Supporting TABLE S1. Baseline Laboratory Values of All Glucose-Lowering Agent Users

Characteristic	All Users n = 207,367		TZD Users n = 2,104		SU Users n = 29,732		GLP-1 Receptor Agonist Users n = 871		Insulin Users n = 10,467	
Most recent HbA1c record,* % (median)	7.9	(7.1-9.4)	7.5	(6.7-8.8)	8.5	(7.3-10.7)	7.8	(6.8-9.2)	8.8	(7.7-10.1)
Unknown (n)	71,408	(34.4)	1,312	(62.4)	15,841	(53.3)	530	(60.8)	4,423	(42.3)
Most recent FPG level,* mmol/L (median)	8.5	(7.1-11.9)	7.8	(6.6-10.6)	10.6	(7.5-16.1)	7.9	(6.0-12.1)	9.6	(6.5-15.6)
Unknown (n)	153,932	(74.2)	1,977	(94.0)	25,439	(85.6)	827	(94.9)	9,600	(91.7)
Most recent ALT level,* U/L (median)	29	(20-42)	22	(16-32)	26	(18-38)	29	(20-41)	24	(17-34)
Unknown (n)	87,123	(42.0)	1,631	(77.5)	17,905	(60.2)	696	(79.9)	6,136	(58.6)
Most recent AST level,* U/L (median)	24	(19-32)	24	(19-29)	22	(17-30)	22	(20-28)	22	(17-28)
Unknown (n)	184,072	(88.8)	1,991	(94.6)	27,334	(91.9)	839	(96.3)	9,642	(92.1)
Most recent GGT level,* U/L (median)	45	(29-78)	35	(19-62)	46	(28-90)	39	(28-71)	34	(21-63)
Unknown (n)	163,674	(78.9)	1,916	(91.1)	25,134	(84.5)	811	(93.1)	9,035	(86.3)
Most recent ALP level,* U/L (median)	84	(69-104)	76	(59-99)	90	(72-116)	82	(66-108)	88	(71-110)
Unknown (n)	73,151	(35.3)	1,541	(73.2)	16,446	(55.3)	679	(78.0)	5,639	(53.9)
Most recent bilirubin level,* µmol/L (median)	10	(7-13)	9	(7-12)	10	(7-13)	9	(6-12)	8	(6-12)
Unknown (n)	74,259	(35.8)	1,560	(74.1)	16,636	(56.0)	682	(78.3)	5,700	(54.5)
Most recent TC level,* mmol/L (median)	4.8	(4.0-5.7)	4.3	(3.7-5.0)	4.6	(3.8-5.6)	4.2	(3.6-5.1)	4.4	(3.7-5.2)
Unknown (n)	62,509	(30.1)	1,297	(61.6)	14,953	(50.3)	549	(63.0)	4,618	(44.1)
Most recent LDL-C level,* mmol/L (median)	2.7	(2.1-3.5)	2.2	(1.7-2.8)	2.6	(1.9-3.4)	2.2	(1.8-3.1)	2.4	(1.8-3.1)
Unknown (n)	105,264	(50.8)	1,648	(78.3)	20,664	(69.5)	703	(80.7)	6,968	(66.6)
Most recent HDL-C level,* mmol/L (median)	1.1	(1.0-1.4)	1.2	(1.0-1.4)	1.1	(0.9-1.4)	1.1	(0.9-1.3)	1.2	(1.0-1.5)
Unknown (n)	80,894	(39.0)	1,503	(71.4)	17,933	(60.3)	643	(73.8)	5,922	(56.6)
Most recent SBP record,* mm Hg (median)	135	(124-144)	134	(122-143)	134	(122-144)	132	(124-142)	132	(120-142)
Unknown (n)	31,568	(15.2)	596	(28.3)	7,524	(25.3)	272	(31.2)	2,089	(20.0)
Most recent DBP record,* mm Hg (median)	80	(71-85)	78	(70-83)	78	(70-84)	80	(72-85)	77	(70-82)
Unknown, (n)	31,566	(15.2)	596	(28.3)	7,523	(25.3)	272	(31.2)	2,089	(20.0)

*Within 1 year prior to index date.

Supporting TABLE S2. Risk of NAFLD in Patients With Type 2 Diabetes Using TZDs Compared With SUs stratified by cumulative dose.

Exposure to glucose-lowering agents	Risk of NAFLD				
	No. of Events (n = 634)	PYs	IR/ 1,000 PYs	Age/Sex aHR (95% CI)	aHR (95% CI)*
Current use of glucose-lowering agents					
SUs	616	172,309	3.6	Reference	Reference
TZDs	18	14,732	1.2	0.32 (0.20-0.51)	0.32 (0.20-0.51)
By cumulative dose (pioglitazone equivalents)					
<5.4 g	7	3,713	1.9	0.47 (0.22-0.99)	0.44 (0.21-0.93)
5.4-21.8 g	<6	5,759	0.9	0.23 (0.09-0.55)	0.23 (0.09-0.55)
≥21.9 g	6	5,260	1.1	0.31 (0.14-0.70)	0.32 (0.14-0.71)

*Statistically adjusted for age, sex, BMI, HbA1c, and use of systemic glucocorticoids and all other exposure categories in this table.
Note: Table shows stratification of TZD users by cumulative dose, other exposure groups included in this analysis were DPP-4 inhibitors, other glucose-lowering agents, concurrent use of SUs and TZDs and past use of any glucose-lowering agents; data shown in Table 2. All groups were mutually exclusive.

Supporting TABLE S3. Baseline Characteristics of Users of TZDs and SUs, Before and After Propensity Score Matching

	Before Propensity Matching					After Propensity Matching				
	SU Users (n = 68,979)		TZD Users* (n = 5,728)			SU Users (n = 5,728)		TZDUsers (n = 5,728)		
	n	%	n	%	SD	n	%	n	%	SD
Follow-up, years (mean, SD)	1.4	1.7	1.4	1.7	−0.01	1.5	1.8	1.4	1.7	−0.02
Sex					−0.05					0.01
Female	28,956	42.0	2,270	39.6		2,250	39.3	2,270	39.6	
Male	40,023	58.0	3,458	60.4		3,478	60.7	3,458	60.4	
Age, years (mean)	62.8	14.4	59.3	12.7	−0.26	58.9	13.8	59.3	12.7	0.03
Smoking status					0.07					0.03
Current smoker	13,445	19.5	1,108	19.3		1,110	19.4	1,108	19.3	
Former smoker	28,435	41.2	2,205	38.5		2,154	37.6	2,205	38.5	
Never smoker	21,841	31.7	1,886	32.9		1,887	32.9	1,886	32.9	
Unknown	5,258	7.6	529	9.2		577	10.1	529	9.2	
Alcohol use					0.06					0.02
Yes	38,758	56.2	3,331	58.2		3,218	56.2	3,331	58.2	
No	19,183	27.8	1,452	25.3		1,447	25.3	1,452	25.3	
Unknown	11,038	16.0	945	16.5		1,063	18.6	945	16.5	
BMI, kg/m^2					0.28					0.05
<20	1,102	1.6	28	0.5		20	0.3	28	0.5	
20-24.9	8,610	12.5	403	7.0		420	7.3	403	7.0	
25-29.9	19,020	27.6	1,351	23.6		1,312	22.9	1,351	23.6	
30-34.9	16,857	24.4	1,515	26.4		1,539	26.9	1,515	26.4	
≥35.0	14,402	20.9	1,637	28.6		1,580	27.6	1,637	28.6	
Unknown	8,988	13.0	794	13.9		857	15.0	794	13.9	
History of disease										
Cardiovascular disease	5,767	8.4	302	5.3	−0.12	273	4.8	302	5.3	0.02
Heart failure	3,194	4.6	71	1.2	−0.20	74	1.3	71	1.2	−0.00
Hypertension	27,803	40.3	2,325	40.6	0.01	2,239	39.1	2,325	40.6	0.03
Chronic liver failure	334	0.5	10	0.2	−0.05	5	0.1	10	0.2	0.02
Chronic renal failure	9,128	13.2	495	8.6	−0.15	472	8.2	495	8.6	0.01
Neuropathy	1,416	2.1	132	2.3	0.02	119	2.1	132	2.3	0.02
Retinopathy	5,348	7.8	510	8.9	0.04	506	8.8	510	8.9	0.00
Microalbuminuria	11,039	16.0	945	16.5	0.01	874	15.3	945	16.5	0.03
Macroalbuminuria	1,534	2.2	97	1.7	−0.04	94	1.6	97	1.7	0.00
Drug use in previous 6 months										
Amiodarone	215	0.3	7	0.1	−0.04	5	0.1	7	0.1	0.01
Methotrexate	433	0.6	26	0.5	−0.02	24	0.4	26	0.5	0.01
Glucocorticoids	6,139	8.9	214	3.7	−0.21	234	4.1	214	3.7	−0.02
Valproate	520	0.8	27	0.5	−0.04	29	0.3	27	0.5	0.02
Most recent HbA1c**					0.12					0.04
<6.5%	2,185	3.2	187	3.3		164	2.9	187	3.3	
6.5%-7.5%	7,391	10.7	676	11.8		626	10.9	676	11.8	
7.6%-8.5%	13,551	19.6	1,361	23.8		1,343	23.4	1,361	23.8	
>8.5%	25,380	36.8	1,878	32.8		1,893	33.0	1,878	32.8	
Missing	20,472	29.7	1,626	28.4		1,702	29.7	1,626	28.4	
Most recent FPG level**					0.12					0.03

<6.0 mmol/L	645	0.9	41	0.7		39	0.7	41	0.7	
6.0-7.4 mmol/L	1,753	2.5	133	2.3		112	2.0	133	2.3	
7.5-8.9 mmol/L	2,322	3.4	183	3.2		181	3.2	183	3.2	
≥9 mmol/L	8,114	11.8	481	8.4		472	8.2	481	8.4	
Missing	56,145	81.4	4,890	85.4		4,924	86.0	4,890	85.4	
Most recent ALT level**					0.11					0.05
<45 U/L	33,001	47.8	2,503	43.7		2,504	43.7	2,503	43.7	
45-70 U/L	6,929	10.0	624	10.9		609	10.6	624	10.9	
71-225 U/L	4,699	6.8	373	6.5		403	7.0	373	6.5	
>225 U/L	481	0.7	19	0.3		34	0.6	19	0.3	
Missing	23,869	34.6	2,209	38.6		2,178	38.0	2,209	38.6	
Mean (SD)	43.1	76.7	41.2	38.8		43.9	55.0	41.2	38.8	
Median (IQR)	29	20-46	31	22-48		31	22-49	31	22-48	
Most recent AST level**					0.11					0.05
<35 U/L	19,987	29.0	1,420	24.8		1,511	26.4	1,420	24.8	
35-55 U/L	6,771	9.8	576	10.1		567	9.9	576	10.1	
56-175 U/L	6,030	8.7	519	9.1		522	9.1	519	9.1	
>175 U/L	699	1.0	36	0.6		51	0.9	36	0.6	
Missing	35,492	51.5	3177	55.5		3,077	53.7	3,177	55.5	
Mean (SD)	45.7	88.4	43.9	44.4		45.6	61.1	43.9	44.4	
Median (IQR)	29	20-48	32	21-52		31	21-51	32	21-52	
Most recent GGT level**					0.12					0.06
<55 U/L	26,005	37.7	1,938	33.8		2,006	35.0	1,938	33.8	
55-85 U/L	4,517	6.5	382	6.7		385	6.7	382	6.7	
86-275 U/L	3,591	5.2	274	4.8		299	5.2	274	4.8	
>275 U/L	581	0.8	19	0.3		35	0.6	19	0.3	
Missing	34,285	49.7	3,115	54.4		3,003	52.4	3,115	54.4	
Mean (SD)	53.5	111.6	48.7	64.7		52.5	100.8	48.7	64.7	
Median (IQR)	32	21-55	34	23-56		33	22-56	34	23-56	
Most recent ALP level**					0.12					0.06
<115 U/L	41,959	60.8	3,356	58.6		3,339	58.3	3,356	58.6	
115-575 U/L	4,912	7.1	300	5.2		363	6.3	300	5.2	
>575 U/L	137	0.2	1	0.0		6	0.1	1	0.0	
Missing	21,971	31.9	2,071	36.2		2,020	35.3	2,071	36.2	
Mean (SD)	65.5	86.3	61.2	47.5		63.8	61.6	61.2	47.5	
Median (IQR)	51	26-84	53	28-81		53	27-84	53	28-81	
Most recent bilirubin level**					0.12					0.05
<20 mmol/L	43,588	63.2	3,381	59.0		3,462	60.4	3,381	59.0	
20-100 mmol/L	2,911	4.2	189	3.3		217	3.8	189	3.3	
>100 mmol/L	50	0.1	1	0.0		3	0.1	1	0.0	
Missing	22,430	32.5	2,157	37.7		2,046	35.7	2,157	37.7	
Mean (SD)	10.7	9.0	10.2	6.2		10.5	6.7	10.2	6.2	
Median (IQR)	9	7-13	9	7-12		9	7-12	9	7-12	
Most recent TC level**					0.12					0.04
≤4.9 mmol/L	32,406	47.0	2,929	51.1		2,820	49.2	2,929	51.1	
5.0-7.9 mmol/L	16,319	23.7	1,163	20.3		1,170	20.4	1,163	20.3	
≥8 mmol/L	940	1.4	32	0.6		34	0.6	32	0.6	
Missing	19,314	28.0	1,604	28.0		1,704	29.7	1,604	28.0	

Most recent LDL-C level[**]					0.10					0.02
≤2.5 mmol/L	16,580	24.0	1,484	25.9		1,451	25.3	1,484	25.9	
2.6-3.5 mmol/L	10,510	15.2	843	14.7		870	15.2	843	14.7	
≥3.6 mmol/L	6,598	9.6	402	7.0		396	6.9	402	7.0	
Missing	35,291	51.2	2,999	52.4		3,011	52.6	2,999	52.4	
Most recent HDL-C level[**]					0.04					0.02
≤1.0 mmol/L	12,899	18.7	1,137	19.8		1,127	19.7	1,137	19.8	
1.1-2.0 mmol/L	29,005	42.0	2,421	42.3		2,373	41.4	2,421	42.3	
≥2.1 mmol/L	984	1.4	63	1.1		59	1.0	63	1.1	
Missing	26,091	37.8	2,107	36.8		2,169	37.9	2,107	36.8	
Most recent SBP record[**]					0.04					0.04
<100 mm Hg	548	0.8	30	0.5		25	0.4	30	0.5	
100-140 mm Hg	41,024	59.5	3,431	59.9		3,448	60.2	3,431	59.9	
>140 mm Hg	14,666	21.3	1,241	21.7		1,166	20.4	1,241	21.7	
Missing	12,741	18.5	1,026	17.9		1,089	19.0	1,026	17.9	
Most recent DBP record[**]					0.03					0.04
<60 mm Hg	1,401	2.0	97	1.7		85	1.5	97	1.7	
60-90 mm Hg	50,307	72.9	4,223	73.7		4,198	73.3	4,223	73.7	
>90 mm Hg	4,532	6.6	382	6.7		357	6.2	382	6.7	
Missing	12,739	18.5	1,026	17.9		1,088	19.0	1,026	17.9	

[*]The number of TZD users is different than the number of TZD users in Table 1 of the manuscript. This is due to a difference in selection of the patients between the analyses. For the propensity score analysis we started follow-up at the first TZD or SU prescription, whereas in the main analysis we started follow-up at the first glucose-lowering drug prescription.
[**]Within 1 year prior to index date.
Abbreviations: IQR, interquartile range; SD, standardized difference.

Supporting TABLE S4. Risk of NAFLD in Patients With Type 2 Diabetes Using TZDs Compared With SUs in a Propensity Score–Matched Analysis

	Risk of NAFLD			
Exposure to glucose-lowering agents*	Patients	No. of Events (n = 57)	IR/ 1,000 PYs	aHR (95% CI)
SUs	5,728	45	5.4	Reference
TZDs	5,728	12	1.5	0.27 (0.14-0.52)

*Current use of the glucose-lowering agent at start of follow-up.

Supporting TABLE S5. Incidence Rate of HCC in Patients With Type 2 Diabetes Using TZDs and SUs

	Latency Period of 6 Months			Latency Period of 24 Months		
Exposure to glucose-lowering agents	No. of Events (n = 213)	PYs	IR/ 1,000 PYs	No. of Events (n = 142)	PYs	IR/ 1,000 PYs
Current use of glucose-lowering agents						
SUs	55	176,845	0.3	42	176,828	0.2
TZDs	<6	15,016	0.3	<6	15,014	0.3
DPP-4 inhibitors	13	46,960	0.3	12	46,958	0.3
Other glucose-lowering agents	96	470,394	0.2	57	470,338	0.1
Current combined use						
TZDs and SUs	<6	9,826	0.2	<6	9,826	0.2
Past use						
Past use of glucose-lowering agents	42	371,335	0.1	25	371,326	0.1

Note: All groups in this table were mutually exclusive. Current use (1-90 days) or past use (>90 days) were defined by the time since the most recent prescription.

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Supporting TABLE S6. Baseline Characteristics of Users of Insulins and GLP-1 Receptor Agonists, Before and After Propensity Score Matching

	Before Propensity Matching					After Propensity Matching				
	Insulin Users (n = 24,302)		GLP-1 Receptor Agonist Users* (n = 7,063)			Insulin Users (n = 4,944)		GLP-1 Receptor Agonist Users (n = 4,944)		
	n	%	n	%	SD	n	%	n	%	SD
Follow-up, years (mean, SD)	1.2	2.0	1.0	1.1	0.85	1.3	1.8	1.0	1.1	0.03
Sex					−0.04					−0.01
Female	12,013	49.4	3,341	47.3		2,423	49.0	2,403	48.6	
Male	12,289	50.6	3,722	52.7		2,521	51.0	2,541	51.4	
Age, years (mean)	55.6	17.8	55.0	11.0	−0.04	55.9	14.9	55.4	11.2	−0.04
Smoking status					0.46					0.06
Current smoker	8,120	33.4	2,112	29.9		1,479	29.9	1,545	31.3	
Former smoker	5,142	21.2	1,455	20.6		1,075	21.7	1,038	21.0	
Never smoker	7,684	31.6	3,280	46.4		2,124	43.0	2,148	43.4	
Unknown	3,356	13.8	216	3.1		266	5.4	213	4.3	
Alcohol use					0.45					0.02
Yes	7,067	29.1	2,094	29.6		1,568	31.7	1,557	31.5	
No	11,250	46.3	4,350	61.6		2,793	56.5	2,825	57.1	
Unknown	5,985	24.6	619	8.8		583	11.8	562	11.4	
BMI, kg/m^2					1.32					0.07
<20	724	3.0	3	0.0		6	0.1	3	0.1	
20-24.9	3,551	14.6	54	0.8		78	1.6	54	1.1	
25-29.9	6,088	25.1	521	7.4		514	10.4	521	10.5	
30-34.9	4,820	19.8	1,702	24.1		1,499	30.3	1,604	32.4	
≥35.0	4,151	17.1	4,424	62.6		2,446	49.5	2,403	48.6	
Unknown	4,968	20.4	359	5.1		401	8.1	359	7.3	
History of disease										
Cardiovascular disease	1,947	8.0	302	4.0	−0.17	230	4.7	249	5.0	0.02
Heart failure	1,085	4.5	71	2.7	−0.09	164	3.3	169	3.4	0.01
Hypertension	7,742	31.9	2,325	44.5	0.26	2,065	41.8	2,054	41.5	−0.00
Chronic liver failure	163	0.7	10	0.2	−0.07	15	0.3	15	0.3	0.00
Chronic renal failure	2,981	12.3	495	6.9	−0.18	441	8.9	431	8.7	−0.01
Neuropathy	881	3.6	132	3.3	−0.02	168	3.4	165	3.3	−0.00
Retinopathy	2,902	11.9	510	11.0	−0.03	561	11.3	563	11.4	0.00
Microalbuminuria	3,491	14.4	945	27.6	0.33	1,190	24.1	1,130	22.9	−0.03
Macroalbuminuria	667	2.7	97	3.4	0.04	155	3.1	159	3.2	0.00
Drug use in previous 6 months										
Amiodarone	71	0.3	13	0.2	−0.02	12	0.2	11	0.2	−0.00
Methotrexate	116	0.5	50	0.7	0.03	34	0.7	32	0.6	−0.01
Glucocorticoids	1,781	7.3	483	6.8	−0.02	361	7.3	385	7.8	0.02
Valproate	189	0.8	57	0.8	0.00	36	0.7	42	0.8	0.01
Most recent HbA1c**					0.85					0.03
<6.5%	917	3.8	174	2.5		144	2.9	161	3.3	
6.5%-7.5%	1,392	5.7	554	7.8		377	7.6	399	8.1	
7.6%-8.5%	1,983	8.2	1,428	20.2		786	15.9	754	15.3	
>8.5%	8,548	35.2	4,016	56.9		2,741	55.4	2,745	55.5	

Missing	11,462	47.2	891	12.6		896	18.1	885	17.9	
Most recent FPG level**					0.17					0.02
<6.0 mmol/L	352	1.4	37	0.5		39	0.8	37	0.7	
6.0-7.4 mmol/L	354	1.5	122	1.7		84	1.7	91	1.8	
7.5-8.9 mmol/L	287	1.2	180	2.5		100	2.0	106	2.1	
≥9 mmol/L	1,661	6.8	683	9.7		431	8.7	444	9.0	
Missing	21,648	89.1	6,041	85.5		4,290	86.8	4,266	86.3	
Most recent ALT level**					0.66					0.12
<45 U/L	9,078	37.4	3,732	52.8		2,529	51.2	2,472	50.0	
45-70 U/L	1,322	5.4	1,094	15.5		508	10.3	679	13.7	
71-225 U/L	1,097	4.5	574	8.1		361	7.3	371	7.5	
>225 U/L	181	0.7	39	0.6		46	0.9	24	0.5	
Missing	12,624	51.9	1,624	23.0		1,500	30.3	1,398	28.3	
Mean (SD)	44.0	131.4	45.0	101.0		47.2	181.6	44.3	101.3	
Median (IQR)	26	18-41	33	23-50		29	20-46	33	23-49	
Most recent AST level**					0.55					0.16
<35 U/L	5,897	24.3	2,262	32.0		1,587	32.1	1,516	30.7	
35-55 U/L	1,330	5.5	1,107	15.7		484	9.8	707	14.3	
56-175 U/L	1,328	5.5	832	11.8		452	9.1	526	10.6	
>175 U/L	246	1.0	50	0.7		57	1.2	29	0.6	
Missing	15,501	63.8	2,812	39.8		2,364	47.8	2,166	43.8	
Mean (SD)	47.1	146.9	46.2	113.4		50.6	209.2	45.3	113.6	
Median (IQR)	25	17-43	33	23-51		28	19-48	32	22-50	
Most recent GGT level**					0.51					0.12
<55 U/L	7,130	29.3	3,246	46.0		2,053	41.5	2,145	43.4	
55-85 U/L	931	3.8	691	9.8		333	6.7	438	8.9	
86-275 U/L	914	3.8	363	5.1		272	5.5	234	4.7	
>275 U/L	229	0.9	35	0.5		62	1.3	28	0.6	
Missing	15,098	62.1	2,728	38.6		2,224	45.0	2,099	42.5	
Mean (SD)	66.8	470.5	50.3	115.2		65.8	367.9	50.2	116.4	
Median (IQR)	27	18-50	35	24-55		31	20-54	34	23-54	
Most recent ALP level**					0.66					0.12
<115 U/L	10,557	43.4	5,144	72.8		3,130	63.3	3,367	68.1	
115-575 U/L	1,536	6.3	444	6.3		398	8.1	290	5.9	
>575 U/L	59	0.2	11	0.2		16	0.3	6	0.1	
Missing	12,150	50.0	1,464	20.7		1,400	28.3	1,281	25.9	
Mean (SD)	75.4	402.0	60.9	102.9		73.8	316.6	60.6	103.4	
Median (IQR)	45	22-87	48	27-78		48	24-86	47	27-78	
Most recent bilirubin level**					0.67					0.05
<20 mmol/L	11,192	46.1	5,382	76.2		3,334	67.4	3,514	71.1	
20-100 mmol/L	711	2.9	194	2.7		168	3.4	128	2.6	
>100 mmol/L	54	0.2	1	0.0		7	0.1	1	0.0	
Missing	12,345	50.8	1,486	21.0		1,435	29.0	1,301	26.3	
Mean (SD)	10.9	14.3	9.4	4.8		10.2	10.8	9.4	5.0	
Median (IQR)	9	6-12	8	6-11		8	6-12	8	6-11	
Most recent TC level**					0.80					0.02
≤4.9 mmol/L	8,216	33.8	4,427	62.7		2,724	55.1	2,736	55.3	
5.0-7.9 mmol/L	4,075	16.8	1,566	22.2		1,178	23.8	1,168	23.6	

≥8 mmol/L	302	1.2	48	0.7		38	0.8	45	0.9	
Missing	11,709	48.2	1,022	14.5		1,004	20.3	995	20.1	
Most recent LDL-C level[**]					0.62					0.03
≤2.5 mmol/L	3,886	16.0	2,247	31.8		1,377	27.9	1,320	26.7	
2.6-3.5 mmol/L	2,473	10.2	1,387	19.6		857	17.3	872	17.6	
≥3.6 mmol/L	1,543	6.3	752	10.6		516	10.4	500	10.1	
Missing	16,400	67.5	2,677	37.9		2,194	44.4	2,252	45.6	
Most recent HDL-C level[**]					0.78					0.02
≤1.0 mmol/L	3,304	13.6	2,110	29.9		1,341	27.1	1,326	26.8	
1.1-2.0 mmol/L	6,677	27.5	3,299	46.7		2,056	41.6	2,087	42.2	
≥2.1 mmol/L	384	1.6	30	0.4		34	0.7	30	0.6	
Missing	13,937	57.3	1,624	23.0		1,513	30.6	1,501	30.4	
Most recent SBP record[**]					0.47					0.05
<100 mm Hg	385	1.6	37	0.5		34	0.7	32	0.6	
100-140 mm Hg	13,725	56.5	4,909	69.5		3,253	65.8	3,330	67.4	
>140 mm Hg	3,901	16.1	1,473	20.9		1,023	20.7	1,019	20.6	
Missing	6,291	25.9	644	9.1		634	12.8	563	11.4	
Most recent DBP record[**]					0.50					0.05
<60 mm Hg	677	2.8	56	0.8		59	1.2	52	1.1	
60-90 mm Hg	16,098	66.2	5,731	81.1		3,842	77.7	3,936	79.6	
>90 mm Hg	1,234	5.1	632	8.9		409	8.3	393	7.9	
Missing	6,293	25.9	644	9.1		634	12.8	563	11.4	

[*]The number of GLP-1 receptor agonist users is different than the number of GLP-1 receptor agonist users in Table 1 of the manuscript. This is due to a difference in selection of the patients between the analyses. For the propensity score analysis we started follow-up at the first GLP-1 receptor agonist or insulin prescription, whereas in the main analysis we started follow-up at the first glucose-lowering drug prescription.
[**]Within 1 year prior to index date.

Supporting TABLE S7. Risk of NAFLD in Patients With Type 2 Diabetes Using Insulins Compared With GLP-1 Receptor Agonists in a Propensity Score–Matched analysis

		Risk of NAFLD		
Exposure to glucose-lowering agents*	Patients	No. of Events (n = 65)	IR/ 1,000 PYs	aHR (95% CI)
Insulins	4,944	31	6.4	Reference
GLP-1 receptor agonists	4,944	34	5.4	1.08 (0.66-1.77)

*Current use of the glucose-lowering agent at start of follow-up.

Supporting TABLE S8. Risk of NAFLD in Patients With Type 2 Diabetes Using GLP-1 Receptor Agonists Compared With SUs

	Risk of NAFLD				
Exposure to glucose-lowering agents	No. of Events (n = 2,526)	PYs	IR/ 1,000 PYs	Age/Sex aHR (95% CI)	aHR (95% CI)*
Current use of glucose-lowering agents					
SUs	605	175,010	3.5	Reference	Reference
GLP-1 receptor agonists	52	10,578	4.9	1.06 (0.80-1.41)	0.85 (0.64-1.13)
Other glucose-lowering agents	1,678	509,445	3.3	0.87 (0.80-0.96)	0.90 (0.82-0.99)
Current combined use					
GLP-1 receptor agonists and SUs	31	6,923	4.5	1.03 (0.72-1.47)	0.77 (0.53-1.10)
Past use					
Past use of glucose-lowering agents	160	363,620	0.4	0.11 (0.09-0.13)	0.22 (0.18-0.27)

*Statistically adjusted for age, sex, smoking, alcohol use, BMI, HbA1c, FPG, TC, HDL-C, LDL-C, SBP, DBP, hypertension, retinopathy, microalbuminuria, and use of systemic glucocorticoids.

Note: All groups in this table were mutually exclusive. Current use (1-90 days) or past use (>90 days) were defined by the time since the most recent prescription.

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Supporting TABLE S9. Incidence Rate of HCC in Patients With Type 2 Diabetes Using GLP-1 Receptor Agonists and Insulins

	Latency Period of 6 Months			Latency Period of 24 Months		
Exposure to glucose-lowering agents	No. of Events (n = 213)	PYs	IR/ 1,000 PYs	No. of Events (n = 142)	PYs	IR/ 1,000 PYs
Current use of glucose-lowering agents						
Insulins	22	60,688	0.4	14	60,678	0.2
GLP-1 receptor agonists	<6	14,412	0.1	<6	14,412	0.1
Other glucose-lowering agents	146	639,968	0.2	101	639,902	0.2
Current combined use						
GLP-1 receptor agonists and insulins	<6	3,972	0.5	<6	3,971	0.3
Past use						
Past use of glucose-lowering agents	42	371,335	0.1	25	371,326	0.1

Note: All groups in this table were mutually exclusive. Current use (1-90 days) or past use (>90 days) were defined by the time since the most recent prescription.

Supporting Information

Propensity score–matched sensitivity analyses

Study population

Comparing use of sulfonylureas with use of thiazolidinediones

In the first sensitivity analysis, we used propensity score matching to control for confounding in the analysis comparing use of thiazolidinediones (TZDs) with use of sulfonylureas (SUs). For the propensity score analyses we included all patients who were new users of SUs or TZDs during the study period. The date of the first prescription (of an SU or TZD) determined the index date. Patients who were prescribed both an SU and a TZD at the index date were excluded. Patients with a history of polycystic ovarian syndrome (PCOS), nonalcoholic fatty liver disease (NAFLD), or hepatocellular carcinoma (HCC) were excluded as well.

Comparing use of glucagon-like peptide-1 receptor agonists with use of insulin

We also performed a propensity score–matched sensitivity analysis comparing use of glucagon-like peptide-1 (GLP-1) receptor agonists with use of insulin. In this analysis we included all patients who were new users of GLP-1 receptor agonists or insulin during the study period. The date of the first prescription (of a GLP-1 receptor agonist or insulin) determined the index date. Patients who were prescribed both a GLP-1 receptor agonist and an insulin at the index date were excluded. Patients with a history of PCOS, NAFLD, or HCC were excluded as well.

Follow-up

Comparing use of SUs with use of TZDs

Patients were followed from their index date until the date of the event of interest, end of data collection, death, switch to the comparator drug, or treatment discontinuation, whichever came first. The expected end date was calculated for each prescription based on the prescribed quantity and written dosage instructions. Treatment discontinuation was defined as no refill after the last prescription or within 30 days after the expected end date of the last prescription.

Comparing use of GLP-1 receptor agonists with use of insulin

Patients were followed from their index date until the date of the event of interest, end of data collection, death, switch to the comparator drug, or treatment discontinuation, whichever came first. The total amount of defined daily dosages (DDDs) was calculated for each prescription based on the prescribed number of pens and the amount of DDDs per pen.[(1)] The expected end date of a prescription was calculated as the date of the prescription plus the number of prescribed DDDs, assuming that patients used 1 DDD per day. Treatment discontinuation was defined as no refill after the last prescription or within 30 days after the expected end date of the last prescription.

Baseline covariates

For both propensity score analyses

Based on the literature, we selected covariates related to NAFLD and the exposure of interest. We determined the presence of the following covariates at index date: age, sex, smoking status, body mass index (BMI), and alcohol use. A history of the following covariates was also determined at index date: cardiovascular disease, chronic kidney disease, heart failure, chronic liver disease, hypertension, neuropathy, retinopathy, microalbuminuria, and macroalbuminuria, as well as use of the following drugs in the 6 months before the index date: amiodarone, methotrexate, systemic glucocorticoids, and valproate. Furthermore, we

determined the following most recently recorded laboratory values in the year prior to the index date: hemoglobin A1c (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), systolic blood pressure (SBD), and diastolic blood pressure (DBD). If two or more laboratory measurements were recorded on the same date, the average value was used in the analysis. An indicator variable was used to account for missing data.

Statistical analysis

For both propensity score analyses

Multivariable logistic regression, including all baseline covariates mentioned in the previous section, was used to estimate the probability of receiving a TZD versus an SU or a GLP-1 receptor agonist versus an insulin, respectively. A histogram of the estimated probabilities per exposure was created to check for the overlap in the estimated probabilities (Supporting Fig. S5). This was done both before and after matching. Patients initiating TZDs or GLP-1 receptor agonists were matched (without replacement) to one patient initiating SUs or insulins, respectively, on their estimated propensity score using nearest neighbor matching with a matching caliper of 0.02 on the propensity score scale.[2, 3] Standardized differences were calculated to check the balance after matching. After matching, Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for NAFLD associated with use of TZDs compared with use of SUs and use of GLP-1 receptor agonists compared with use of insulins. A Kaplan-Meier curve was used to visualize the time to NAFLD for both exposure groups.

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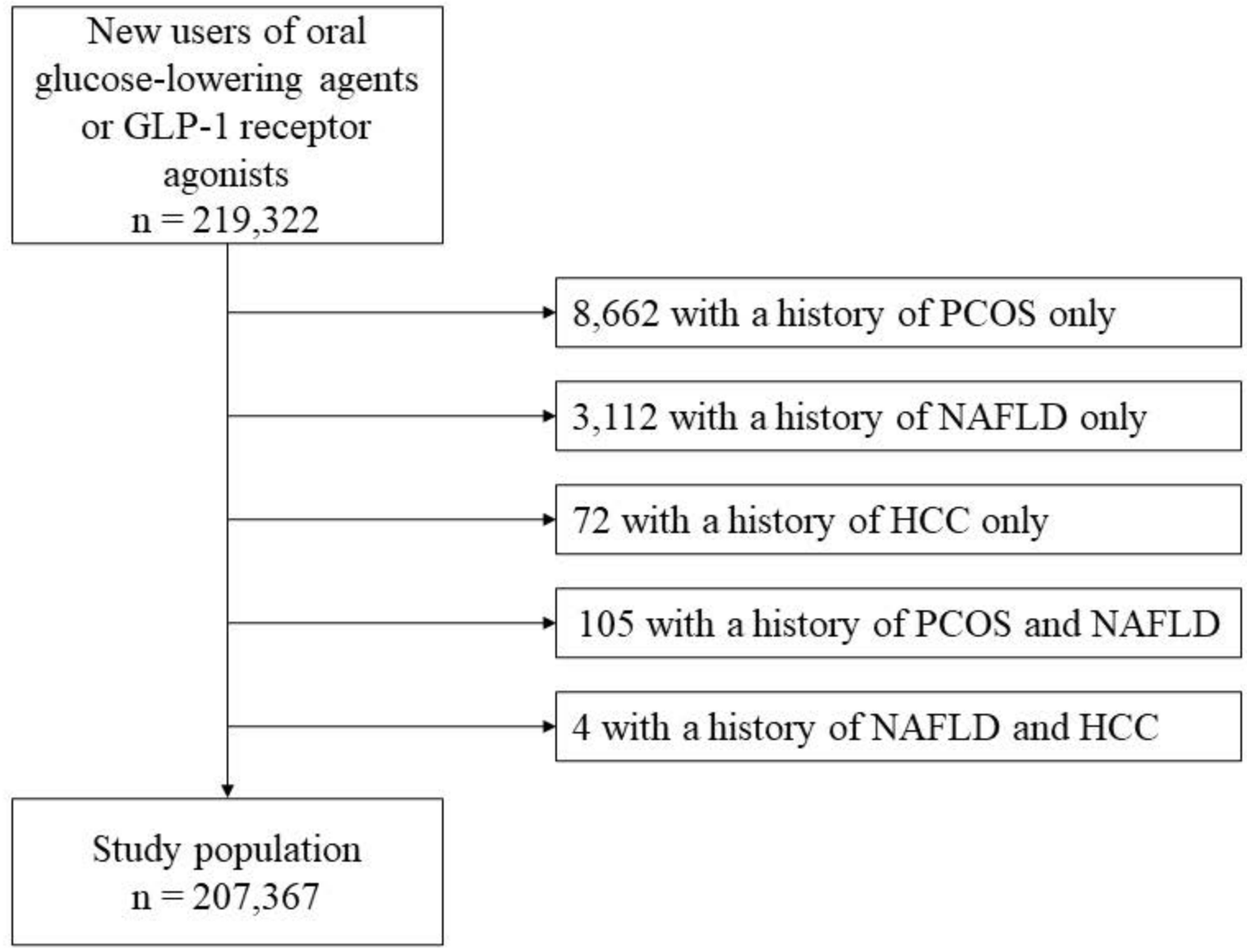
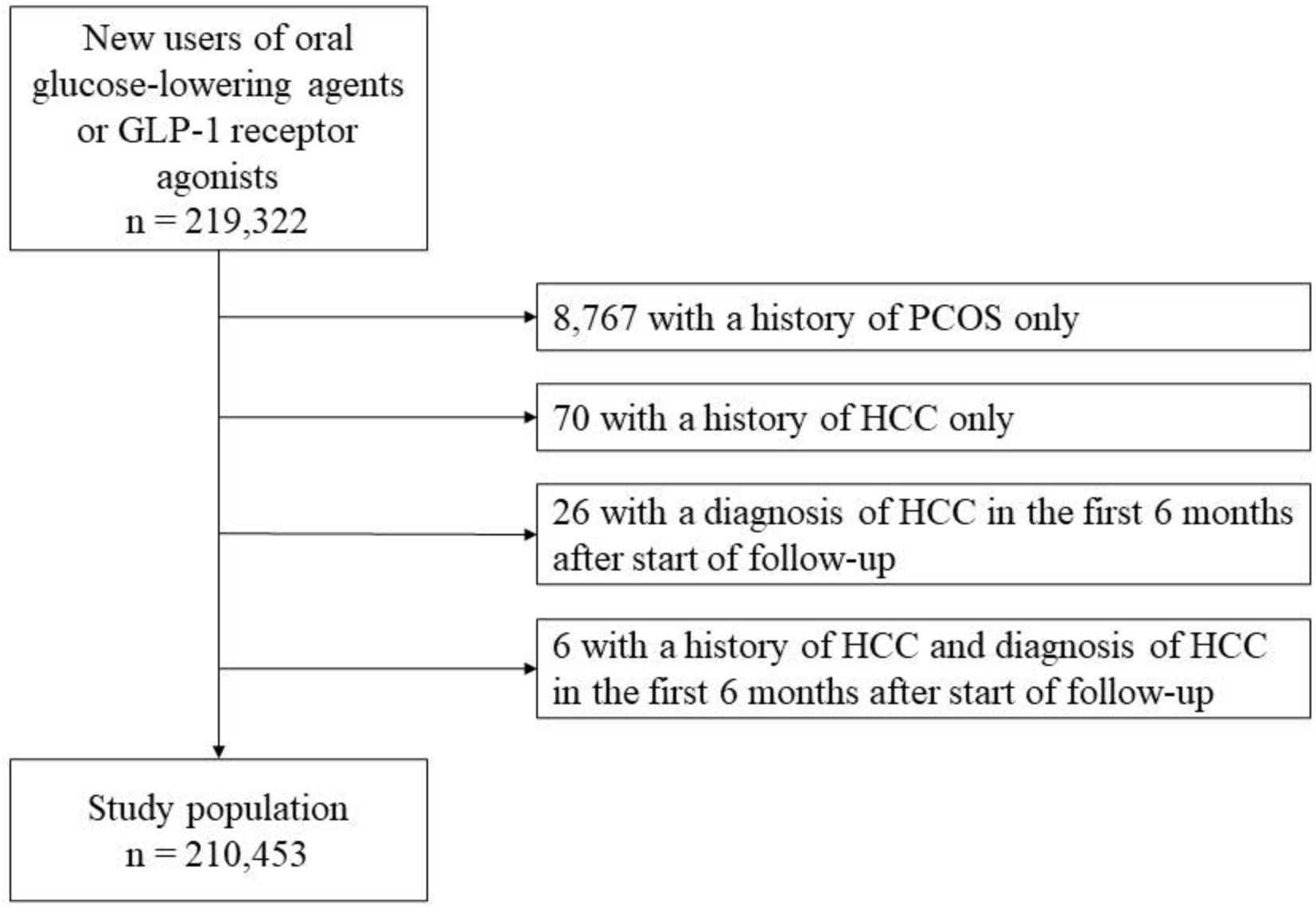
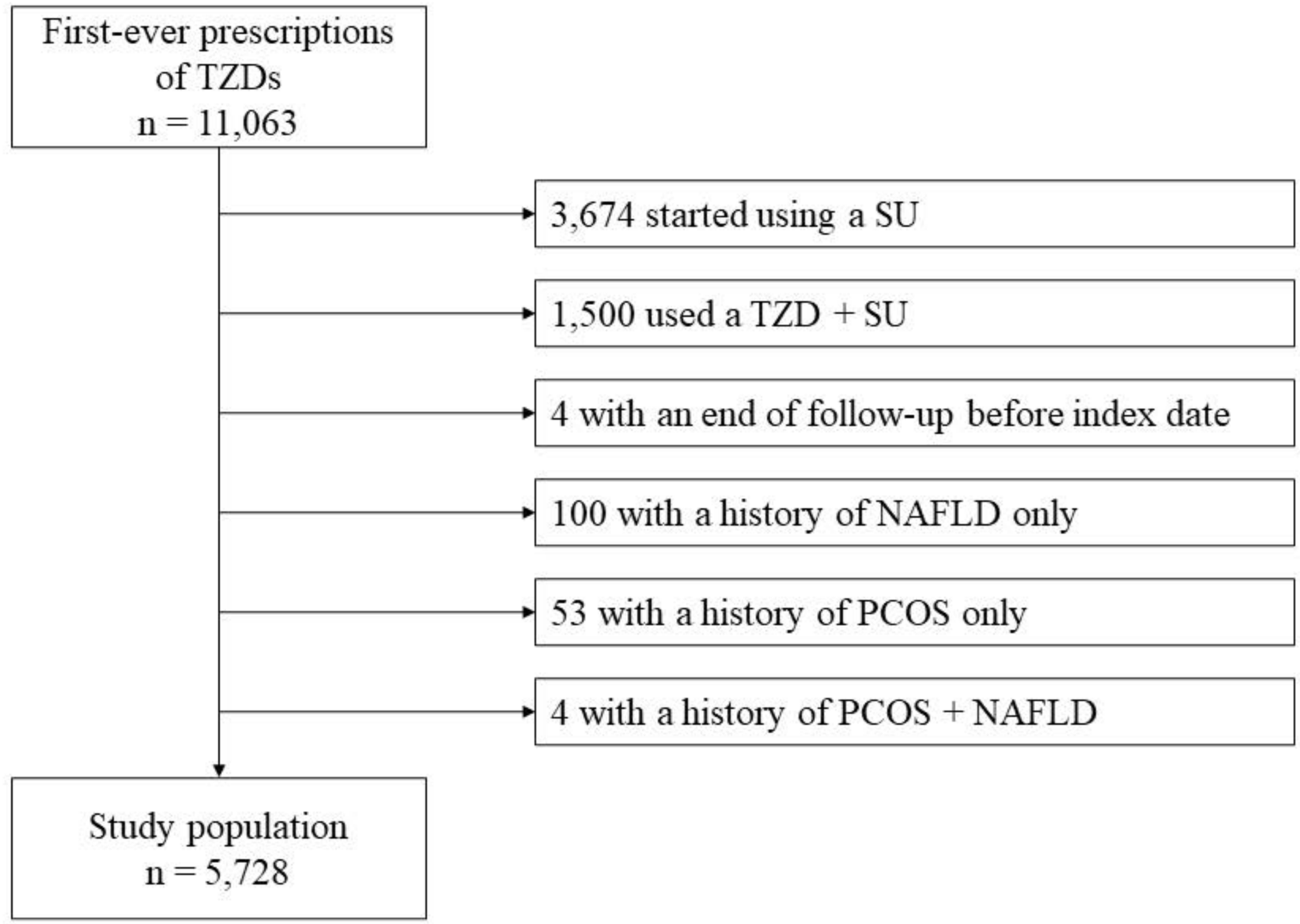
1) WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2021. https://www.whocc.no/atc_ddd_index/. Last updated December 17, 2020. Accessed September 16, 2020.

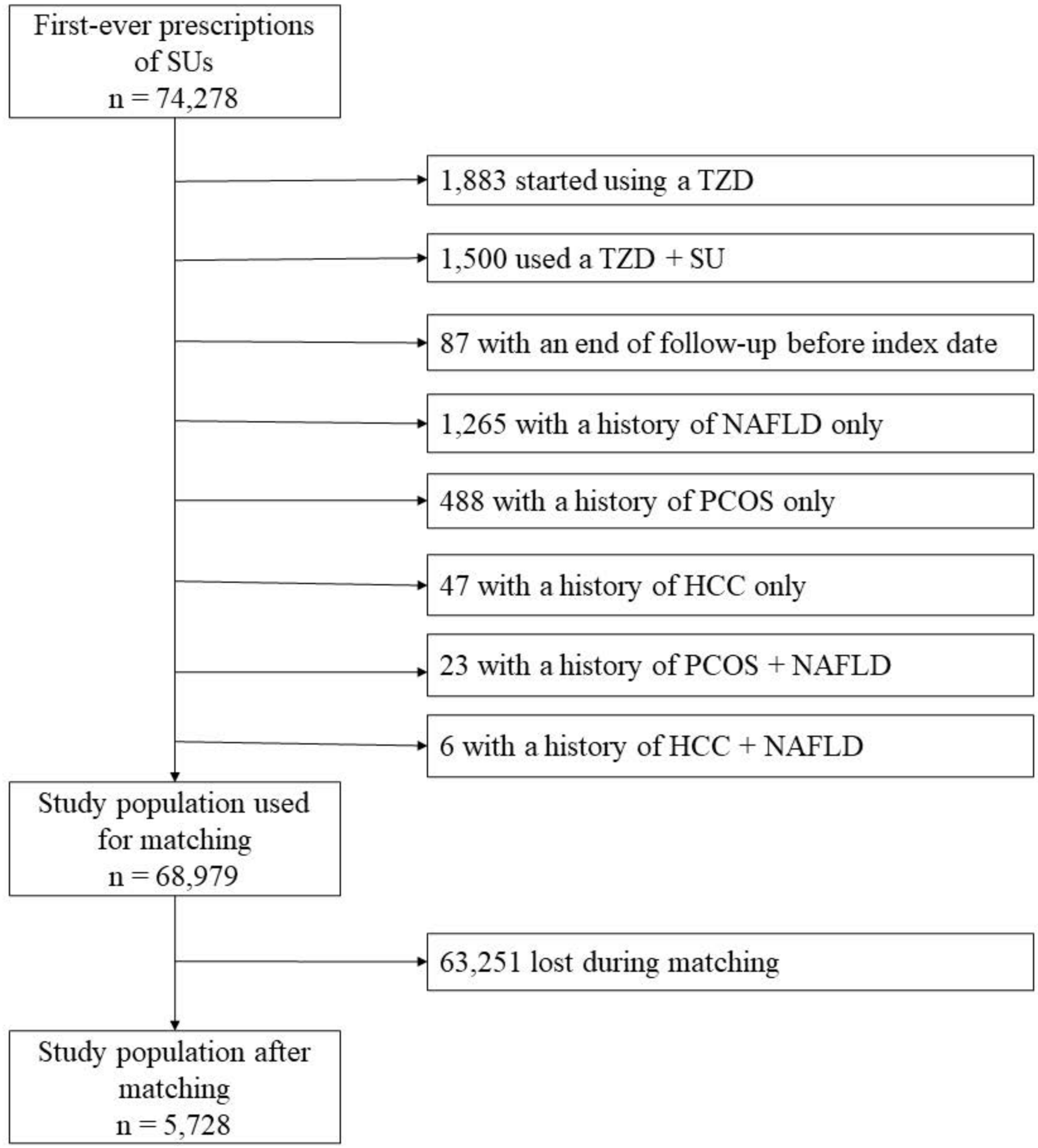
2) Austin PC**.** Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biom J 2009;51:171-184.

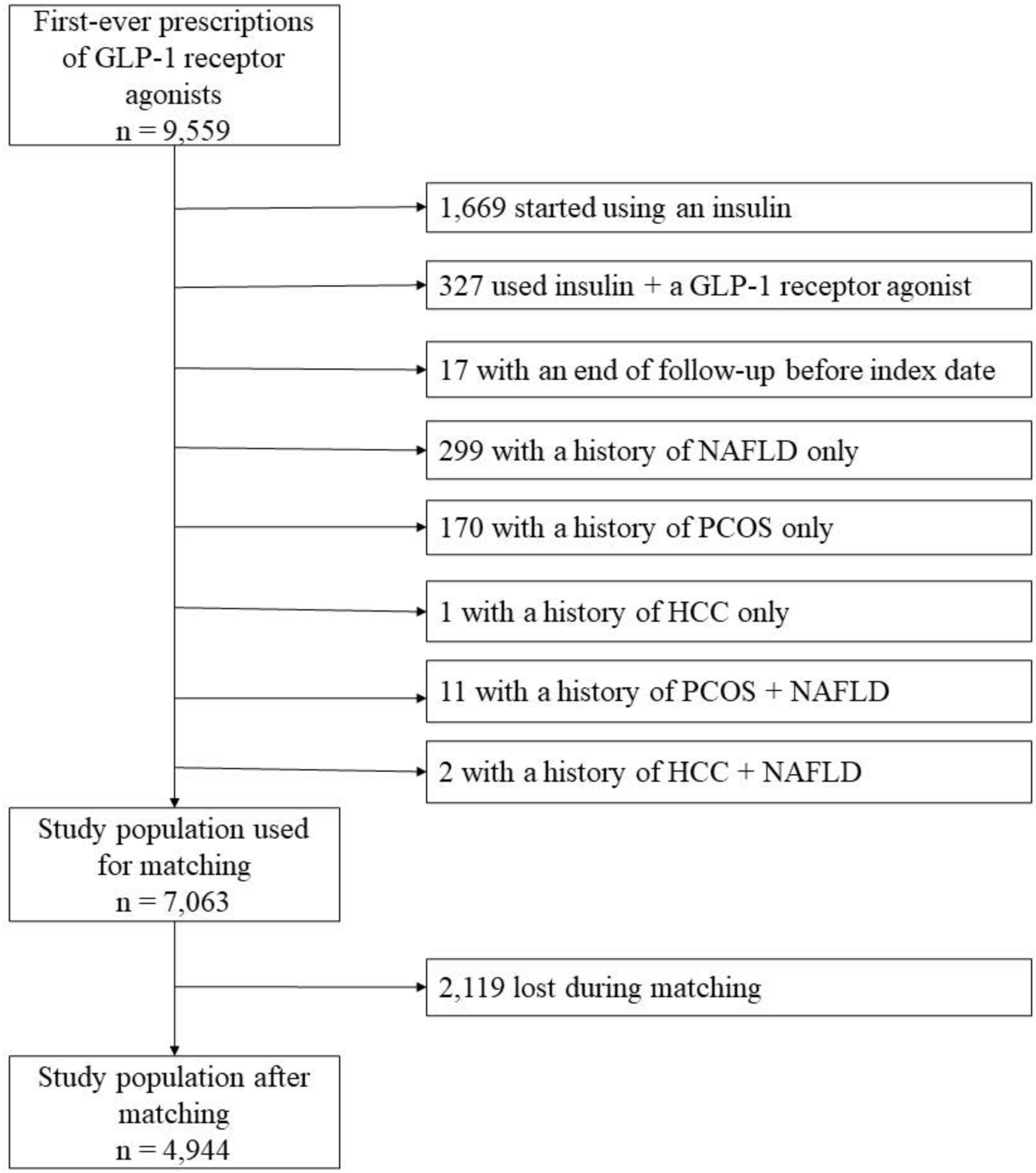
3) Rassen JA , Doherty M, Huang W, Schneeweiss S. Pharmacoepidemiology Toolbox. Boston MA. http://www.hdpharmacoepi.org. Accessed 6 May 2020

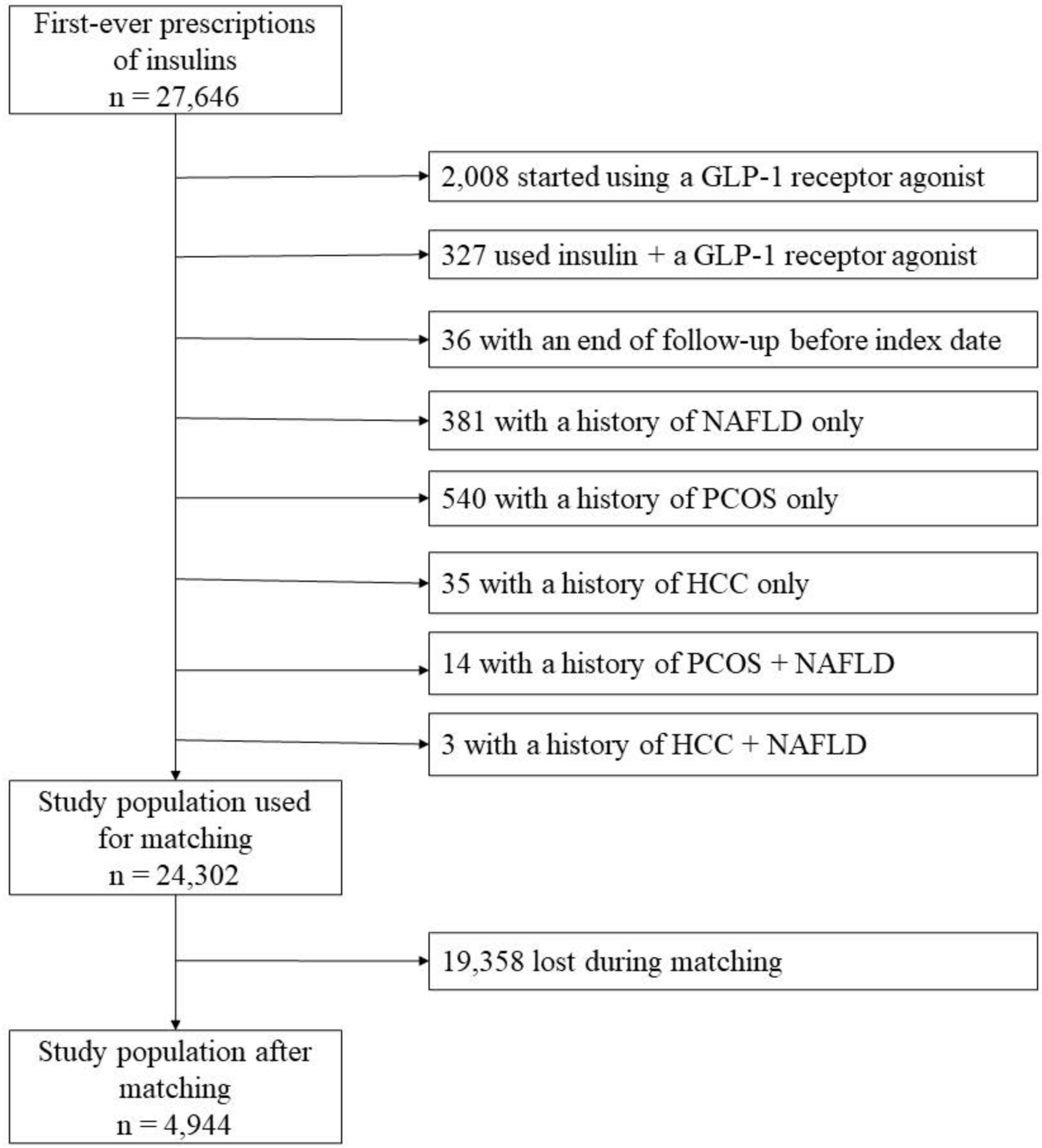

New users of oral glucose-lowering agents or GLP-1 receptor agonists
n = 219,322
8,662 with a history of PCOS only
3,112 with a history of NAFLD only
72 with a history of HCC only
105 with a history of PCOS and NAFLD
4 with a history of NAFLD and HCC
Study population
n = 207,367

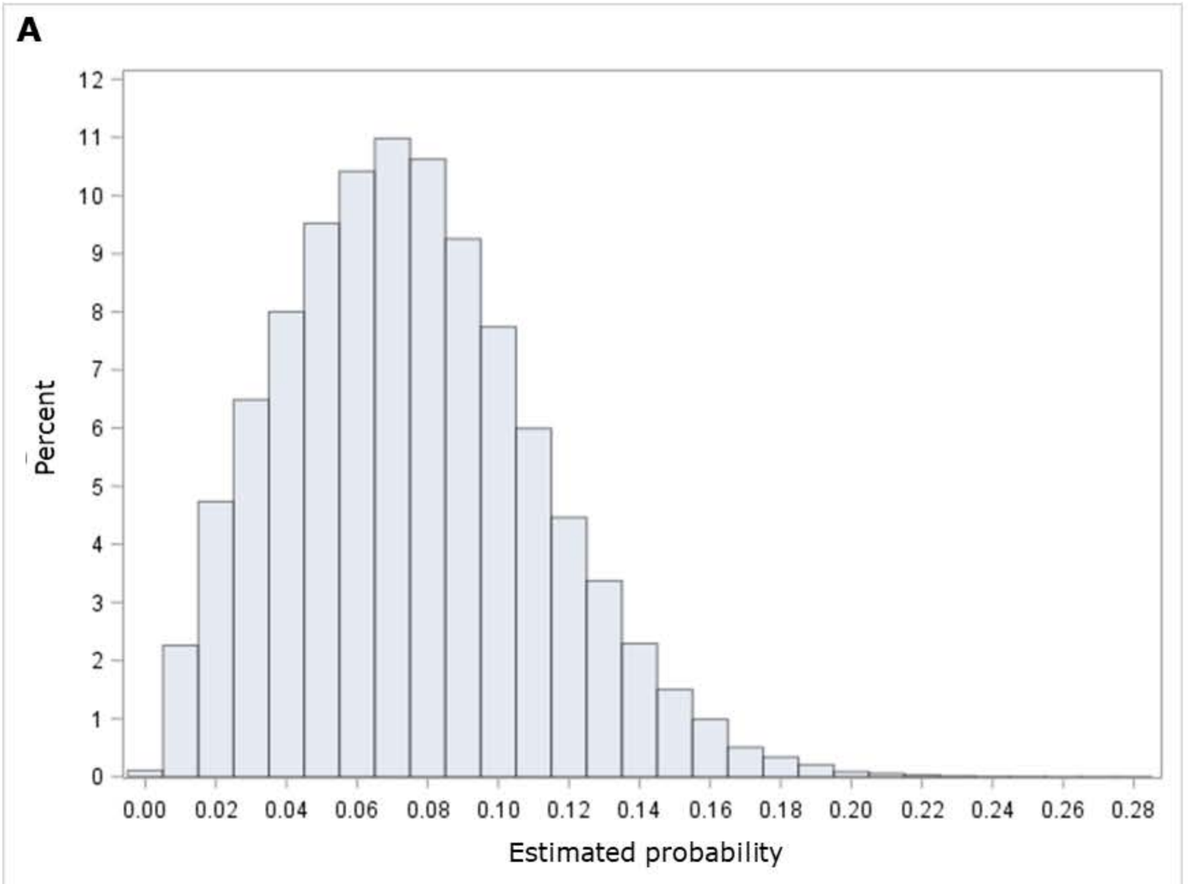

New users of oral glucose-lowering agents or GLP-1 receptor agonists
n = 219,322
8,767 with a history of PCOS only
70 with a history of HCC only
26 with a diagnosis of HCC in the first 6 months after start of follow-up
6 with a history of HCC and diagnosis of HCC in the first 6 months after start of follow-up
Study population
n = 210,453


First-ever prescriptions of TZDs n = 11,063
3,674 started using a SU
1,500 used a TZD + SU
4 with an end of follow-up before index date
100 with a history of NAFLD only
53 with a history of PCOS only
4 with a history of PCOS + NAFLD
Study population n = 5,728


First-ever prescriptions of SUs n = 74,278
1,883 started using a TZD
1,500 used a TZD + SU
87 with an end of follow-up before index date
1,265 with a history of NAFLD only
488 with a history of PCOS only
47 with a history of HCC only
23 with a history of PCOS + NAFLD
6 with a history of HCC + NAFLD
Study population used for matching n = 68,979
63,251 lost during matching
Study population after matching n = 5,728


First-ever prescriptions of GLP-1 receptor agonists n = 9,559
1,669 started using an insulin
327 used insulin + a GLP-1 receptor agonist
17 with an end of follow-up before index date
299 with a history of NAFLD only
170 with a history of PCOS only
1 with a history of HCC only
11 with a history of PCOS + NAFLD
2 with a history of HCC + NAFLD
Study population used for matching n = 7,063
2,119 lost during matching
Study population after matching n = 4,944


First-ever prescriptions of insulins n = 27,646
2,008 started using a GLP-1 receptor agonist
327 used insulin + a GLP-1 receptor agonist
36 with an end of follow-up before index date
381 with a history of NAFLD only
540 with a history of PCOS only
35 with a history of HCC only
14 with a history of PCOS + NAFLD
3 with a history of HCC + NAFLD
Study population used for matching n = 24,302
19,358 lost during matching
Study population after matching n = 4,944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Percent
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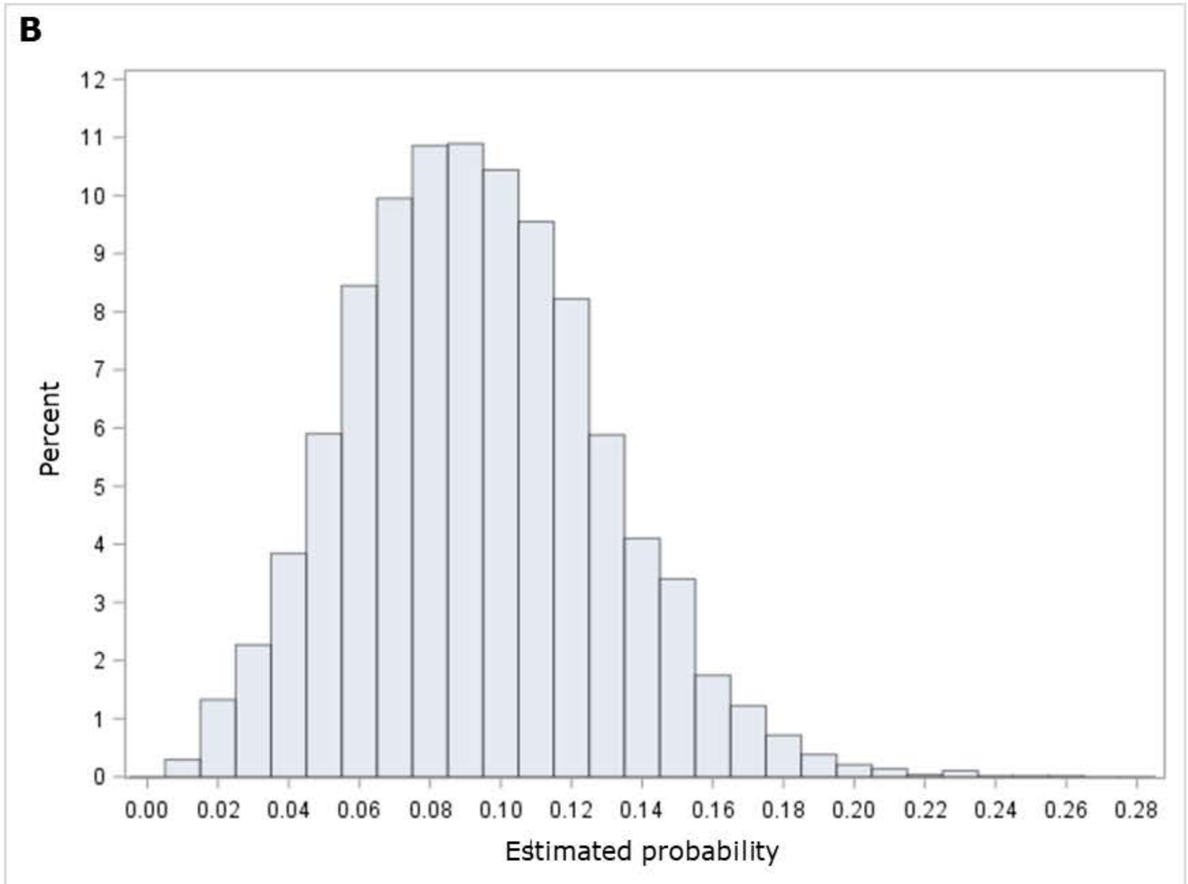
Estimated probability


B
Percent
0 1 2 3 4 5 6 7 8 9 10 11 12
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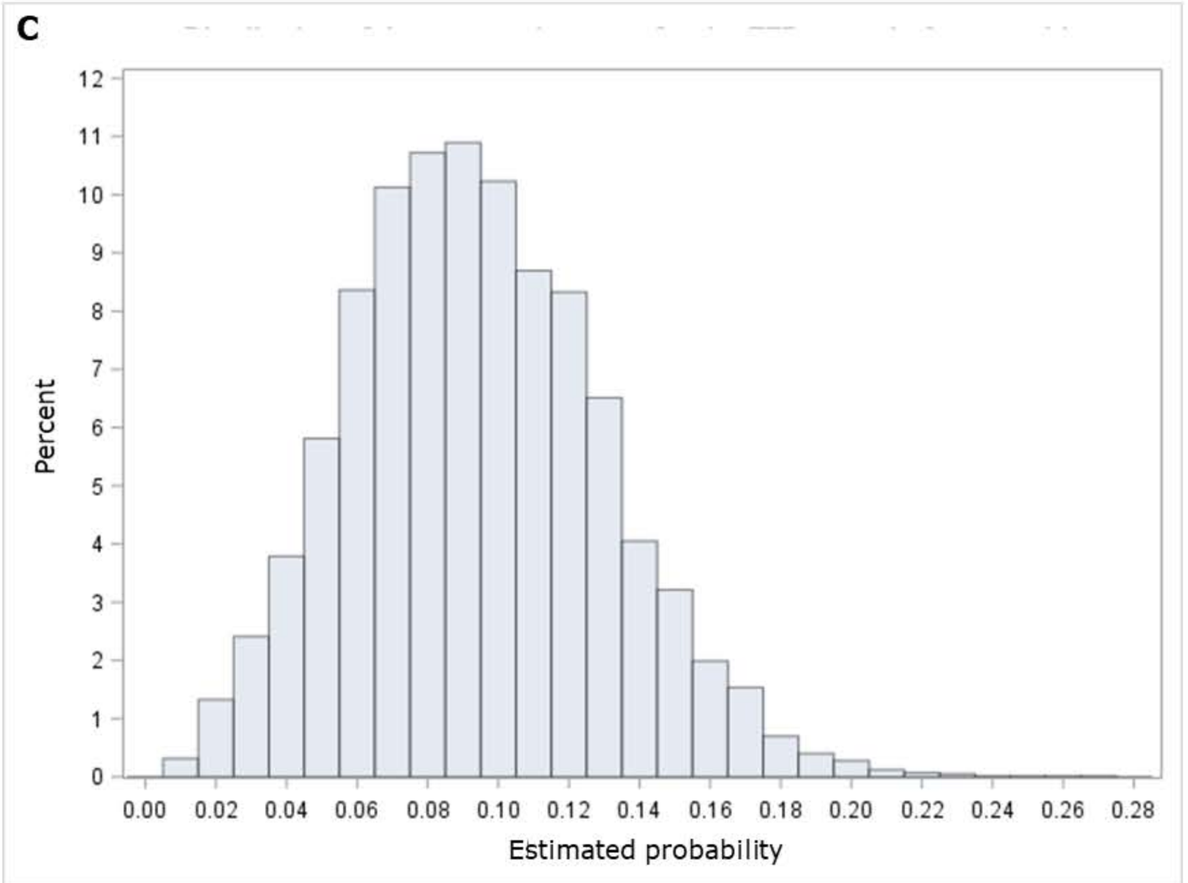
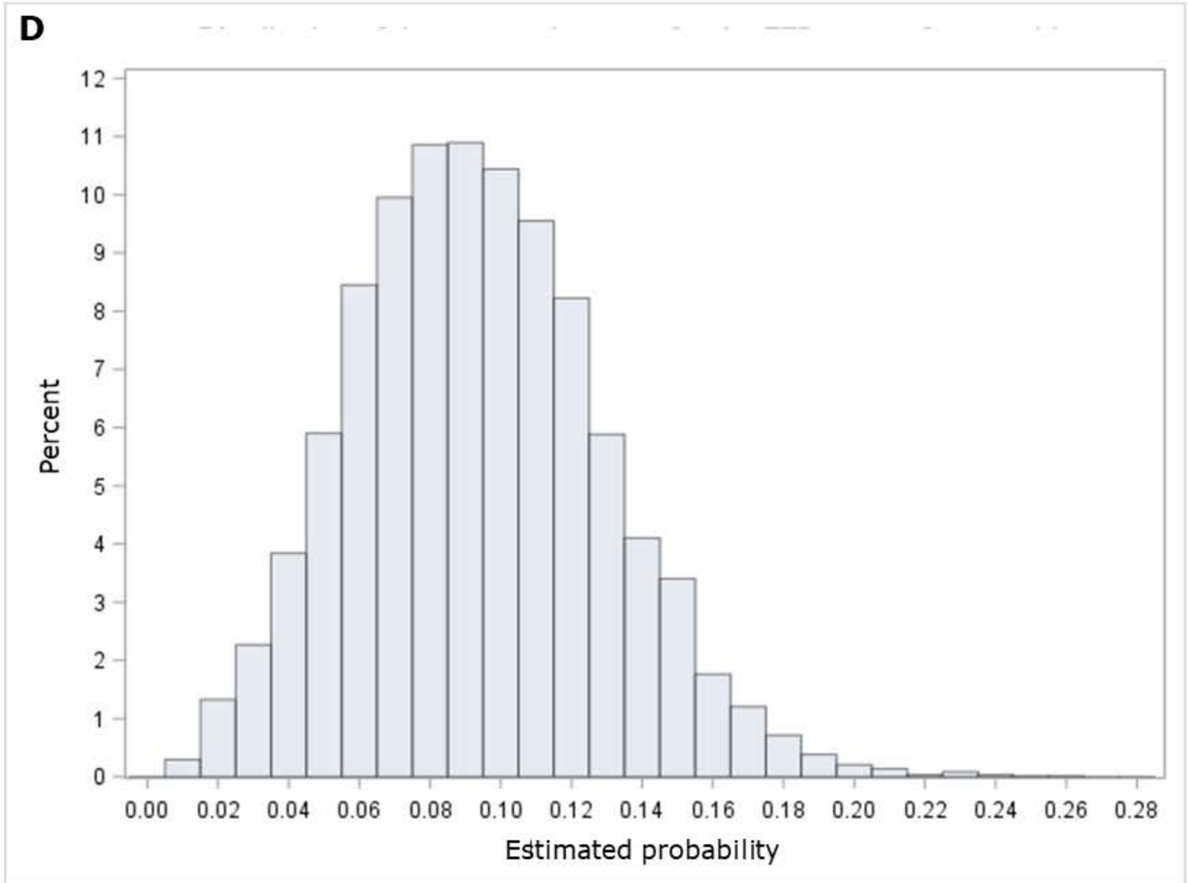
Estimated probability


C
Percent
0 1 2 3 4 5 6 7 8 9 10 11 12
0.00 0.02 0.04 0.06 0.08 0.10 0.12 0.14 0.16 0.18 0.20 0.22 0.24 0.26 0.28
Estimated probability


D
Percent
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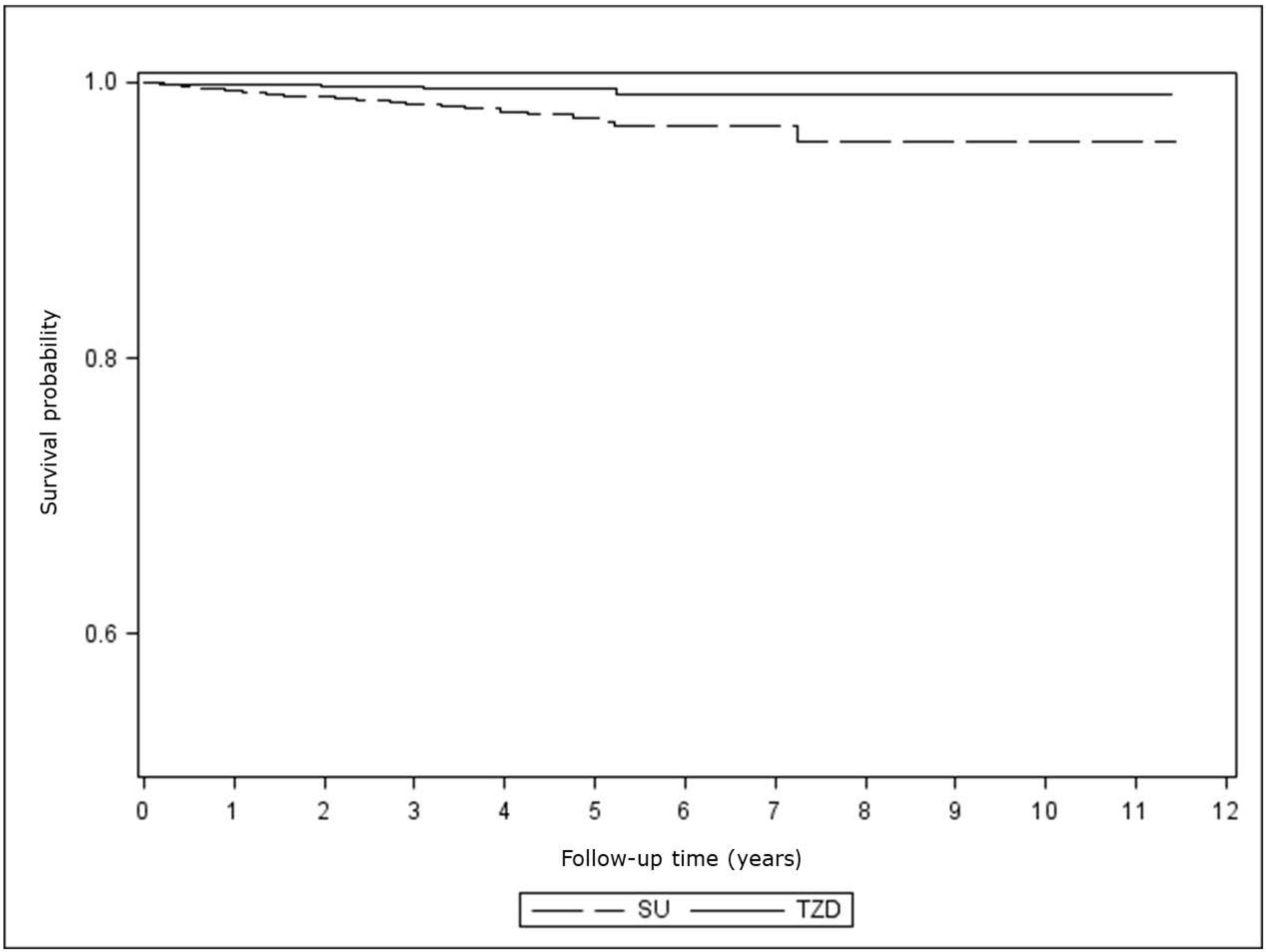
Estimated probability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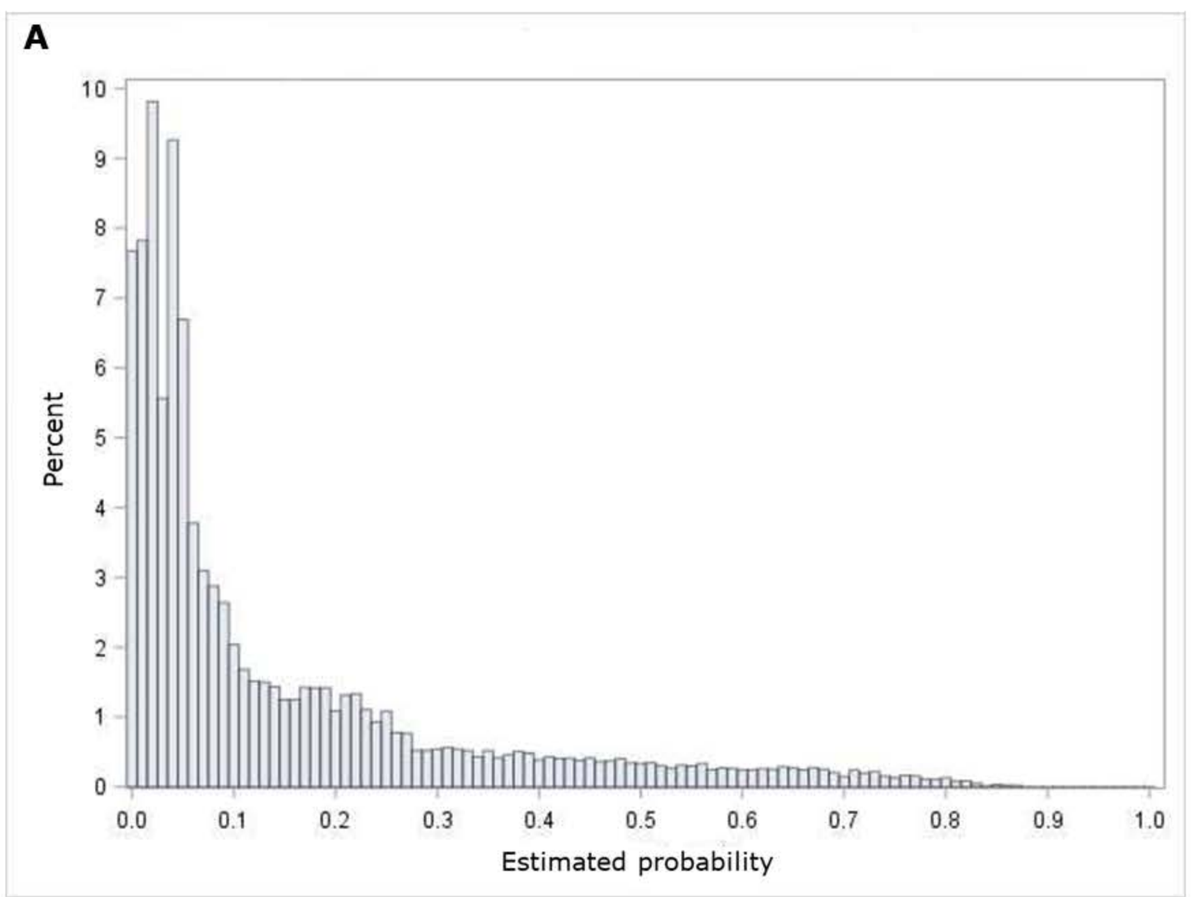
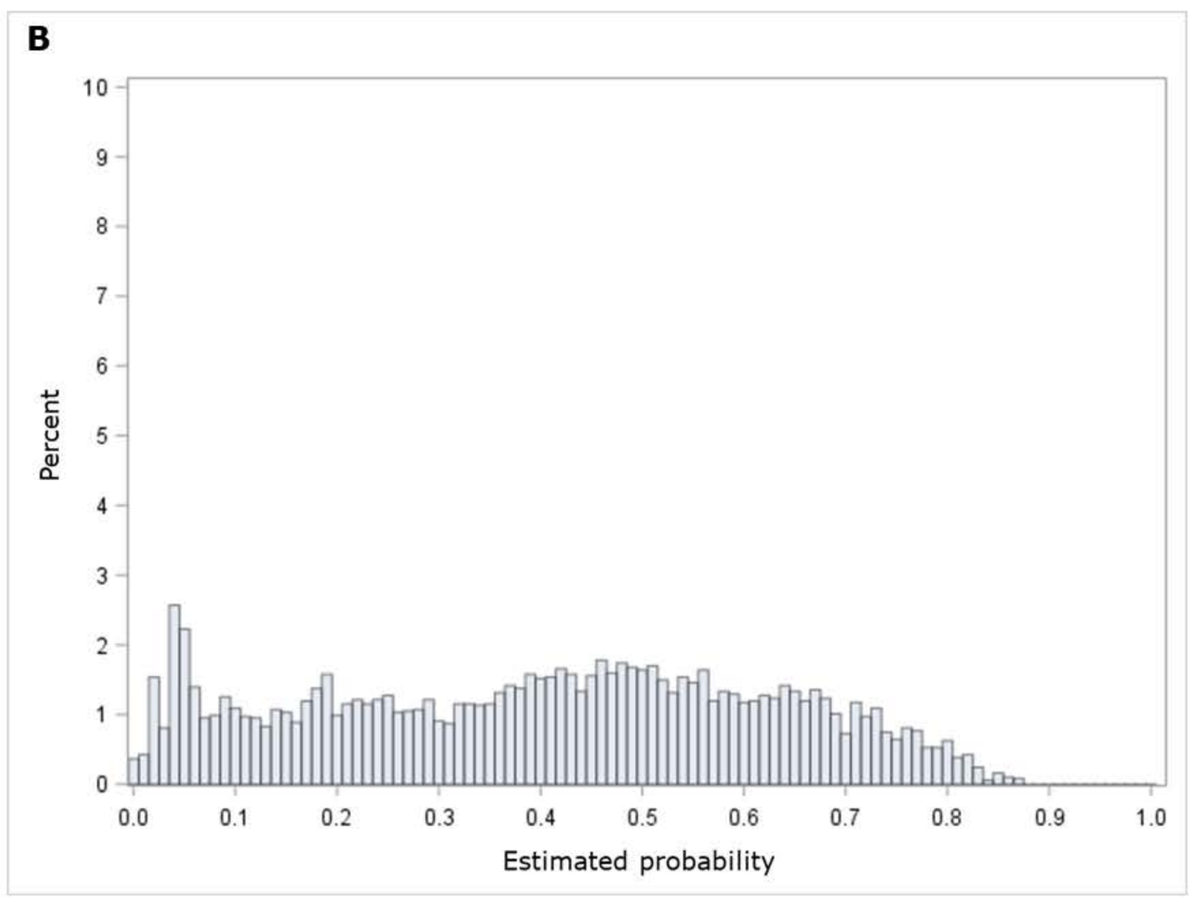
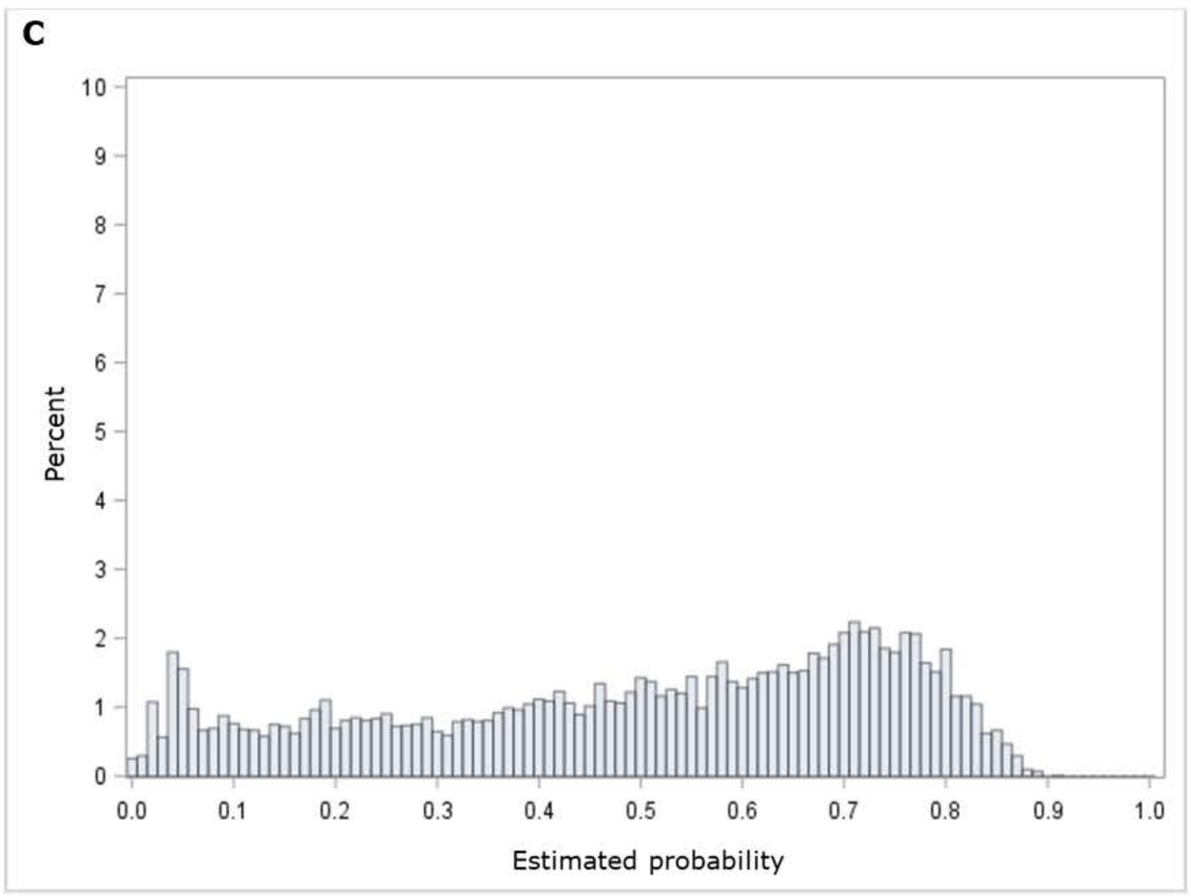
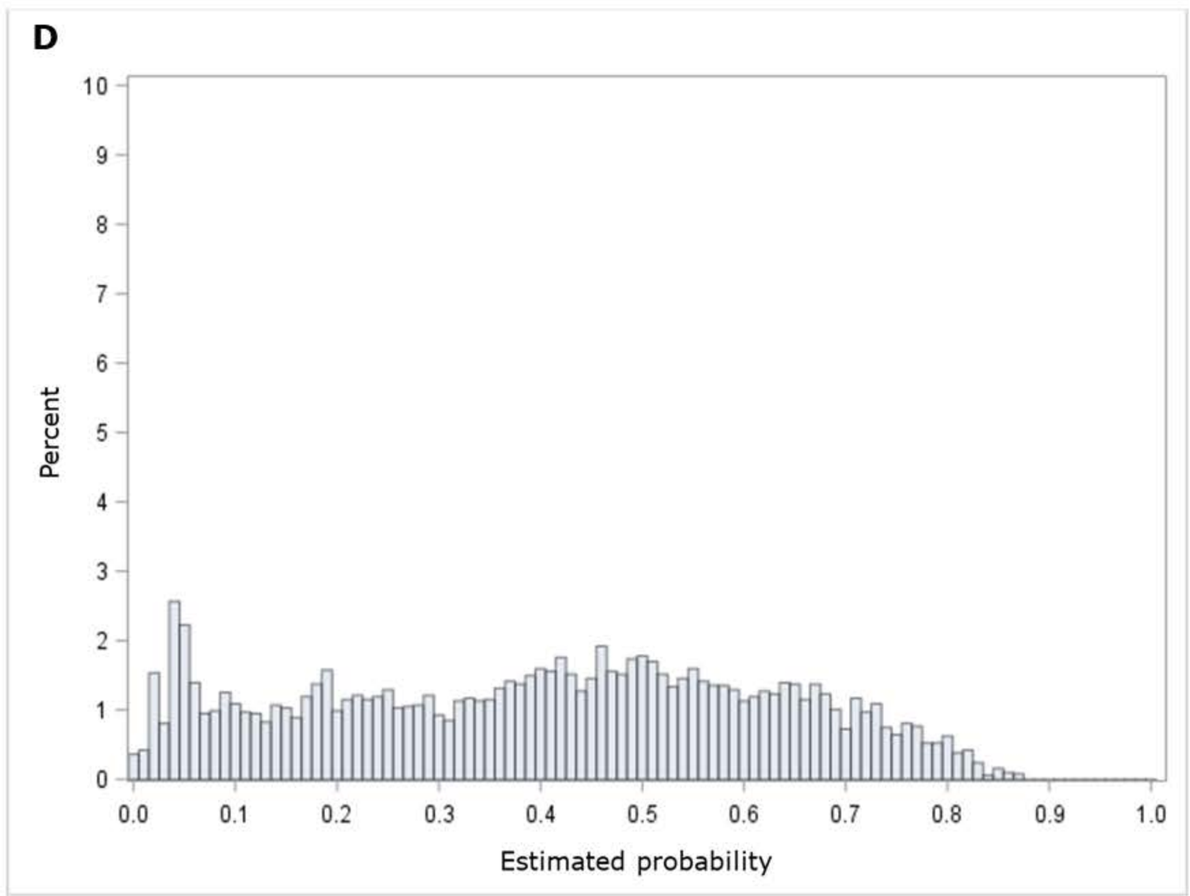
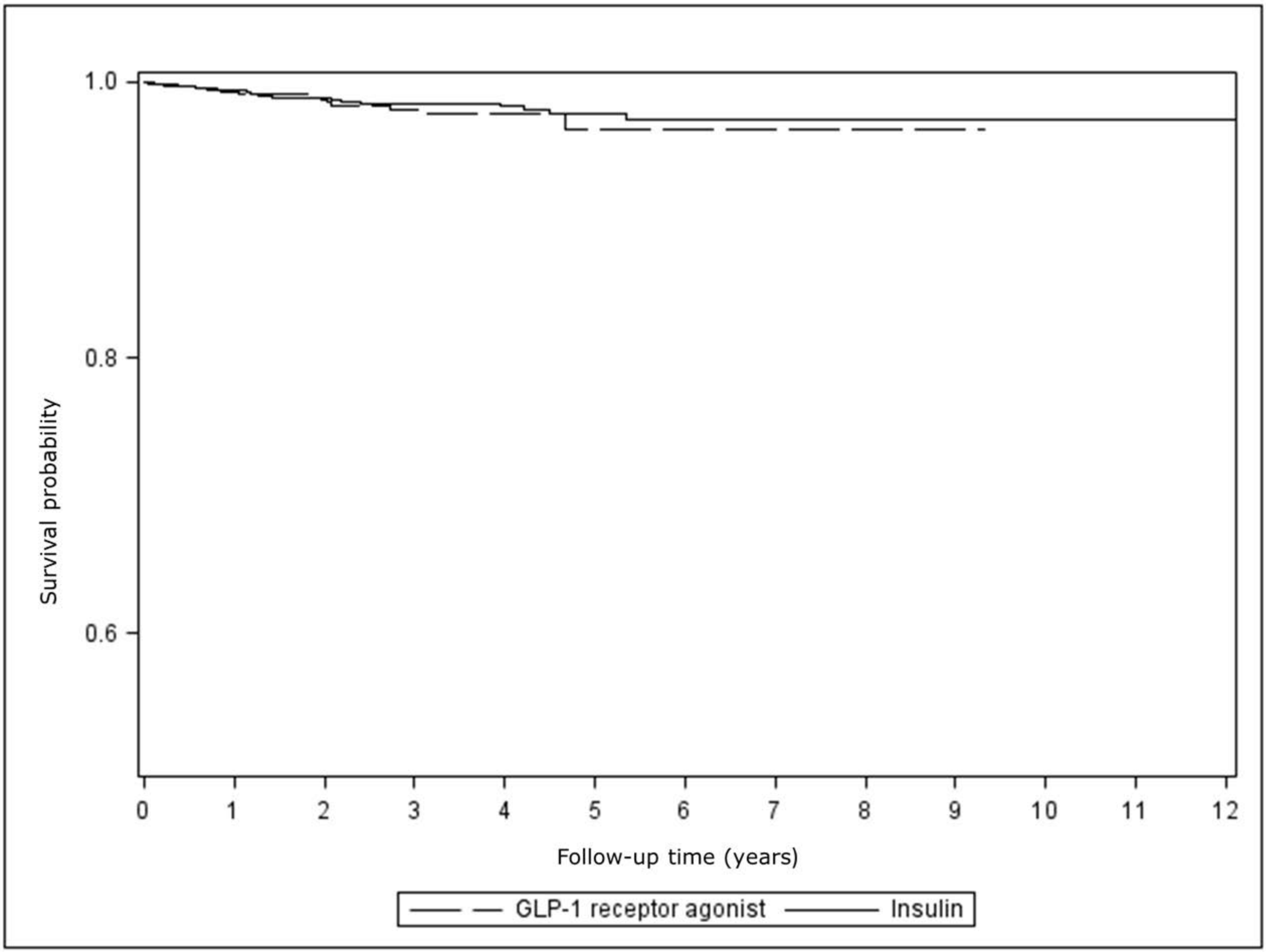
0.8
0.6
Survival probability
0
1
2
3
4
5
6
7
8
9
10
11
12
Follow-up time (years)
SU
TZD


A
Percent
Estimated probability


B
Percent
Estimated probability


C
Percent
Estimated probability


D
Percent
Estimated probability


1.0
0.8
0.6
Survival probability
0
1
2
3
4
5
6
7
8
9
10
11
12
Follow-up time (years)
GLP-1 receptor agonist
Insulin