

Table S1. ICD-9 codes for cancer diagnoses

Diabetes-related cancers		ICD-9 code
Malignant neoplasm of female breast		174-175
Malignant neoplasm of colon and rectum		153, 154.0, 154.1, 154.8
Malignant neoplasm of esophagus		150
Malignant neoplasm of liver and intrahepatic bile ducts		155-156
Malignant neoplasm of pancreas		157
Malignant neoplasm of stomach		151
Malignant neoplasm of endometrium		179, 182
Renal		189.0, 189.1
Non-diabetes related cancers		ICD-9 code
Prostate		185
Lung		162
Bladder/Urinary tract (excluding kidney)		188, 189.2-189.9
Head/Neck		140-149, 160-161, 190, 195.0
Small intestine		152
Bone		170
Brain		191
Melanoma		172
Endocrine tumor		193, 194
Neuroendocrine tumor		209
Male genital, NOS		186.0, 186.9, 187
Female reproductive, NOS		180, 181, 183, 184
Hematologic		200, 202.20-202.28, 202.68-202.98, 203.0-203.12, 204, 205-208
Metastatic, unknown primary		196-199
Other		154.2, 154.3, 158, 159, 163, 164.2, 164.3, 164.8, 164.9, 165, 176, 192, 195.1-195.8, 199.1, 199.2, 202.30-202.67, 203.8-203.82

Table S2. Standardized difference of propensity score variables before and after inverse probability weighting (IPTW)

Descriptor	Unadjusted			IPTW-adjusted		
	Metformin	Sulfonylurea	Standardized difference	Metformin	Sulfonylurea	Standardized difference
Race						
Black	7,727 (12.8)	3,476 (12.3)	1.4	10,841 (12.3)	10,499 (11.9)	1.2
White	50,657 (83.8)	23,915 (84.7)	2.6	74,642 (84.4)	75,040 (84.9)	1.4
Other	2,092 (3.5)	846 (3.0)	2.6	2,953 (3.3)	2,846 (3.2)	0.7
Male sex	58,844 (97.3)	27,844 (98.6)	9.2	86,209 (97.5)	86,334 (97.7)	1.3
BMI category (kg/m ²)						
Underweight (< 20.0)	147 (0.2)	143 (0.5)	4.3	306 (0.3)	296 (0.3)	0.2
Normal weight (20.0-24.9)	3,589 (5.9)	2,817 (10.0)	15.0	6,500 (7.3)	6,496 (7.3)	0.0
Overweight (25.0-29.9)	18,448 (30.5)	10,692 (37.9)	15.6	29,176 (33.0)	29,232 (33.1)	0.2
Obese (≥ 30)	38,292 (63.3)	14,585 (51.7)	23.8	52,454 (59.3)	52,362 (59.2)	0.1
Glomerular filtration rate						
30.0-44.9	273 (0.5)	3,760 (13.3)	52.5	3,744 (4.2)	4,033 (4.6)	1.6
45.0-59.9	6,022 (10.0)	7,583 (26.9)	44.7	13,628 (15.4)	13,590 (15.4)	0.1
≥ 60	54,181 (89.6)	16,894 (59.8)	72.9	71,064 (80.4)	70,763 (80.1)	0.7
US geographic region						
Northeast	13,225 (21.9)	5,062 (17.9)	9.9	18,273 (20.7)	18,022 (20.4)	0.7
Southeast	7,570 (12.5)	5,265 (18.6)	17.0	12,863 (14.5)	12,884 (14.6)	0.1
Central	25,020 (41.4)	11,419 (40.4)	1.9	36,346 (41.1)	36,344 (41.1)	0.0
West	14,661 (24.2)	6,491 (23.0)	3.0	20,954 (23.7)	21,136 (23.9)	0.5
Major psych. disease	6,317 (10.4)	2,272 (8.0)	8.3	8,570 (9.7)	8,425 (9.5)	0.5
Arthritis	16,251 (26.9)	7,654 (27.1)	0.5	23,889 (27.0)	23,916 (27.1)	0.1
Coronary artery disease	21,007 (34.7)	13,347 (47.3)	25.7	34,216 (38.7)	34,608 (39.2)	1.0
Heart failure	3,432 (5.7)	3,341 (11.8)	21.9	6,641 (7.5)	6,844 (7.7)	0.9
Hypertension	51,547 (85.2)	24,776 (87.7)	7.3	76,055 (86.0)	76,048 (86.0)	0.1
Eye disease	10,899 (18.0)	5,965 (21.1)	7.8	16,970 (19.2)	17,095 (19.3)	0.4
Smoking	42,952 (71.0)	18,544 (65.7)	11.5	61,207 (69.2)	61,245 (69.3)	0.2
Alcohol abuse	6,240 (10.3)	2,092 (7.4)	10.3	8,342 (9.4)	8,223 (9.3)	0.4
Statins	36,284 (60.0)	15,430 (54.6)	10.8	51,504 (58.2)	51,310 (58.1)	0.4
CVD	7,564 (12.5)	5,497 (19.5)	19.1	13,054 (14.8)	13,219 (15.0)	0.5
COPD	11,624 (19.2)	6,750 (23.9)	11.4	18,266 (20.7)	18,658 (21.1)	1.1
Cirrhosis	1,616 (2.7)	719 (2.5)	0.8	2,345 (2.7)	2,462 (2.8)	0.8
Number of visits, mean (SD)	9 (12.4)	9 (11.3)	4.3	9 (14.9)	9 (20.3)	0.3
Number of RX, mean (SD)	7 (3.8)	7 (3.8)	8.6	7 (4.6)	7 (6.7)	0.3
Year of first RX, mean (SD)	2007 (3.2)	2005 (3.1)	78.3	2007 (4.0)	2006 (5.9)	2.3

All numbers in the table represent N (%) unless otherwise noted.

Table S3. Frequency of individual cancer subtypes for diabetes-related and non-diabetes-related cancers, by treatment group

	Metformin users	Sulfonylurea users	Total
Diabetes-related cancer	N = 858 cancer cases	N = 675 cancer cases	N = 1,533 cancer cases
Colorectal	303 (35.3)	258 (38.2)	561 (36.6)
Renal	184 (21.5)	105 (15.6)	289 (18.9)
Liver	114 (13.3)	114 (16.9)	228 (14.9)
Esophageal	86 (10.0)	67 (9.9)	153 (10.0)
Pancreas	74 (8.6)	61 (9.0)	135 (8.8)
Stomach	50 (5.8)	38 (5.6)	88 (5.7)
Breast	32 (3.7)	13 (1.9)	45 (2.9)
Endometrial	4 (0.5)	2 (0.3)	6 (0.4)
≥ 2 cancer types at time of initial diagnosis*	11 (1.3)	17 (2.5)	28 (1.8)
Non-diabetes-related cancer	N = 3,533 cancer cases	N = 2,316 cancer cases	N = 5,849 cancer cases
Prostate	1,377 (39.0)	744 (32.1)	2,121 (36.3)
Lung	598 (16.9)	431 (18.6)	1,029 (17.6)
Bladder	370 (10.5)	278 (12.0)	648 (11.1)
Hematologic	369 (10.4)	263 (11.4)	632 (10.8)
ENT	255 (7.2)	172 (7.4)	427 (7.3)
Melanoma	230 (6.5)	143 (6.2)	373 (6.4)
Other	117 (3.3)	98 (4.2)	215 (3.7)
Endocrine	41 (1.2)	26 (1.1)	67 (1.2)
Brain	37 (1.1)	28 (1.2)	65 (1.1)
Neuroendocrine	26 (0.7)	15 (0.7)	41 (0.7)
Male genital tract, NOS	8 (0.2)	11 (0.5)	19 (0.3)
Bone	7 (0.2)	3 (0.1)	10 (0.2)
Small intestine	4 (0.1)	5 (0.2)	9 (0.2)
Female reproductive, NOS	1 (0.03)	1 (0.04)	2 (0.03)
Metastatic, unknown primary cancer type	74 (2.1)	90 (3.9)	164 (2.8)
≥ 2 cancer types at time of initial diagnosis*	19 (0.5)	8 (0.4)	27 (0.5)

The numbers in the table represent N (%). The denominator is the number of cancer cases.

*For participants with ≥ 2 cancer types at time of initial diagnosis, if they had at least one diabetes-related cancer diagnosis, they were classified as having diabetes-related cancer. Otherwise, they were classified as having non-diabetes related cancer.

Table S4. Hazards ratios for the association between treatment (metformin vs. sulfonylureas) and non-diabetes-related cancer subtypes

Outcome	Metformin users (N = 60,311)		Sulfonylurea users (N = 28,078)		Unadjusted model		IPTW adjusted model	
	No. Events	Rate (per 1,000 p-yr)	No. Events	Rate (per 1,000 p-yr)	HR (95% CI)	P-value	HR (95% CI)	P-value
Prostate*	1,377	5.64	744	6.19	0.87 (0.79-0.95)	0.003	1.06 (0.94-1.19)	0.327
Lung	598	2.38	431	3.54	0.73 (0.64-0.83)	< 0.001	0.94 (0.80-1.10)	0.437
Bladder	370	1.47	278	2.28	0.82 (0.70-0.96)	0.016	1.00 (0.83-1.21)	0.968
Hematologic	369	1.47	263	2.16	0.80 (0.68-0.95)	0.009	0.86 (0.70-1.05)	0.128
ENT	255	1.02	172	1.41	0.76 (0.62-0.93)	0.008	0.79 (0.59-1.04)	0.097
Melanoma	230	0.92	143	1.17	0.91 (0.73-1.12)	0.369	1.03 (0.79-1.34)	0.823
Other	117	0.47	98	0.80	0.68 (0.51-0.90)	0.006	0.77 (0.55-1.10)	0.149
Endocrine	41	0.16	26	0.21	0.72 (0.43-1.20)	0.207	0.89 (0.52-1.51)	0.667
Brain	37	0.15	28	0.23	0.69 (0.41-1.15)	0.151	1.35 (0.64-2.82)	0.428
Neuroendocrine	26	0.10	15	0.12	0.96 (0.50-1.86)	0.906	1.05 (0.51-2.18)	0.893
Male genital tract, NOS*	8	0.03	11	0.09	0.35 (0.14-0.88)	0.026	0.31 (0.11-0.83)	0.021
Bone	7	0.03	3	0.02	***	---	***	---
Small intestine	4	0.02	5	0.04	***	---	***	---
Female reproductive, NOS**	1	0.15	1	0.62	***	---	***	---

Any participant with cancer where the primary cancer type could not be identified (≥ 2 cancer types at the time of initial diagnosis [N = 90] or a diagnosis of metastatic-unknown primary type [N = 234]) was excluded from the analysis of the individual cancer subtypes.

No., number; IPTW, inverse probability of treatment weighting; HR, hazards ratio; CI, confidence interval.

*Male participants only (N = 58,681 metformin, N = 27,687 sulfonylurea).

**Female participants only (N = 1,630 metformin, N = 391 sulfonylurea).

***Insufficient sample size.

Table S5. Hazards ratios for the association between treatment (metformin vs. sulfonylureas) and diabetes-related cancers and non-diabetes-related cancers, using an intention-to-treat (ITT) analysis

Outcome	Metformin users (N = 126,494)		Sulfonylurea users (N = 68,957)		Unadjusted model		IPTW adjusted model	
	No. Events	Rate (per 1,000 p-yr)	No. Events	Rate (per 1,000 p-yr)	HR (95% CI)	P-value	HR (95% CI)	P-value
Any cancer	13,415	18.7	9,957	22.8	0.86 (0.83-0.88)	< 0.001	0.97 (0.94-1.00)	0.038
Diabetes related cancer	2,819	3.9	2,279	5.2	0.78 (0.73-0.82)	< 0.001	0.87 (0.81-0.92)	< 0.001
Non-diabetes related cancer	10,596	14.8	7,678	17.6	0.88 (0.85-0.91)	< 0.001	1.00 (0.97-1.03)	0.99

No., number; IPTW, inverse probability of treatment weighting; HR, hazards ratio; CI, confidence interval.

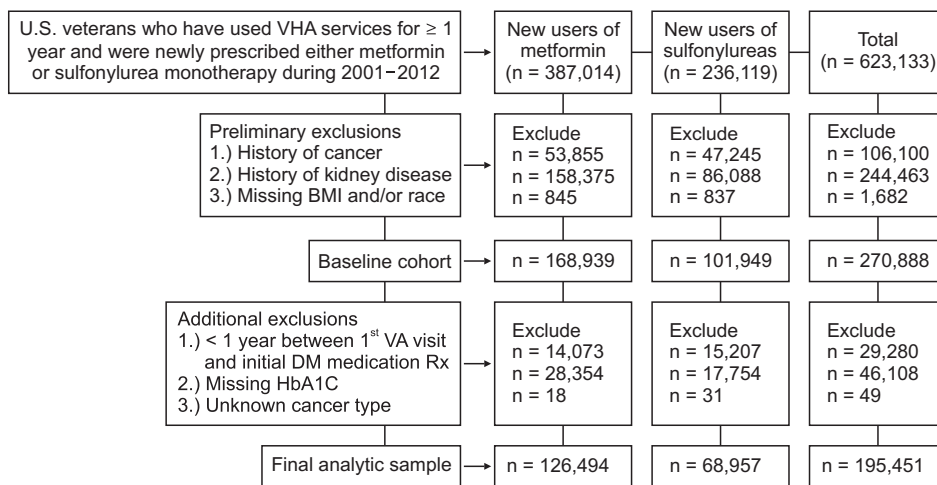
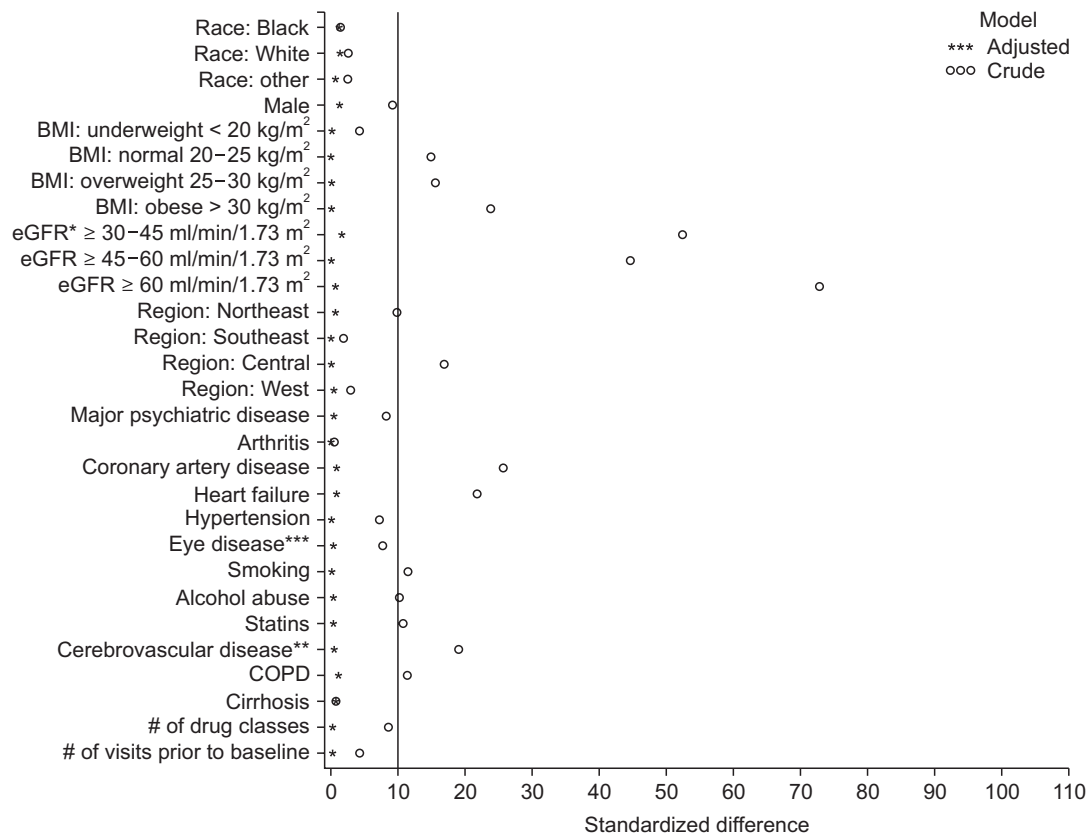


Figure S1. Study sample flow chart for the intention-to-treat (ITT) analysis.



*eGFR = estimated glomerular filtration rate by measured lab value or ICD code

**Cerebrovascular disease = TIA, stroke, CVD

***Eye disease = macular degeneration, glaucoma, impaired vision

Figure S2. Standardized difference of propensity score variables before and after inverse probability weighting (IPTW).