

Supplementary Material

Table S1 Diseases and related ICD-9-CM, ICD-10-CM codes

Disease	ICD-9-CM Codes	ICD-10-CM Codes
Type 2 diabetes	250.xx, except 250.x1 and 250.x3	E08-E13, except E10
Type 1 diabetes	250.x1 and 250.x3	E10
Cellulitis	680-686	L00-L08
Cellulitis and abscess of oral soft tissues	528.3	K12.2
Gangrene	040.0x, 785.4x, or 440.24, 250.7x, 440.2x, 440.21, 440.22, or 440.23	A48, I96, I70.2, I70.9, I75, I09.5, I10.5, I11.5, I13.5
Osteomyelitis	707.1x, 707.14, 707.15, 730.07, 730.17, 730.27, or 730.97	L97, M86
Necrotizing fasciitis	728.86	M72.6
Pyomyositis	728.0	M60
Amputation	V49.7x, V52.1x, or 84.1x	Z89, Z44
Malignant neoplasm of urinary tract	179-189	C64-C68
Malignant neoplasm of lymphatic and hematopoietic tissue	200-208	C81-C96
Dialysis	V56.0, V56.8, V45.1	Z49.31, Z49.32, Z99.2
Hepatic failure	570, 572.2, 572.4, 572.8	K72.00, K72.01, K72.10, K72.11, K72.90, K76.2, K72.90, K72.91, K76.7, K76.81

Overweight	278.02, 783.1, V85.2	R63.5
Obesity	278.00, 649.1, V77.8, V85.3	E66.09, E66.1, E66.8, E66.9, Z13.89
Severe obesity	278.01, 649.2, V45.86, V85.4	E66.01, E66.2
Smoking status	305.1, V15.82	F17, Z87.891
Alcohol-related disorders	291, 303, 305.0, 571.0-571.3, V11.3, V79.1	F10, K70, R78.0, Z65.8
Hypertension	401–405	I10, I15
Dyslipidemia	272	E71.30, E71.31, E71.32, E71.39, E75.21, E75.22, E75.23, E75.24, E75.25, E75.29, E75.3, E75.4, E75.5, E75.6, E77, E78.0, E78.1, E78.2, E78.3, E78.4, E78.5, E78.6, E78.70, E78.71, E78.72, E78.79, E78.8, E78.9
Coronary artery disease	410-414, 429	I20-I25
Chronic kidney disease	585, 586, 593.9, 791.0	N18, N19, R80.9
Stroke	430-438	I60-I69
Atrial fibrillation	427	I45.0, I45.1, I45.2, I45.3, I45.4, I45.5, I45.6
Heart failure	428	I50
Peripheral arterial disease	440.0, 440.2-440.24, 440.3, 440.4, 443.81, 443.89, 443.9	I70.2, I70.92, I73.9, I75.0
Retinopathy	362.02, 362.07, 362.0	H35.0, E08.311-E08.359, E09.311-E09.359, E11.311-E11.359, E13.311-E13.359

Chronic obstructive pulmonary disease	491, 492, 496	J41- J44
Rheumatoid arthritis	714.0	M06.9
Systemic lupus erythematosus	710.0	M32.10
Liver cirrhosis	571.5, 571.2, 571.6	K70.2, K70.30, K70.31, K74.0, K74.5 K74.60, K74.69
Cancers	140-209	C00-C96
Psychosis	295, 297, 298	F20-29
Depression	296.2, 296.3, 296.82, 296.99, 298.0,311	F32, F33
Dementia	290, 294.1, 331.0, 331.1, 331.2, 331.7, 331.8, 331.9	F01.50, F01.51, F02.80, F02.81, F03.90, F03.91, F05, G30, G31

Table S2 Incidence rate and hazard ratio of cellulitis in patients with type 2 diabetes

Variable	Cellulitis								
	Event	PY	IR2	cHR	(95% CI)	<i>p</i>	aHR ¹	(95% CI)	<i>p</i>
Metformin									
No	5070	112654	45.00	1.00	(reference)	-	1.00	(reference)	-
Yes	6310	126227	49.99	1.11	(1.07, 1.15)	<0.001	1.08	(1.04, 1.12)	<0.001
Sex									
Female	6009	128771	46.66	1.00	(reference)	-	1.00	(reference)	-
Male	5371	110111	48.78	1.05	(1.01, 1.08)	0.0178	1.04	(1, 1.08)	0.047
Age (years)									
20-39	922	19329	47.70	1.00	(reference)	-	1.00	(reference)	-
40-59	4650	105824	43.94	0.92	(0.86, 0.99)	0.0237	0.83	(0.76, 0.91)	<0.001
60 +	5808	113729	51.07	1.07	(1, 1.15)	0.0506	0.83	(0.72, 0.95)	0.0068
Comorbidities									
Obesity									
No	11272	236576	47.65	1.00	(reference)	-	1.00	(reference)	-
Yes	108	2306	46.83	0.98	(0.81, 1.19)	0.868	1	(0.83, 1.21)	0.9879
Smoking status									
						-			

No	11230	236026	47.58	1.00	(reference)	-	1.00	(reference)	-
Yes	150	2856	52.52	1.1	(0.94, 1.3)	0.226	1.07	(0.91, 1.26)	0.4119
Alcohol related disorders						-			
No	11015	233720	47.13	1.00	(reference)	-	1.00	(reference)	-
Yes	365	5162	70.71	1.5	(1.35, 1.67)	<0.001	1.34	(1.2, 1.49)	<0.001
Hypertension									
No	4622	103821	44.52	1.00	(reference)	-	1.00	(reference)	-
Yes	6758	135061	50.04	1.12	(1.08, 1.17)	<0.001	1.01	(0.97, 1.05)	0.7346
Dyslipidemia						-			
No	4911	99798	49.21	1.00	(reference)	-	1.00	(reference)	-
Yes	6469	139084	46.51	0.95	(0.91, 0.98)	0.0029	0.94	(0.9, 0.98)	0.0042
Coronary artery disease						-			
No	7662	171757	44.61	1.00	(reference)	-	1.00	(reference)	-
Yes	3718	67125	55.39	1.24	(1.19, 1.29)	<0.001	1.08	(1.03, 1.13)	0.0026
Stroke									
No	9420	205098	45.93	1.00	(reference)	-	1.00	(reference)	-
Yes	1960	33784	58.02	1.26	(1.2, 1.33)	<0.001	1.05	(0.99, 1.11)	0.0871
Atrial fibrillation						-			
No	11126	234400	47.47	1.00	(reference)	-	1.00	(reference)	-

Yes	254	4481	56.68	1.2	(1.06, 1.35)	0.005	0.93	(0.82, 1.06)	0.303
Heart failure						-			
No	10621	227478	46.69	1.00	(reference)	-	1.00	(reference)	-
Yes	759	11403	66.56	1.43	(1.32, 1.54)	<0.001	1.12	(1.04, 1.22)	0.0051
Peripheral arterial disease									
No	11079	233352	47.48	1.00	(reference)	-	1.00	(reference)	-
Yes	301	5529	54.44	1.15	(1.02, 1.29)	0.019	1.01	(0.9, 1.13)	0.8798
Chronic kidney disease						-			
No	10555	225840	46.74	1.00	(reference)	-	1.00	(reference)	-
Yes	825	13042	63.26	1.36	(1.26, 1.46)	<0.001	1.19	(1.11, 1.29)	<0.001
Retinopathy and other retinal disorders						-			
No	10579	224662	47.09	1.00	(reference)	-	1.00	(reference)	-
Yes	801	14220	56.33	1.2	(1.11, 1.29)	<0.001	1.1	(1.02, 1.18)	0.0124
Chronic obstructive pulmonary disease									
No	9037	200599	45.05	1.00	(reference)	-	1.00	(reference)	-
Yes	2343	38283	61.20	1.36	(1.3, 1.42)	<0.001	1.2	(1.14, 1.26)	<0.001
Rheumatoid arthritis						-			
No	11127	234596	47.43	1.00	(reference)	-	1.00	(reference)	-
Yes	253	4286	59.03	1.25	(1.1, 1.41)	<0.001	1.16	(1.02, 1.31)	0.0231

Systemic lupus erythematosus						-			
No	11358	238367	47.65	1.00	(reference)	-	1.00	(reference)	-
Yes	22	515	42.76	0.9	(0.59, 1.37)	0.6274	0.77	(0.5, 1.17)	0.2134
Liver cirrhosis									
No	11049	234116	47.19	1.00	(reference)	-	1.00	(reference)	-
Yes	331	4766	69.45	1.47	(1.32, 1.64)	<0.001	1.22	(1.09, 1.37)	<0.001
Cancers						-			
No	10968	231273	47.42	1.00	(reference)	-	1.00	(reference)	-
Yes	412	7609	54.15	1.14	(1.04, 1.26)	0.008	1.01	(0.91, 1.12)	0.882
Psychosis						-			
No	11147	234948	47.44	1.00	(reference)	-	1.00	(reference)	-
Yes	233	3934	59.23	1.25	(1.1, 1.42)	<0.001	1.19	(1.04, 1.36)	0.0092
Depression									
No	10775	227310	47.40	1.00	(reference)	-	1.00	(reference)	-
Yes	605	11572	52.28	1.1	(1.02, 1.2)	0.0185	0.96	(0.88, 1.04)	0.3181
Dementia						-			
No	11081	234692	47.22	1.00	(reference)	-	1.00	(reference)	-
Yes	299	4190	71.36	1.51	(1.35, 1.7)	<0.001	1.24	(1.1, 1.4)	<0.001
Charlson Comorbidity Index									

0	8103	181827	44.56	1.00	(reference)	-	1.00	(reference)	-
1	1391	26687	52.12	1.17	(1.11, 1.24)	<0.001	1.05	(0.99, 1.11)	0.0976
2+	1886	30367	62.11	1.4	(1.33, 1.47)	<0.001	1.12	(1.06, 1.19)	<0.001
Diabetes Complications Severity Index						-			
0	3746	91146	41.10	1.00	(reference)	-	1.00	(reference)	-
1	2202	49191	44.76	1.09	(1.03, 1.15)	0.0013	1.05	(0.99, 1.1)	0.105
2+	5432	98544	55.12	1.34	(1.29, 1.4)	<0.001	1.14	(1.08, 1.2)	<0.001
Medications									
Numbers of oral antidiabetic drugs									
< 2	11157	234421	47.59	1.00	(reference)	-	1.00	(reference)	-
≥2	223	4462	49.98	1.06	(0.93, 1.21)	0.3837	0.97	(0.85, 1.11)	0.6918
Insulins									
No	8593	190261	45.16	1.00	(reference)	-	1.00	(reference)	-
Yes	2787	48620	57.32	1.27	(1.22, 1.32)	<0.001	1.12	(1.07, 1.17)	<0.001
Corticosteroids						-			
No	5717	132140	43.26	1.00	(reference)	-	1.00	(reference)	-
Yes	5663	106742	53.05	1.23	(1.18, 1.27)	<0.001	1.12	(1.08, 1.17)	<0.001
Statins						-			
No	8455	175574	48.16	1.00	(reference)	-	1.00	(reference)	-

Yes	2925	63308	46.20	0.96	(0.92, 1)	0.0584	0.91	(0.86, 0.95)	<0.001
Non-steroidal anti-inflammatory drugs						-			
No	1595	38774	41.14	1.00	(reference)	-	1.00	(reference)	-
Yes	9785	200107	48.90	1.19	(1.13, 1.25)	<0.001	1.1	(1.04, 1.16)	0.0013
Aspirin						-			
No	7948	175066	45.40	1.00	(reference)	-	1.00	(reference)	-
Yes	3432	63816	53.78	1.19	(1.14, 1.23)	<0.001	1	(0.95, 1.05)	0.9415

¹: Adjusted HR estimated by the model including the variables of metformin, gender, age, comorbidities, and medications.

²: Per 1,000 person-year.

CI=confidence interval; HR=hazard ratio; IR=incidence rate; T2D=type 2 diabetes mellitus.

Table S3 Incidence and risk of outcomes between metformin use versus no-use in patients with T2D

Variable	Crude		Adjusted ¹	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Inverse probability of treatment weighting (IPTW)				
Cellulitis	1.19 (1.17, 1.22)	<0.0001	1.03 (1.00, 1.05)	0.0353
Recurrence of cellulitis	1.68 (1.53, 1.84)	<0.0001	1.21 (1.09, 1.34)	0.0003
Foot infections	2.26 (2.14, 2.38)	<0.0001	1.79 (1.69, 1.90)	<0.0001

Amputation	1.7 (1.41, 2.04)	<0.0001	1.56 (1.27, 1.92)	<0.0001
Time-varying exposure of metformin				
Cellulitis	1.13 (1.03, 1.23)	0.0063	1.12 (1.03, 1.22)	0.0108
Recurrence of cellulitis	0.80 (0.38, 1.71)	0.5661	0.82 (0.38, 0.75)	0.6076
Foot infections	2.27 (1.81, 2.84)	<0.0001	2.25 (1.78, 2.83)	<0.0001
Amputation	1.18 (0.53, 2.64)	0.6841	1.28 (0.57, 2.86)	0.5482

¹: Adjusted HR estimated by the Cox proportional hazards model, including the variates of metformin, gender, age, comorbidities, medications, enrolment years 2000-2005, 2006-2011, 2012-2017, and duration of T2D.

IR=Incidence Rate (per 1,000 person-years); HR=Hazard Ratio; CI=Confidence Interval; T2D=Type 2 Diabetes.

Table S4 Various models of the risk of outcomes between metformin use and no use in patients with T2D

Variable	Non-metformin Users		Metformin Users		Crude		Adjusted ^I	Adjusted ^{II}	Adjusted ^{III}
	Event	Person-years	IR	Event	Person-years	IR	HR (95% CI)	HR (95% CI)	HR (95% CI)
Cellulitis	5,070	112,654	45.00	6,310	126,227	49.99	1.11 (1.07, 1.15)	1.1 (1.06, 1.14)	1.1 (1.06, 1.14)
Recurrent cellulitis	261	134,431	1.94	458	155,210	2.95	1.46 (1.25, 1.7)	1.4 (1.2, 1.63)	1.39 (1.19, 1.61)
Foot infections	2319	130,535	17.77	3,351	146,608	22.86	1.28 (1.21, 1.35)	1.26 (1.19, 1.33)	1.25 (1.19, 1.32)
Amputation	51	135,067	0.38	124	156,232	0.79	2.07 (1.50, 2.87)	2.01 (1.45, 2.78)	2 (1.45, 2.78)

^I: adjust age and sex;

^{II}: adjust age, sex, obesity, smoking, alcohol disorders

^{III}: adjust age, sex obesity, smoking, alcohol disorders, peripheral arterial disease, chronic kidney disease, retinopathy and other retinal disorders, COPD, liver cirrhosis, rheumatoid arthritis, systemic lupus erythematosus, corticosteroids, duration of T2D.

IR=Incidence Rate (per 1,000 person-years); HR=Hazard Ratio; CI=Confidence Interval; T2D=Type 2 Diabetes.

Table S5 Competing risk analysis using mortality as the competing risk between metformin users and nonusers

Variable	Non-metformin Users			Metformin Users			Crude		Adjusted ¹	
	Event	Person-years	IR	Event	Person-years	IR	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Cellulitis	5,070	112,654	45.00	6,310	126,227	49.99	1.21 (1.17, 1.25)	<0.0001	1.21 (1.17, 1.25)	<0.0001
Recurrent cellulitis	261	134,431	1.94	458	155,210	2.95	1.60 (1.37, 1.86)	<0.0001	1.59 (1.36, 1.85)	<0.0001
Foot infections	2319	130,535	17.77	3,351	146,608	22.86	1.39 (1.32, 1.47)	<0.0001	1.38 (1.31, 1.45)	<0.0001
Amputation	51	135,067	0.38	124	156,232	0.79	2.25 (1.63, 3.12)	<0.0001	2.27 (1.64, 3.14)	<0.0001

¹: adjust age, sex obesity, smoking, alcohol disorders, peripheral arterial disease, chronic kidney disease, retinopathy and other retinal disorders, COPD, liver cirrhosis, rheumatoid arthritis, systemic lupus erythematosus, corticosteroids, duration of T2D.

IR=Incidence Rate (per 1,000 person-years); HR=Hazard Ratio; CI=Confidence Interval; T2D=Type 2 Diabetes.