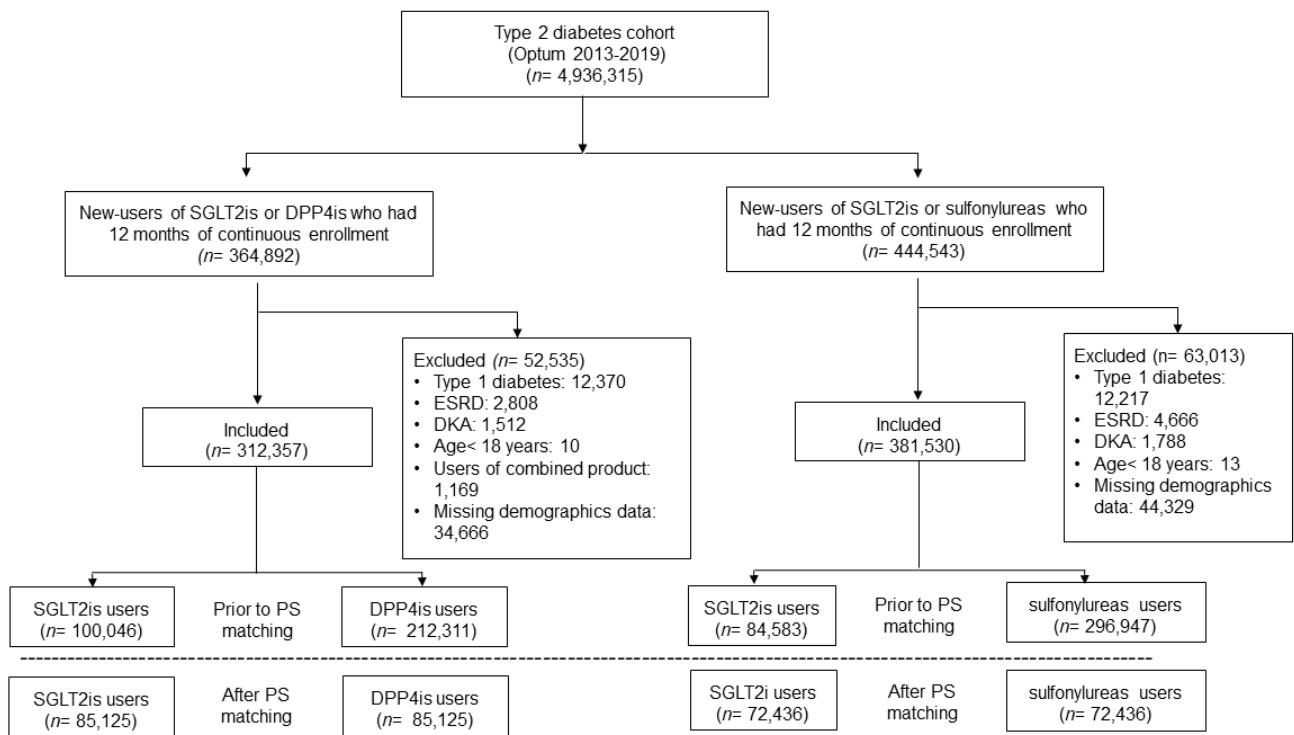
- < 18 years
- < 12 months of continuous eligibility
- ESRD
- Diagnosis of DKA
- Initiation of treatment with SGLT2i or the comparator on the same date

### Censoring criteria:

- DKA
- Discontinuation of index-medication
- Start of comparator
- End of enrollment
- End of study period

DKA, diabetic ketoacidosis, DPP4is, dipeptidyl peptidase-4 inhibitors, ESRD, end-stage renal disease, SGLT2is, sodium-glucose co-transporter-2 inhibitors

## Appendix Figure S2. Study flow diagram.



DKA, diabetic ketoacidosis, DPP4is, dipeptidyl peptidase-4 inhibitors, ESRD, end-stage renal disease, PS, propensity score, SGLT2is, sodium-glucose co-transporter-2 inhibitors

Combined products included dapagliflozin/saxagliptin and empagliflozin/linagliptin

**Appendix Table S1. Demographics and clinical characteristics of new-users of sodium-glucose co-transporter-2 inhibitors, dipeptidyl peptidase-4 inhibitors and sulfonylureas prior to propensity score matching**

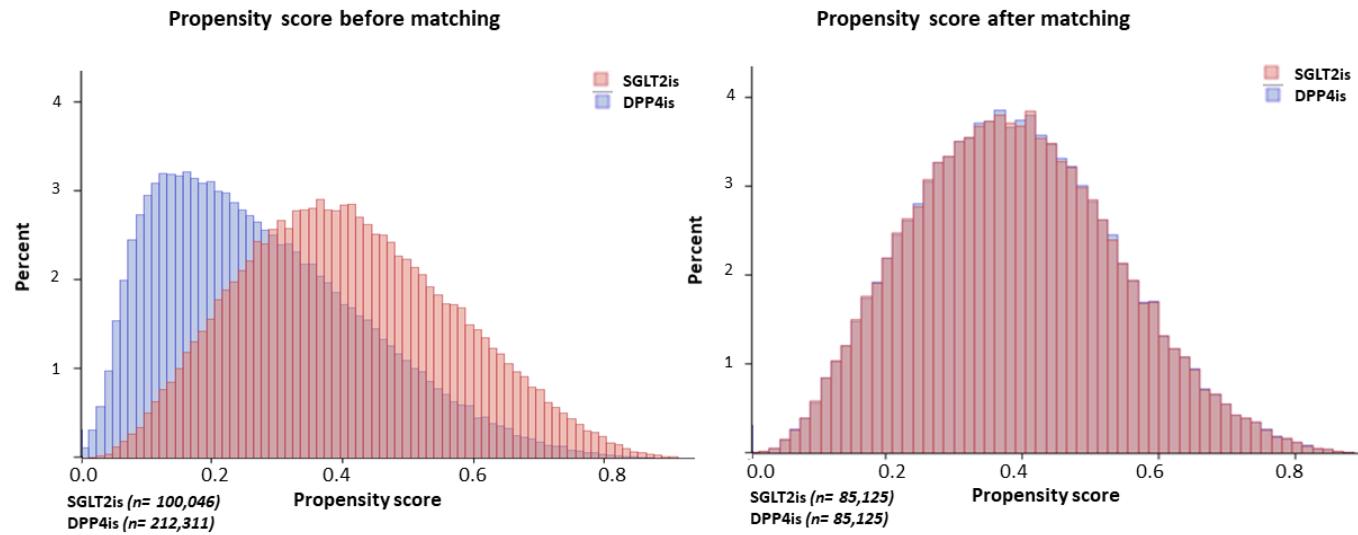
	SGLT2is (n= 100,046)		DPP4is (n= 212,311)		Standardized Difference	SGLT2is (n= 84,583)		Sulfonylureas (n= 296,947)		Standardized Difference
<b>Demographic characteristics</b>										
Mean age (SD), y	59.6	(12.9)	67.9	(12.9)	0.74	59.1	(11.2)	66.3	(13.3)	0.64
Male sex, n (%)	57,246	(57.2)	110,358	(52.0)	0.10	47489	(56.2)	163106	(55.0)	0.02
Education level					0.08					0.14
Less than 12th grade	885	(0.8)	2,509	(1.2)		731	(0.8)	3092	(1.0)	
High school diploma	34,717	(34.8)	80,786	(38.0)		28101	(33.2)	113605	(38.2)	
Less than bachelor degree	52,939	(53.0)	106,378	(50.2)		44758	(53.0)	152542	(51.4)	
Bachelor degree plus	11,152	(11.2)	21,862	(10.2)		10714	(12.6)	26608	(9.0)	
Race, n (%)					0.16					0.08
Asian	3,560	(3.6)	11,743	(5.6)		3301	(4.0)	13420	(4.6)	
Black	12,951	(13.0)	34,571	(16.2)		10894	(12.8)	44985	(15.2)	
Hispanic	16,591	(16.6)	38,836	(18.2)		14078	(16.6)	52275	(17.6)	
White	66,944	(67.0)	127,161	(59.8)		56310	(66.6)	186267	(62.8)	
Unknown	15,036	(15.0)	31,856	(15.0)		12726	(15.0)	46402	(15.6)	
Income, n (%)					0.14					0.22
<\$40K	21,436	(21.4)	57,669	(27.2)		17267	(20.4)	82994	(28.0)	
\$40K-\$49K	6,806	(6.8)	16,053	(7.6)		5391	(6.4)	23582	(8.0)	
\$50K-\$59K	7,187	(7.2)	16,943	(8.0)		5746	(6.8)	24160	(8.2)	
\$60K-\$74K	9,997	(10.0)	21,624	(10.2)		8197	(9.6)	30409	(10.2)	
\$75K-\$99K	14,641	(14.6)	27,648	(13.0)		12320	(14.6)	38848	(13.0)	
\$100K+	24,943	(25.0)	40,518	(19.0)		22936	(27.2)	50552	(17.0)	
Division, n (%)					0.08					0.10
East North Central	13,555	(13.6)	27,528	(13.0)		10681	(12.6)	44236	(14.8)	
East South Central	5,599	(5.6)	9,529	(4.4)		4870	(5.8)	12465	(4.2)	
Middle Atlantic	5,155	(5.2)	17,681	(8.4)		5074	(6.0)	18678	(6.2)	
Mountain	7,189	(7.2)	16,025	(7.6)		6167	(7.2)	24749	(8.4)	
New England	2,041	(2.0)	6,827	(3.2)		1684	(2.0)	9269	(3.2)	
South Atlantic	27,248	(27.2)	60,461	(28.4)		23205	(27.4)	79081	(26.6)	
West North Central	8,834	(8.8)	13,357	(6.2)		6552	(7.8)	25815	(8.6)	
West South Central	22,403	(22.4)	39,352	(18.6)		19843	(23.4)	51754	(17.4)	
<b>Baseline comorbidities, n (%)</b>										
Heart failure	5,701	(5.6)	20,862	(9.8)	0.18	4515	(5.4)	23857	(8.0)	0.12
Peripheral vascular disease	6,706	(6.8)	21,537	(10.2)	0.14	5366	(6.4)	23776	(8.0)	0.06
Hypertension	69,481	(69.4)	155,719	(73.4)	0.08	57629	(68.2)	183569	(61.8)	0.14

Cancer	4,362	(4.4)	13,619	(6.4)	0.10	3742	(4.4)	17431	(5.8)	0.08
Chronic lung disease	13,504	(13.4)	35,188	(16.6)	0.10	11393	(13.4)	43383	(14.6)	0.04
Hyperlipidemia	46,800	(46.8)	107,621	(50.6)	0.08	39096	(46.2)	119801	(40.4)	0.12
Chronic kidney disease	11,056	(11)	46,860	(22.0)	0.36	8902	(10.6)	51059	(17.2)	0.22
Stroke	67	(0.1)	285	(0.2)	0.02	50	(0.1)	337	(0.2)	0.02
Tobacco use	6,598	(6.6)	14,0502	(6.6)	0.00	5414	(6.4)	19633	(6.6)	0.00
Arthritis	4,242	(4.2)	10,552	(5.0)	0.04	3498	(4.2)	12884	(4.4)	0.02
Liver disease	5,065	(5.0)	7,828	(3.6)	0.06	4318	(5.2)	10717	(3.6)	0.06
Alcohol abuse	1,015	(1.0)	2,392	(1.2)	0.02	846	(1.0)	3638	(1.2)	0.02
Drug abuse	1,336	(1.4)	2,812	(1.4)	0.00	1114	(1.4)	4044	(1.4)	0.00
Venous thromboembolism	1,643	(1.6)	5,536	(2.6)	0.08	1359	(1.6)	6744	(2.2)	0.06
Depression	3,644	(3.6)	11,885	(5.6)	0.10	3238	(3.8)	13125	(4.4)	0.04
<b>Baseline medications, n (%)</b>										
ACEs	40,017	(40)	85,375	(40.2)	0.00	31509	(37.2)	97722	(33.0)	0.08
Alpha adrenergic blockers	5,697	(5.6)	17,469	(8.2)	0.10	4457	(5.2)	20434	(6.8)	0.08
ARBs	24,644	(24.6)	54,143	(25.6)	0.02	21797	(25.8)	54916	(18.4)	0.16
Beta blockers	22,340	(22.4)	57,847	(27.2)	0.12	17874	(21.2)	65565	(22.0)	0.02
CCBs	19,863	(19.8)	54,182	(25.6)	0.14	16228	(19.2)	60348	(20.4)	0.02
Direct vasodilators	1,201	(1.2)	4,869	(2.2)	0.10	913	(1)	5151	(1.8)	0.06
Thiazide diuretics	26,730	(26.8)	60,142	(28.4)	0.04	21977	(26)	68002	(23.0)	0.08
Loop diuretics	8,532	(8.6)	27,691	(13)	0.16	6738	(8)	30336	(10.2)	0.08
Potassium diuretics	2,900	(2.8)	6,968	(3.2)	0.02	2439	(2.8)	8061	(2.8)	0.02
Aldosterone antagonists	2,761	(2.8)	6,603	(3.2)	0.02	2316	(2.8)	7691	(2.6)	0.00
PPI	19,576	(19.6)	48,110	(22.6)	0.08	16736	(19.8)	53427	(18.0)	0.04
SSRI	14,139	(14.2)	29,306	(13.8)	0.00	11968	(14.2)	34692	(11.6)	0.08
Statin	60,125	(60)	129,017	(60.8)	0.02	50390	(59.6)	139079	(46.8)	0.26
Metformin	65,583	(65.6)	128,786	(60.6)	0.10	55005	(65)	147658	(49.8)	0.32
Amylin	117	(0.2)	54	(0.1)	0.02	5540	(6.6)	10219	(3.4)	0.12
TZDs	7,489	(7.4)	13,638	(6.4)	0.04	22683	(26.8)	27775	(9.4)	0.40
Insulin	26,030	(26.0)	32,235	(15.2)	0.24	180	(0.2)	553	(0.2)	0.00
GLP1	18,923	(18.9)	6,792	(3.2)	0.40	14198	(16.8)	8722	(3.0)	0.38
<b>Diabetes Complications Severity Index</b>										
0	72,250	(72.2)	139,501	(65.8)	0.20	62654	(74)	218071	(73.4)	0.06
1	12,648	(12.6)	23,997	(11.4)		10024	(11.8)	26646	(9.0)	
2	8,539	(8.6)	25,609	(12.0)		6689	(8.0)	29821	(10.0)	
>2	6,609	(6.6)	23,204	(11.0)		5216	(6.2)	22409	(7.6)	
<b>Measures of health care use</b>										
Mean inpatient visits (SD), n	0.1	(0.5)	0.3	(0.9)	0.32	0.1	(0.5)	0.2	(8.0)	0.26
Mean prescriptions (SD), n	35.5	(34.1)	38.1	(37.2)	0.08	34.8	(34.5)	26.3	(32.0)	0.24

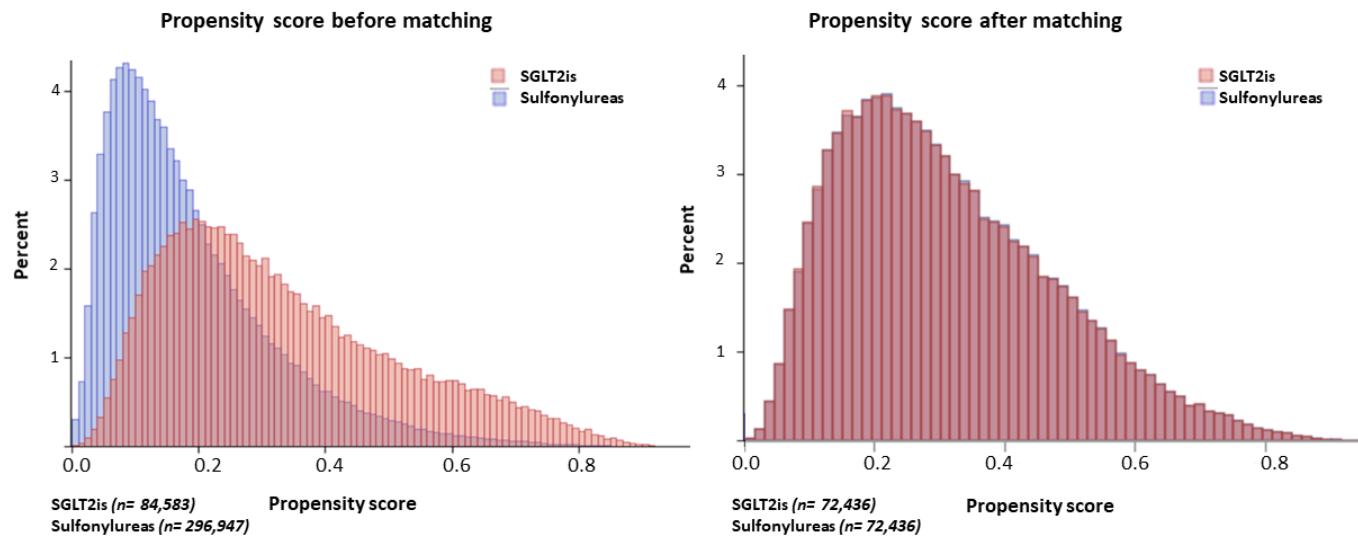
ACEs, angiotensin converting enzyme inhibitors, ARBs, angiotensin II receptor blockers, CCBs, calcium channel blockers, DPP4is, dipeptidyl peptidase-4 inhibitors, GLP1, Glucagon-like peptide-1 agonist, PPIs, proton pump inhibitors, SD, standard deviation, SGLT2is, sodium-glucose co-transporter-2 inhibitors, SSRIs, selective serotonin reuptake inhibitors, TZDs, thiazolidinediones

**Appendix Figure S3.** Distribution of propensity score among new-users of sodium-glucose co-transporter-2 inhibitors vs. dipeptidyl peptidase-4 inhibitors (*Panel A*), and vs. sulfonylureas (*Panel B*) before and after matching

A) SGLT2is vs DPP4is



B) SGLT2is vs. sulfonylureas



DPP4is, dipeptidyl peptidase-4 inhibitors, SGLT2is, sodium-glucose co-transporter-2 inhibitors

**Appendix Table S2.** Rate of diabetic ketoacidosis with sodium-glucose co-transporter-2 inhibitors compared to dipeptidyl peptidase-4 inhibitors and sulfonylureas among patients with type 2 diabetes.

Drug	N	Events, n	PYs of follow-up	Incidence rate per 1000 PYs	aHR, 95% CI
SGLT2is	85,125	343	56958	6.0	1.63 (1.36, 1.96)
DPP4is	85,125	256	59147	4.3	Reference
Canagliflozin	44,486	235	31008	7.6	1.49 (1.19, 1.87)
DPP4is	44,486	147	33352	4.4	Reference
Dapagliflozin	9,714	41	4936	8.3	2.16 (1.13, 4.10)
DPP4is	9,714	18	6680	2.7	Reference
Empagliflozin	35,345	102	19282	5.3	1.69 (1.19, 2.40)
DPP4is	35,345	96	24475	3.9	Reference
SGLT2is	72,436	313	50058	6.3	1.56 (1.30, 1.87)
Sulfonylureas	72,436	227	50250	4.5	Reference
Canagliflozin	37,401	225	29125	7.7	1.73 (1.38, 2.18)
Sulfonylureas	37,401	116	25811	4.5	Reference
Dapagliflozin	8,769	42	4628	9.1	1.64 (0.96, 2.80)
Sulfonylureas	8,769	24	5833	4.1	Reference
Empagliflozin	30,850	81	17397	4.7	1.19 (0.85, 1.68)
Sulfonylureas	30,850	94	21456	4.4	Reference

aHR, adjusted hazard ratio, DPP4is, dipeptidyl peptidase-4 inhibitors, PY, person-year, SGLT2is, sodium-glucose co-transporter-2 inhibitors

**Appendix Table S3.** Baseline laboratory measures among a subset of the matched cohort of type 2 diabetes patients who were new-users of sodium-glucose cotransporter-2 inhibitors compared to dipeptidyl peptidase-4 inhibitors and sulfonylureas

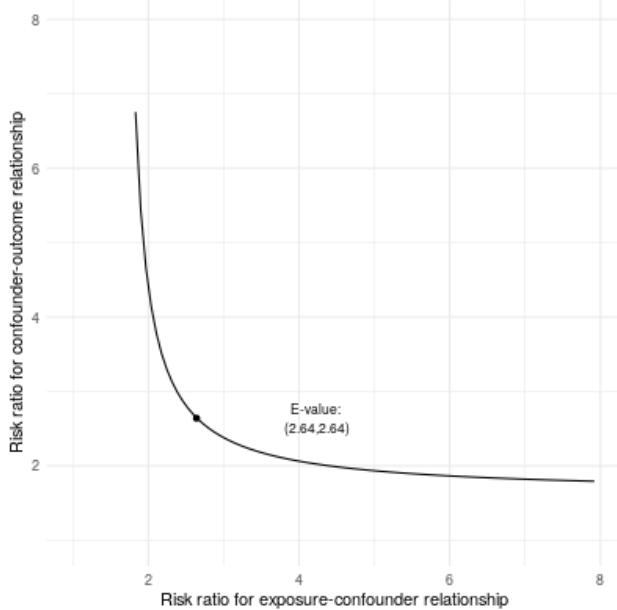
Laboratory Measure*	SGLT2is vs. DPP4is										
	Pre-matching cohort				Standardized Difference	Post-matching cohort				Standardized Difference	
	SGLT2is (n= 28,392)		DPP4is (n= 54,596)			SGLT2is (n= 23,567)		DPP4is (n= 23,567)			
Mean ( $\pm$ SD)											
Cholesterol level, mg/dL	176.9	45.1	174.2	43.2	0.06	177.3	44.9	177.7	44.3	0.00	
Hemoglobin A1c level	8.5	1.9	8.1	1.8	0.23	8.5	1.9	8.3	1.9	0.06	
AST, U/L	24.1	12.5	22.8	11.5	0.09	23.9	12.4	23.9	12.5	0.00	
ALT, U/L	30.5	20.7	26.4	18.8	0.20	30.1	20.4	29.8	21.1	0.01	
Triglyceride level, mg/dL	204.4	160.5	182.0	128.4	0.14	202.2	157.6	195.8	148.3	0.04	
SGLT2i vs. sulfonylureas											
	Pre-matching cohort				Standardized Difference	Post-matching cohort				Standardized Difference	
	SGLT2is (n= 26,099)		Sulfonylureas (n= 65,595)			SGLT2is (n= 22,098)		Sulfonylureas (n= 22,098)			
Mean ( $\pm$ SD)											
Cholesterol level, mg/dL	176.7	45.2	178.7	45.6	0.05	177.3	44.9	180.6	46.7	0.08	
Hemoglobin A1c level	8.3	1.9	8.1	1.9	0.10	8.3	1.9	8.4	2.0	0.09	
AST, U/L	24.4	12.9	23.3	12.2	0.09	24.4	12.8	24.4	13.2	0.01	
ALT, U/L	31.1	21.8	27.5	22.2	0.16	30.9	21.7	31.0	22.9	0.00	
Triglyceride level, mg/dL	200.5	158.7	192.4	146.1	0.05	198.6	155.1	207.1	167.0	0.05	

ALT, alanine aminotransferase, AST, aspartate aminotransferase, DPP4is, dipeptidyl peptidase-4 inhibitors, SD, standard deviation, SGLT2is, sodium-glucose co-transporter-2 inhibitors

\* Laboratory measures were not included in the propensity score model

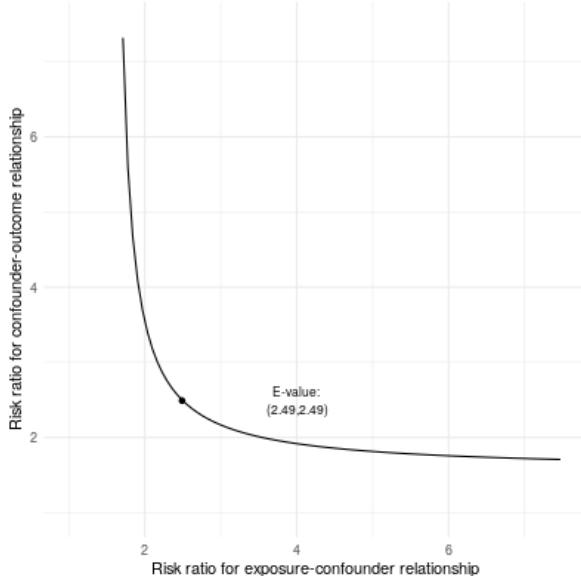
**Appendix Figure S4.** E-value representing the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the use of SGLT2is or DPP4is and diabetic ketoacidosis (*Panel A*), or sulfonylureas (*Panel B*) to fully explain away an observed treatment–outcome hazard ratio of 1.63 (with SGLT2is vs. DPP4is) and 1.56 (with SGLT2is vs. sulfonylureas).

A) SGLT2is vs. DPP4is



E-value for point estimate: 2.64 and for confidence interval: 2.06

B) SGLT2is vs. sulfonylureas



E-value for point estimate: 2.49 and for confidence interval: 1.92

DPP4is, dipeptidyl peptidase-4 inhibitors, SGLT2is, sodium-glucose co-transporter-2 inhibitors