Postdiagnostic Metformin Use and Survival of Patients With Colorectal Cancer: A Nationwide Cohort study

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Contents

Supplementary methods

Method for stabilized inverse probability of treatment weighting using generalized boosting

The propensity score (PS) method was first described by Rosenbaum et al.[1] in 1983. It approximates a clinical trial by balancing covariates between the treated group and control group and then examines the effect of treatment on various diseases. Matching, weighting, stratification, and adjustment for the PS have been proposed to estimate treatment effects. In PS weighting, the average treatment effect for treated persons (ATT) and the population (ATE) is estimated in relation to the manner in which the treated and control groups are weighted.[2] For ATT, the treated group is not weighted (ie, weight=1) and the control group is weighted as the estimated PS (π_i) dividing by 1 minus the estimated PS (ie, weight = $\pi_i/(1-\pi_i)$). Hence, a pseudo-control group with a distribution of comorbidities similar to that of the treated group is created. For ATE, treated patients are weighted by the inverse of the estimated PS (π_i) (ie, weight = $1/\pi_i$), and control patients are weighted by the inverse of 1 minus the estimated PS (ie, weight = $1/(1- \pi_i)$.[3] Note that both a pseudo-treated group and pseudo-control group with comorbidity distributions similar to those of the total population are created. Inverse probability of treatment weighting (IPTW) is often referred to as PS weighting for ATE. More importantly, IPTW is subject to high type I error because of the increase in sample size.[4] Xu et al proposed a stabilized IPTW method that multiplies the IPTW by the proportion of the treated group and control group.[5] The advantage of stabilized IPTW is that it maintains the sample size of the original data, thus yielding appropriate estimation of the variance of the main effect and satisfactory risk of type I error. When there are only 2 groups (treated and control), logistic regression is most often used to obtain PS. However, Lee et al suggested that the boosted method performs best in varied scenarios (the model is

additivity and linearity, mild non-additivity and non-linearity, and moderate non-additivity and non-linearity) and with various weight trimming percentiles (from 50 to 100).[6] In this study, we used the generalized boosting method to obtain the stabilized IPTW.

E-values for evaluating unmeasured confounding in observational studies

The E-value, introduced by VanderWeele and Ding in 2016,[7] was developed to evaluate how strong the unmeasured confounder (U) must be to negate observed results (RR_{ED}^{true}, where RR is the risk ratio between exposure of interested (E) and the outcome (D)) in observational studies. When $RR_{ED}^{true} = 1$ (no association between E and D) and $RR_{EU} = RR_{UD}$,

$$\text{E-value} = RR_{ED}^{obs} + \sqrt{RR_{ED}^{obs} \times \left(RR_{ED}^{obs} - 1\right)}$$

Hence, the E-value is the minimum strength of association measured by a risk ratio scale that an unmeasured confounder would need to have with both the exposure and the outcome, after adjustment for the measured covariates, to fully explain away the specific exposure–outcome association. The E-value does not require any assumptions about unmeasured confounders—for example, that the unmeasured confounders are not necessarily binary, that more than 1 unmeasured confounder is present, and that there is no interaction between E, U, and D. An E-value can be calculated for unadjusted and adjusted odds ratios (OR), hazard ratios (HR), and risk differences (RD) after simple transformation of OR, HR, or RD to RR. For example, when the outcome is relatively rare (<15%) by the end of follow-up, the HR is similar to the RR. When the outcome is common (>15% at the end of follow-up), the RR = $(1-0.5^{sqrt(HR)})/(1-0.5^{sqrt(1/HR)})$. An online E-value calculator

(https://evalue.hmdc.harvard.edu/app/) is available to calculate E-values and their lower limits.[8]

In our study, the exposure of interest was metformin use versus nonuse. The disease or outcome was all-cause mortality and CRC-specific mortality. The outcome is common, ranging from the highest proportion for overall all-cause mortality (41.9%) to the lowest proportion of CRC-specific mortality without prediagnostic metformin (29.5%) (Table 2). Hence, we used the equation $RR = (1-0.5^{sqrt(HR)})/(1-0.5^{sqrt(1/HR)})$ and the online E-value calculator for our study.

References

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Supplementary Table S1. Codes for Comorbidities and Outcomes

	International Classification of Disease 9th revision (ICD-9) code
Comorbidities	
Hypertension	401, 402
Myocardial infarction	410, 412
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428
Peripheral vascular disease	437.3, 440, 441, 443.1-443.9, 557.1, 557.9, V43.4
Cerebrovascular disease	362.34, 430-438
Ischemic stroke	433-434, 436
Rheumatic disease	446.5, 710.0-710.4, 714.0-714.2, 714.8, 725
Diabetes with complications	250.4-250.7
Chronic pulmonary disease	416.8, 416.9, 490-505, 506.4, 508.1, 508.8
Chronic obstructive pulmonary disease	490, 491.0, 491.1, 491.2, 491.8, 491.9, 492.0, 492.8, 494, 496
Peptic ulcer disease	531-534
Mild liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570, 571, 573.3, 573.4, 573.8, 573.9
Moderate or severe liver disease	456.0-456.2, 572.2-572.8
Chronic kidney disease	580-589
Hemiplegia or paraplegia	334.1, 342, 343, 344.0-344.6, 344.9
Dementia	290, 294.1. 331.2
Obesity	278

	International Classification of Disease 9th revision (ICD-9) code	International Classification of Disease 10th revision (ICD-10) code
Outcomes		
All-cause mortality	All	All
CRC-specific mortality	153, 154	C18-C20

Supplementary Table S2. Anatomical-Therapeutic-Chemical (ATC) Codes for Antidiabetic Medications, Aspirin, Statins, and Beta-Blockers Used in This Study

Antidiabetic medications	ATC codes
Metformin	A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13
Sulfonylurea	A10BB01, A10BB02, A10BB03, A10BB04, A10BB05, A10BB07, A10BB08, A10BB09, A10BB12, A10BB31, A10BD02
Alpha-Glucosidase Inhibitor	A10BF01, A10BF02
Meglitinide	A10BX02, A10BX03, A10BX08
Thiazolidinedione	A10BD03, A10BD05, A10BD09, A10BG02, A10BG03
Dipeptidyl Peptidase 4	A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD13, A10BH01, A10BH02, A10BH03, A10BH04, A10BH05
Glucagon-Like Peptide 1	A10BJ01, A10BJ02, A10BJ05
Insulin	A10AB01, A10AB03, A10AB04, A10AB05, A10AB06, A10AB30, A10AC01, A10AC03, A10AC30, A10AD01, A10AD03, A10AD05, A10AE01, A10AE04, A10AE05
Aspirin	B01AC06, B01AC30
Statin	C10AA01, C10AA02, C10AA03, C10AA04, C10AA05, C10AA07, C10AA08, C10BA01, C10BA02, C10BA03, C10BX03
Beta-blocker	C07AA01, C07AA02, C07AA03, C07AA05, C07AA06, C07AA07, C07AA12, C07AA15, C07AA19, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AG01, C07AG02, C07BA68, C07BB02, C07BB03, C07CA03

Supplementary Table S3. Baseline Characteristics of Postdiagnostic Metformin Users and Nonusers Among Diabetic Patients With Newly Diagnosed Colorectal Cancer[a]

		Before Stabilized Inverse Probability of Treatment Weighting			After Stabilized Inverse Probability of Treatment Weighting[b]		
	Total population (n=16676)	Nonusers (n=5238)	Users (n=11438)	SMD	Nonusers (n=4914.46)	Users (n=11157.4)	SMD
Age at CRC diagnosis, y				-0.38			-0.05
Median (IQR)	69 (67-77)	73 (64-80)	68 (60-75)		70 (62-77)	69 (61-76)	
Range	27-101	27-101	29-100		27-101	29-100	
≤ 50	527 (3.16%)	137 (2.62%)	390 (3.41%)	0.36	141.81 (2.89%)	346.43 (3.1%)	0.04
50 - 60	2704 (16.21%)	587 (11.21%)	2117 (18.51%)		753.29 (15.33%)	1838.03 (16.47%)	
60 - 70	5187 (31.1%)	1333 (25.45%)	3854 (33.69%)		1498.16 (30.48%)	3477.58 (31.17%)	
> 70	8258 (49.52%)	3181 (60.73%)	5077 (44.39%)		2521.20 (51.3%)	5495.36 (49.25%)	
Sex				0.00			-0.01
Men	9723 (58.31%)	3055 (58.32%)	6668 (58.3%)		2878.44 (58.57%)	6494.79 (58.21%)	
Women	6953 (41.69%)	2183 (41.68%)	4770 (41.7%)		2036.02 (41.43%)	4662.63 (41.79%)	
Monthly income[c]				0.20			0.04
Quartile 1	6632 (39.77%)	2176 (41.54%)	4456 (38.96%)		1959.00 (39.86%)	4410.12 (39.53%)	
Quartile 2	3176 (19.05%)	1107 (21.13%)	2069 (18.09%)		959.60 (19.53%)	2114.85 (18.95%)	
Quartile 3	4862 (29.16%)	1517 (28.96%)	3345 (29.24%)		1442.67 (29.36%)	3272.27 (29.33%)	
Quartile 4	2006 (12.03%)	438 (8.36%)	1568 (13.71%)		553.19 (11.26%)	1360.18 (12.19%)	
Enrolle category[d]				0.12			0.03
1	1235 (7.41%)	370 (7.06%)	865 (7.56%)		364.05 (7.41%)	827.58 (7.42%)	
2	4343 (26.04%)	1262 (24.09%)	3081 (26.94%)		1232.00 (25.07%)	2894.25 (25.94%)	
3	6919 (41.49%)	2151 (41.07%)	4768 (41.69%)		2058.70 (41.89%)	4655.39 (41.72%)	
4	4179 (25.06%)	1455 (27.78%)	2724 (23.82%)		1259.72 (25.63%)	2780.20 (24.92%)	
Duration of diabetes at CRC diagnosis, y				0.02			-0.01
Median (IQR)	7.74 (4.59-10.95)	8.15 (4.59-11.71)	7.58 (4.59-10.61)		7.73 (4.50-10.87)	7.68 (4.56-10.86)	
≥ 2	1816 (10.89%)	593 (11.32%)	1223 (10.69%)		520.89 (10.6%)	1221.46 (10.95%)	
0 - 2 (new-onset)	14860 (89.11%)	4645 (88.68%)	10215 (89.31%)		4393.58 (89.4%)	9935.95 (89.05%)	
aDSCI score at CRC diagnosis[e]				0.31			0.03
Median (IQR)	1 (0-2)	1 (0-3)	1 (0-2)		1 (0-2)	1 (0-2)	
0	7179 (43.05%)	1895 (36.18%)	5284 (46.2%)		2135.70 (43.46%)	4852.08 (43.49%)	
1	3682 (22.08%)	987 (18.84%)	2695 (23.56%)		1041.21 (21.19%)	2484.55 (22.27%)	
≥ 2	5815 (34.87%)	2356 (44.98%)	3459 (30.24%)		1737.56 (35.36%)	3820.79 (34.24%)	
Antidiabetic medications within 1 year before CRC diagnosis[f]				-0.04			-0.01
Monotherapy/dual therapy	12158 (72.91%)	3877 (74.02%)	8281 (72.4%)		3590.02 (73.05%)	8107.28 (72.66%)	
Triple therapy or more	4518 (27.09%)	1361 (25.98%)	3157 (27.6%)		1324.44 (26.95%)	3050.14 (27.34%)	
Insulin use	2415 (14.48%)	1152 (21.99%)	1263 (11.04%)	-0.30	718.89 (14.63%)	1528.83 (13.7%)	-0.03

Calender year of CRC diagnosis				0.19			0.04
2004 - 2006	2396 (14.37%)	616 (11.76%)	1780 (15.56%)		680.03 (13.84%)	1621.78 (14.54%)	
2007 - 2010	5623 (33.72%)	1576 (30.09%)	4047 (35.38%)		1610.65 (32.77%)	3777.58 (33.86%)	
2011 - 2014	8657 (51.91%)	3046 (58.15%)	5611 (49.06%)		2623.79 (53.39%)	5758.05 (51.61%)	
Primary site				0.07			0.04
Colon	9935 (59.58%)	3237 (61.8%)	6698 (58.56%)		2933.17 (59.68%)	6647.78 (59.58%)	
Rectosigmoid	1223 (7.33%)	387 (7.39%)	836 (7.31%)		386.20 (7.86%)	816.24 (7.32%)	
Rectum	5518 (33.09%)	1614 (30.81%)	3904 (34.13%)		1595.10 (32.46%)	3693.39 (33.1%)	
Grade				0.10			0.04
Well or moderately differentiated	13105 (78.59%)	3991 (76.19%)	9114 (79.68%)		3851.15 (78.36%)	8789.62 (78.78%)	
Poorly differentiated	1054 (6.32%)	380 (7.25%)	674 (5.89%)		328.66 (6.69%)	671.13 (6.02%)	
Unknown	2517 (15.09%)	867 (16.55%)	1650 (14.43%)		734.66 (14.95%)	1696.66 (15.21%)	
Stage				0.19			0.05
I	3443 (20.65%)	994 (18.98%)	2449 (21.41%)		991.72 (20.18%)	2305.02 (20.66%)	
II	4221 (25.31%)	1243 (23.73%)	2978 (26.04%)		1241.12 (25.25%)	2847.81 (25.52%)	
III	4782 (28.68%)	1392 (26.58%)	3390 (29.64%)		1417.80 (28.85%)	3217.92 (28.84%)	
IV	2538 (15.22%)	1063 (20.29%)	1475 (12.9%)		783.44 (15.94%)	1667.02 (14.94%)	
Unknown	1692 (10.15%)	546 (10.42%)	1146 (10.02%)		480.39 (9.77%)	1119.65 (10.03%)	
Treatment type[g]				0.20			0.04
Primary treatment alone	7318 (43.88%)	2307 (44.04%)	5011 (43.81%)		2163.62 (44.03%)	4875.23 (43.7%)	
With adjuvant treatment	6693 (40.14%)	1878 (35.85%)	4815 (42.1%)		1956.73 (39.82%)	4547.99 (40.76%)	
With neoadjuvant Treatment	825 (4.95%)	256 (4.89%)	569 (4.97%)		254.74 (5.18%)	550.96 (4.94%)	
Systemic treatment alone	448 (2.69%)	228 (4.35%)	220 (1.92%)		141.43 (2.88%)	286.06 (2.56%)	
Unknown	1392 (8.35%)	569 (10.86%)	823 (7.2%)		397.95 (8.1%)	897.17 (8.04%)	
Comorbidities at CRC diagnosis							
Hypertension	10884 (65.27%)	3541 (67.6%)	7343 (64.2%)	-0.07	3201.70 (65.15%)	7279.30 (65.24%)	0.00
Myocardial infarction	275 (1.65%)	119 (2.27%)	156 (1.36%)	-0.07	78.52 (1.6%)	167.12 (1.5%)	-0.01
Congestive heart failure	1163 (6.97%)	563 (10.75%)	600 (5.25%)	-0.20	365.94 (7.45%)	746.10 (6.69%)	-0.03
Peripheral vascular disease	462 (2.77%)	170 (3.25%)	292 (2.55%)	-0.04	136.04 (2.77%)	307.10 (2.75%)	0.00
Cerebrovascular disease	2168 (13%)	810 (15.46%)	1358 (11.87%)	-0.10	666.50 (13.56%)	1450.92 (13%)	-0.02
Ischemic stroke	1324 (7.94%)	490 (9.35%)	834 (7.29%)	-0.07	399.21 (8.12%)	873.85 (7.83%)	-0.01
Rheumatic disease	177 (1.06%)	74 (1.41%)	103 (0.9%)	-0.05	52.35 (1.07%)	113.08 (1.01%)	-0.01
Diabetes with complications	3607 (21.63%)	1376 (26.27%)	2231 (19.51%)	-0.16	1064.99 (21.67%)	2352.74 (21.09%)	-0.01
Chronic pulmomary disease	1706 (10.23%)	621 (11.86%)	1085 (9.49%)	-0.08	508.62 (10.35%)	1135.66 (10.18%)	-0.01
Chronic obstructive pulmonary disease	1233 (7.39%)	466 (8.9%)	767 (6.71%)	-0.08	369.90 (7.53%)	817.17 (7.32%)	-0.01
Peptic ulcer disease	3062 (18.36%)	1078 (20.58%)	1984 (17.35%)	-0.08	932.92 (18.98%)	2024.45 (18.14%)	-0.02
Mid liver disease	1724 (10.34%)	458 (8.74%)	1266 (11.07%)	0.08	473.13 (9.63%)	1156.50 (10.37%)	0.02
Moderate or severe liver disease	32 (0.19%)	19 (0.36%)	13 (0.11%)	-0.05	10.03 (0.2%)	16.61 (0.15%)	-0.01
Chronic kidney disease	1571 (9.42%)	1112 (21.23%)	459 (4.01%)	-0.54	484.80 (9.86%)	938.24 (8.41%)	-0.05
Hemiplegia/paraplegia	113 (0.68%)	44 (0.84%)	69 (0.6%)	-0.03	33.76 (0.69%)	69.89 (0.63%)	-0.01

Dementia	496 (2.97%)	234 (4.47%)	262 (2.29%)	-0.12	154.63 (3.15%)	329.27 (2.95%)	-0.01
Obesity	78 (0.47%)	17 (0.32%)	61 (0.53%)	0.03	20.79 (0.42%)	51.46 (0.46%)	0.01
Medications[h]							
Prediagnostic metformin	14974 (89.79%)	4273 (81.58%)	10701 (93.56%)	0.37	4395.97 (89.45%)	10093.52 (90.46%)	0.03
Aspirin	5540 (33.22%)	1785 (34.08%)	3755 (32.83%)	-0.03	1645.35 (33.48%)	3729.56 (33.43%)	0.00
Statin	4678 (28.05%)	1415 (27.01%)	3263 (28.53%)	0.03	1349.00 (27.45%)	3123.86 (28%)	0.01
Beta-blocker	5842 (35.03%)	2010 (38.37%)	3832 (33.5%)	-0.10	1739.52 (35.4%)	3856.83 (34.57%)	-0.02

[a]Postdiagnostic metformin use was defined as metformin use after a colorectal cancer diagnosis. Categorial variables are presented as numbers and percentages; continuous variables are presented as medians and IQRs.
[b]Based on stabilized inverse probability of treatment weighting of propensity score by using generalized boosting method that estimates each patient's probability of receiving metformin, adjusted for the covariates at baseline.
[c]Quartile 1, dependent; quartile 2, <15,000; quartile 3, 15,000 - 24,999; quartile 4, ≥25,000; the currency unit is new Taiwan dollars.

[d]Category 1, civil servants, full-time or regularly paid personnel with a government or public affiliation; category 2, employees of privately owned institutions; category 3, self-employed individuals, other employees, and members of farmers' or fishermen's associations; category 4, veterans, members of low-income families, and substitute service draftees.
[e]A 13-point scale from 7 diabetic complications (retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease and metabolic emergency) scored by severity as 0, 1, or 2.
[f]Metformin, sulfonylurea, alpha-glucosidase inhibitor, meglitinide, thiazolidinedione, dipeptidyl peptidase 4, glucagon-like peptide 1, and insulin.
[g]Primary treatment including surgical removal and concurrent chemoradiotherapy.

[h]Within the 1 year before CRC diagnosis.
Abbreviations: CRC, colorectal cancer; IQR, interquartile range; SMD, standardized mean difference; aDCSI, adapted Diabetes Complications Severity Index

Supplementary Table S4. Baseline Characteristics of Postdiagnostic Metformin Users and Nonusers Among Diabetic Patients with Newly Diagnosed Colorectal Cancer: Subgroup without Prediagnostic Metformin Use[a]

		Before Stabilized Inverse Probability of Treatment Weighting			After Stabilized Inverse Probability of Treatment Weighting[b]		
	Total population (n=2112)	Nonusers (n=1120)	Users (n=992)	SMD	Nonusers (n=1040.88)	Users (n=890.59)	SMD
Age at CRC diagnosis, y							
Median (IQR)	70 (67-77)	72 (64-79)	67 (59-74)		70 (62-77)	69 (61-77)	
Range	32-98	33-98	32-93		33-98	32-93	
< 50	65 (3.08%)	29 (2.59%)	36 (3.63%)	0.38	31.13 (2.99%)	29.20 (3.28%)	0.04
50 - 59	365 (17.28%)	140 (12.5%)	225 (22.68%)		172.47 (16.57%)	164.57 (18.48%)	
60 - 69	615 (29.12%)	287 (25.63%)	328 (33.06%)		291.71 (28.03%)	260.45 (29.24%)	
≥ 70	1067 (50.52%)	664 (59.29%)	403 (40.63%)		545.58 (52.41%)	436.36 (49%)	
Sex				0.02			0.00
Men	1260 (59.66%)	663 (59.2%)	597 (60.18%)		620.17 (59.58%)	529.57 (59.46%)	
Women	852 (40.34%)	457 (40.8%)	395 (39.82%)		420.71 (40.42%)	361.02 (40.54%)	
Monthly income[c]				0.22			0.05
Quartile 1	776 (36.74%)	445 (39.73%)	331 (33.37%)		387.71 (37.25%)	314.78 (35.35%)	
Quartile 2	387 (18.32%)	223 (19.91%)	164 (16.53%)		192.05 (18.45%)	157.48 (17.68%)	
Quartile 3	717 (33.95%)	354 (31.61%)	363 (36.59%)		354.73 (34.08%)	319.47 (35.87%)	
Quartile 4	232 (10.98%)	98 (8.75%)	134 (13.51%)		106.39 (10.22%)	98.86 (11.1%)	
Enrollee category[d]				0.16			0.03
1	157 (7.43%)	80 (7.14%)	77 (7.76%)		72.13 (6.93%)	65.97 (7.41%)	
2	524 (24.81%)	285 (25.45%)	239 (24.09%)		263.99 (25.36%)	210.30 (23.61%)	
3	925 (43.8%)	463 (41.34%)	462 (46.57%)		452.83 (43.5%)	403.99 (45.36%)	
4	506 (23.96%)	292 (26.07%)	214 (21.57%)		251.93 (24.2%)	210.34 (23.62%)	
Duration of diabetes at CRC diagnosis, y				-0.12			-0.01
Median (IQR)	4.31 (1.22-7.45)	4.84 (1.54-8.04)	3.89 (0.94-6.81)		4.3 (1.3-7.44)	4.1 (1.14-7.18)	
≥ 2	673 (31.87%)	328 (29.29%)	345 (34.78%)		332.79 (31.97%)	290.80 (32.65%)	
0 - 2 (new-onset)	1439 (68.13%)	792 (70.71%)	647 (65.22%)		708.09 (68.03%)	599.79 (67.35%)	
aDSCI score at CRC diagnosis[e]				0.29			0.06
Median (IQR)	0 (0-2)	1 (0-2)	0 (0-1)		0 (0-2)	0 (0-2)	
0	1125 (53.27%)	530 (47.32%)	595 (59.98%)		549.17 (52.76%)	496.37 (55.73%)	
1	392 (18.56%)	211 (18.84%)	181 (18.25%)		197.68 (18.99%)	163.29 (18.33%)	
≥ 2	595 (28.17%)	379 (33.84%)	216 (21.77%)		294.02 (28.25%)	230.93 (25.93%)	
Antidiabetic medications within 1 year before diagnosis[f]				0.00			-0.02
Monotherapy/dual therapy	2009 (95.12%)	1065 (95.09%)	944 (95.16%)		994.13 (95.51%)	846.43 (95.04%)	
Triple therapy or more	103 (4.88%)	55 (4.91%)	48 (4.84%)		46.75 (4.49%)	44.16 (4.96%)	

Insulin use	118 (5.59%)	76 (6.79%)	42 (4.23%)	-0.11	57.36 (5.51%)	40.48 (4.55%)	-0.04
Year of Diagnosis				0.30			0.07
2004 - 2006	486 (23.01%)	206 (18.39%)	280 (28.23%)		228.23 (21.93%)	214.46 (24.08%)	
2007 - 2010	785 (37.17%)	398 (35.54%)	387 (39.01%)		385.56 (37.04%)	342.05 (38.41%)	
2011 - 2014	841 (39.82%)	516 (46.07%)	325 (32.76%)		427.09 (41.03%)	334.09 (37.51%)	
Primary site				0.10			0.04
Colon	1231 (58.29%)	678 (60.54%)	553 (55.75%)		618.03 (59.38%)	516.42 (57.99%)	
Rectosigmoid	171 (8.1%)	85 (7.59%)	86 (8.67%)		78.54 (7.55%)	78.63 (8.83%)	
Rectum	710 (33.62%)	357 (31.88%)	353 (35.58%)		344.30 (33.08%)	295.54 (33.18%)	
Grade				0.16			0.08
Well or moderately differentiated	1657 (78.46%)	855 (76.34%)	802 (80.85%)		810.25 (77.84%)	702.75 (78.91%)	
Poorly differentiated	154 (7.29%)	100 (8.93%)	54 (5.44%)		86.67 (8.33%)	55.68 (6.25%)	
Unknown	301 (14.25%)	165 (14.73%)	136 (13.71%)		143.96 (13.83%)	132.16 (14.84%)	
Stage				0.31			0.06
I	400 (18.94%)	190 (16.96%)	210 (21.17%)		184.09 (17.69%)	170.39 (19.13%)	
II	553 (26.18%)	278 (24.82%)	275 (27.72%)		276.72 (26.59%)	239.35 (26.88%)	
III	613 (29.02%)	305 (27.23%)	308 (31.05%)		305.11 (29.31%)	265.76 (29.84%)	
IV	341 (16.15%)	240 (21.43%)	101 (10.18%)		181.74 (17.46%)	132.47 (14.87%)	
Unknown	205 (9.71%)	107 (9.55%)	98 (9.88%)		93.22 (8.96%)	82.63 (9.28%)	
Treatment type[g]				0.26			0.09
Primary treatment alone	901 (42.66%)	470 (41.96%)	431 (43.45%)		448.46 (43.08%)	376.66 (42.29%)	
With adjuvant treatment	889 (42.09%)	442 (39.46%)	447 (45.06%)		426.62 (40.99%)	391.15 (43.92%)	
With neoadjuvant treatment	101 (4.78%)	56 (5%)	45 (4.54%)		52.78 (5.07%)	41.14 (4.62%)	
Systemic treatment alone	60 (2.84%)	47 (4.2%)	13 (1.31%)		33.72 (3.24%)	20.63 (2.32%)	
Unknown	161 (7.62%)	105 (9.38%)	56 (5.65%)		79.30 (7.62%)	61.02 (6.85%)	
Comorbidities							
Hypertension	1306 (61.84%)	743 (66.34%)	563 (56.75%)	-0.20	652.64 (62.7%)	539.04 (60.53%)	-0.04
Myocardial infarction	26 (1.23%)	20 (1.79%)	6 (0.6%)	-0.11	13.71 (1.32%)	5.70 (0.64%)	-0.07
Congestive heart failure	144 (6.82%)	89 (7.95%)	55 (5.54%)	-0.10	70.95 (6.82%)	55.81 (6.27%)	-0.02
Peripheral vascular disease	54 (2.56%)	37 (3.3%)	17 (1.71%)	-0.10	28.52 (2.74%)	17.01 (1.91%)	-0.06
Cerebrovascular disease	235 (11.13%)	151 (13.48%)	84 (8.47%)	-0.16	120.06 (11.53%)	91.53 (10.28%)	-0.04
Ischemic stroke	139 (6.58%)	90 (8.04%)	49 (4.94%)	-0.13	71.47 (6.87%)	54.12 (6.08%)	-0.03
Rheumatic disease	22 (1.04%)	15 (1.34%)	7 (0.71%)	-0.06	12.93 (1.24%)	7.41 (0.83%)	-0.04
Diabetes with complications	271 (12.83%)	175 (15.63%)	96 (9.68%)	-0.18	136.96 (13.16%)	97.33 (10.93%)	-0.07
Chronic pulmonary disease	230 (10.89%)	138 (12.32%)	92 (9.27%)	-0.10	116.03 (11.15%)	89.75 (10.08%)	-0.03
Chronic obstructive pulmonary disease	166 (7.86%)	100 (8.93%)	66 (6.65%)	-0.09	82.36 (7.91%)	67.72 (7.6%)	-0.01
Peptic ulcer disease	364 (17.23%)	209 (18.66%)	155 (15.63%)	-0.08	178.00 (17.1%)	139.28 (15.64%)	-0.04
Mild liver disease	225 (10.65%)	108 (9.64%)	117 (11.79%)	0.07	109.89 (10.56%)	96.61 (10.85%)	0.01
Moderate or severe liver disease	1306 (61.84%)	743 (66.34%)	563 (56.75%)	-0.20	652.64 (62.7%)	539.04 (60.53%)	-0.04
Chronic kidney disease	209 (9.9%)	174 (15.54%)	35 (3.53%)	-0.42	110.67 (10.63%)	64.68 (7.26%)	-0.12

Hemiplegia/paraplegia	10 (0.47%)	7 (0.63%)	3 (0.3%)	-0.05	5.59 (0.54%)	2.90 (0.33%)	-0.03
Dementia	46 (2.18%)	34 (3.04%)	12 (1.21%)	-0.13	24.86 (2.39%)	14.84 (1.67%)	-0.05
Obesity							
Medications[h]							
Aspirin	601 (28.46%)	340 (30.36%)	261 (26.31%)	-0.09	291.03 (27.96%)	256.08 (28.75%)	0.02
Statin	448 (21.21%)	258 (23.04%)	190 (19.15%)	-0.10	219.26 (21.07%)	175.25 (19.68%)	-0.03
Beta-blocker	737 (34.9%)	424 (37.86%)	313 (31.55%)	-0.13	371.71 (35.71%)	301.26 (33.83%)	-0.04

Abbreviations: IQR, interquartile range; SMD, standardized mean difference; aDCSI, adapted Diabetes Complications Severity Index
[a]Postdiagnostic metformin use was defined as metformin use after a colorectal cancer diagnosis.
Categorial variables are presented as numbers and percentages; continuous variables are presented as medians (IQR).
[b]Based on a propensity score constructed by using generalized boosting method that estimates each patient's probability of receiving metformin, adjusted for the covariates at baseline.
[c]Quartile 1, dependent; quartile 2, <15,000; quartile 3, 15,000 - 24,999; quartile 4, ≥ 25,000; the currency unit is new Taiwan dollars.
[d]Category 1, civil servants, full-time or regularly paid personnel with a government or public affiliation; category 2, employees of privately owned institutions; category 3, self-employed individuals, other employees, and members of farmers' or fishermen's associations; category 4, veterans, members of low-income families, and substitute service draftees.
[e]A 13-point scale from 7 diabetic complications (retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease and metabolic) scored by severity as 0, 1, or 2.
[f]Metformin, sulfonylurea, alpha-glucosidase inhibitor, meglitinide, thiazolidinedione, dipeptidyl peptidase 4, glucagon-like peptide 1, and insulin.
[g]Primary treatment including surgical removal and concurrent chemoradiotherapy.
[h]Received during the year before colorectal cancer diagnosis.

Supplementary Table S5. Baseline Characteristics of Postdiagnostic Metformin Users and Nonusers Among Diabetic Patients with Newly Diagnosed Colorectal Cancer: Subgroup with Prediagnostic Metformin Use[a]

		Before Stabilized Inverse Probability of Treatment Weighting			After Stabilized Inverse Probability of Treatment Weighting[b]		
	Total population (n=14564)	Nonusers (n=4118)	Users (n=10446)	SMD	Nonusers (n=3817.43)	Users (n=10230)	SMD
Age at CRC diagnosis, y							
Median (IQR)	69 (62-77)	73 (64-80)	68 (61-75)		70 (62-77)	69 (61-76)	
Range	27-101	27-101	29-100		27-101	29-100	
< 50	462 (3.17%)	108 (2.62%)	354 (3.39%)		105.61 (2.77%)	318.62 (3.11%)	
50 - 59	2339 (16.06%)	447 (10.85%)	1892 (18.11%)	0.34	576.33 (15.1%)	1660.97 (16.24%)	0.03
60 - 69	4572 (31.39%)	1046 (25.4%)	3526 (33.75%)		1175.99 (30.81%)	3218.45 (31.46%)	
≥ 70	7191 (49.38%)	2517 (61.12%)	4674 (44.74%)		1959.50 (51.33%)	5031.94 (49.19%)	
Sex				0.00			-0.01
Men	8463 (58.11%)	2392 (58.09%)	6071 (58.12%)		2231.17 (58.45%)	5939.58 (58.06%)	
Women	6101 (41.89%)	1726 (41.91%)	4375 (41.88%)		1586.27 (41.55%)	4290.40 (41.94%)	
Monthly income[c]				0.17			0.04
Quartile 1	5856 (40.21%)	1731 (42.03%)	4125 (39.49%)		1552.22 (40.66%)	4085.36 (39.94%)	
Quartile 2	2789 (19.15%)	884 (21.47%)	1905 (18.24%)		748.55 (19.61%)	1948.94 (19.05%)	
Quartile 3	4145 (28.46%)	1163 (28.24%)	2982 (28.55%)		1085.20 (28.43%)	2930.62 (28.65%)	
Quartile 4	1774 (12.18%)	340 (8.26%)	1434 (13.73%)		431.47 (11.3%)	1265.06 (12.37%)	
Enrollee category[d]				0.11			0.03
1	1078 (7.4%)	290 (7.04%)	788 (7.54%)		284.02 (7.44%)	759.23 (7.42%)	
2	3819 (26.22%)	977 (23.73%)	2842 (27.21%)		963.06 (25.23%)	2683.14 (26.23%)	
3	5994 (41.16%)	1688 (40.99%)	4306 (41.22%)		1585.70 (41.54%)	4228.79 (41.34%)	
4	3673 (25.22%)	1163 (28.24%)	2510 (24.03%)		984.66 (25.79%)	2558.83 (25.01%)	
Duration of diabetes at CRC diagnosis, y				-0.08			-0.02
Median (IQR)	8.22 (5.13-11.27)	9.07 (5.54-12.31)	7.91 (4.99-10.85)		8.23 (5.17-11.19)	8.14 (5.1-11.18)	
≥ 2	1143 (7.85%)	265 (6.44%)	878 (8.41%)		278.43 (7.29%)	811.70 (7.93%)	
0 - 2 (new-onset)	13421 (92.15%)	3853 (93.56%)	9568 (91.59%)		3539.01 (92.71%)	9418.28 (92.07%)	
aDSCI score at CRC diagnosis[e]				0.35			0.04
Median (IQR)	1 (2)	1 (3)	1 (2)		1 (2)	1 (2)	
0	6054 (41.57%)	1365 (33.15%)	4689 (44.89%)		1583.20 (41.47%)	4280.32 (41.84%)	
1	3290 (22.59%)	776 (18.84%)	2514 (24.07%)		836.02 (21.9%)	2340.25 (22.88%)	
≥ 2	5220 (35.84%)	1977 (48.01%)	3243 (31.05%)		1398.21 (36.63%)	3609.41 (35.28%)	
Antidiabetic medications within 1 year before diagnosis[f]				0.04			0.00
Monotherapy/dual therapy	10149 (69.69%)	2812 (68.29%)	7337 (70.24%)		2655.87 (69.57%)	7111.62 (69.52%)	
Triple therapy or more	4415 (30.31%)	1306 (31.71%)	3109 (29.76%)		1161.56 (30.43%)	3118.36 (30.48%)	
Insulin use	2297 (15.77%)	1076 (26.13%)	1221 (11.69%)	-0.38	611.97 (16.03%)	1531.69 (14.97%)	-0.03
Year of Diagnosis				0.21			0.04
2004 - 2006	1910 (13.11%)	410 (9.96%)	1500 (14.36%)		470.22 (12.32%)	1353.93 (13.23%)	

2007 - 2010	4838 (33.22%)	1178 (28.61%)	3660 (35.04%)		1230.24 (32.23%)	3410.34 (33.34%)	
2011 - 2014	7816 (53.67%)	2530 (61.44%)	5286 (50.6%)		2116.97 (55.46%)	5465.71 (53.43%)	
Primary site				0.07			0.04
Colon	8704 (59.76%)	2559 (62.14%)	6145 (58.83%)		2270.11 (59.47%)	6119.59 (59.82%)	
Rectosigmoid	1052 (7.22%)	302 (7.33%)	750 (7.18%)		305.77 (8.01%)	728.16 (7.12%)	
Rectum	4808 (33.01%)	1257 (30.52%)	3551 (33.99%)		1241.56 (32.52%)	3382.23 (33.06%)	
Grade				0.10			0.05
Well or moderately differentiated	11448 (78.6%)	3136 (76.15%)	8312 (79.57%)		2999.28 (78.57%)	8080.66 (78.99%)	
Poorly differentiated	900 (6.18%)	280 (6.8%)	620 (5.94%)		248.63 (6.51%)	607.70 (5.94%)	
Unknown	2216 (15.22%)	702 (17.05%)	1514 (14.49%)		569.53 (14.92%)	1541.62 (15.07%)	
Stage				0.20			0.02
I	3043 (20.89%)	804 (19.52%)	2239 (21.43%)		779.35 (20.42%)	2135.85 (20.88%)	
II	3668 (25.19%)	965 (23.43%)	2703 (25.88%)		960.89 (25.17%)	2596.39 (25.38%)	
III	4169 (28.63%)	1087 (26.4%)	3082 (29.5%)		1090.32 (28.56%)	2944.08 (28.78%)	
IV	2197 (15.09%)	823 (19.99%)	1374 (13.15%)		611.14 (16.01%)	1517.61 (14.83%)	
Unknown	1487 (10.21%)	439 (10.66%)	1048 (10.03%)		375.73 (9.84%)	1036.05 (10.13%)	
Treatment type[g]				0.21			0.04
Primary treatment alone	6417 (44.06%)	1837 (44.61%)	4580 (43.84%)		1678.02 (43.96%)	4475.01 (43.74%)	
With adjuvant treatment	5804 (39.85%)	1436 (34.87%)	4368 (41.82%)		1512.25 (39.61%)	4149.17 (40.56%)	
With neoadjuvant treatment	724 (4.97%)	200 (4.86%)	524 (5.02%)		202.19 (5.3%)	504.33 (4.93%)	
Systemic treatment alone	388 (2.66%)	181 (4.4%)	207 (1.98%)		108.98 (2.85%)	268.18 (2.62%)	
Unknown	1231 (8.45%)	464 (11.27%)	767 (7.34%)		316.01 (8.28%)	833.30 (8.15%)	
Comorbidities							
Hypertension	9578 (65.76%)	2798 (67.95%)	6780 (64.91%)	-0.06	2517.91 (65.96%)	6741.05 (65.89%)	0.00
Myocardial infarction	249 (1.71%)	99 (2.4%)	150 (1.44%)	-0.07	62.59 (1.64%)	164.74 (1.61%)	0.00
Congestive heart failure	1019 (7%)	474 (11.51%)	545 (5.22%)	-0.23	285.49 (7.48%)	679.39 (6.64%)	-0.03
Peripheral vascular disease	408 (2.8%)	133 (3.23%)	275 (2.63%)	-0.04	102.99 (2.7%)	296.02 (2.89%)	0.01
Cerebrovascular disease	1933 (13.27%)	659 (16%)	1274 (12.2%)	-0.11	536.40 (14.05%)	1356.13 (13.26%)	-0.02
Ischemic stroke	1185 (8.14%)	400 (9.71%)	785 (7.51%)	-0.08	324.91 (8.51%)	823.20 (8.05%)	-0.02
Rheumatic disease	155 (1.06%)	59 (1.43%)	96 (0.92%)	-0.05	41.87 (1.1%)	105.39 (1.03%)	-0.01
Diabetes with complications	3336 (22.91%)	1201 (29.16%)	2135 (20.44%)	-0.20	888.87 (23.28%)	2292.44 (22.41%)	-0.02
Chronic pulmonary disease	1476 (10.13%)	483 (11.73%)	993 (9.51%)	-0.07	388.22 (10.17%)	1034.79 (10.12%)	0.00
Chronic obstructive pulmonary disease	1067 (7.33%)	366 (8.89%)	701 (6.71%)	-0.08	281.94 (7.39%)	736.89 (7.2%)	-0.01
Peptic ulcer disease	2698 (18.53%)	869 (21.1%)	1829 (17.51%)	-0.09	738.48 (19.34%)	1878.59 (18.36%)	-0.03
Mild liver disease	1499 (10.29%)	350 (8.5%)	1149 (11%)	0.08	364.59 (9.55%)	1058.52 (10.35%)	0.03
Moderate or severe liver disease	26 (0.18%)	15 (0.36%)	11 (0.11%)	-0.05	7.24 (0.19%)	13.82 (0.14%)	-0.01
Chronic kidney disease	1362 (9.35%)	938 (22.78%)	424 (4.06%)	-0.57	378.62 (9.92%)	862.05 (8.43%)	-0.05
Hemiplegia/paraplegia	103 (0.71%)	37 (0.9%)	66 (0.63%)	-0.03	27.90 (0.73%)	67.18 (0.66%)	-0.01
Dementia	450 (3.09%)	200 (4.86%)	250 (2.39%)	-0.13	125.21 (3.28%)	306.74 (3%)	-0.02
Obesity	72 (0.49%)	13 (0.32%)	59 (0.56%)	0.04	14.32 (0.38%)	51.34 (0.5%)	0.02
Medications[h]							
Aspirin	4939 (33.91%)	1445 (35.09%)	3494 (33.45%)	-0.03	1316.43 (34.48%)	3486.10 (34.08%)	-0.01
Statin	4230 (29.04%)	1157 (28.1%)	3073 (29.42%)	0.03	1101.42 (28.85%)	2970.90 (29.04%)	0.00

Beta-blocker	5105 (35.05%)	1586 (38.51%)	3519 (33.69%)	-0.10	1365.93 (35.78%)	3549.37 (34.7%)	-0.02

Abbreviation: IQR, interquartile range; SMD, standardized mean difference; aDCSI, adapted Diabetes Complications Severity Index;
[a]Postdiagnostic metformin users or nonusers defined by whether metformin was used or not after the colorectal cancer diagnosis.
Categorial variables presented as counts and percentages; continuous variables presented as median (IQR).
[b]Based on a propensity score constructed by using generalized boosting method estimating each patient's probability of receiving metformin adjusted for the covariates at baseline.
[c]Quartile 1, dependent; quartile 2, <15,000; quartile 3, 15,000 - 24,999; quartile 4, ≥ 25,000, and the currency unit is new Taiwan dollars.
[d]Category 1, civil servants, full-time or regularly paid personnel with a government or public affiliation; category 2, employees of privately owned institutions; category 3, self-employed individuals, other employees, and members of the farmers' or fishermen's associations; category 4, veterans, members of low-income families, and substitute service draftees.
[e]A 13-point scale from 7 diabetic complications (retinopathy, nephropathy, neuropathy, cerebrovascular, cardiovascular, peripheral vascular disease and metabolic) scored by severity as 0, 1, or 2.
[f]Metformin, sulfonylurea, alpha-glucosidase inhibitor, meglitinide, thiazolidinedione, dipeptidyl peptidase 4, glucagon-like peptide 1, and insulin.
[g]Primary treatment including surgical removal and concurrent chemoradiotherapy.
[h]Received this year before colorectal cancer diagnosis.

Supplementary Table S6. Dose-response relationship between metformin and mortality

	HR (95% CI)					
	Unadjusted	*P* Value	Multivariable-adjusted analyses[a]	*P* Value	Inverse probability of treatment weighted analyses[b]	*P* Value
All-cause mortality						
Metformin nonuser	reference		reference		reference	
DDD≤180	0.78(0.74-0.83)	<0.0001	0.90(0.85-0.95)	0.0004	1.03(0.97-1.08)	0.3265
180<DDD≤365	0.41(0.38-0.44)	<0.0001	0.47(0.43-0.50)	<0.0001	0.51(0.48-0.55)	<0.0001
DDD>365	0.18(0.17-0.19)	<0.0001	0.21(0.19-0.23)	<0.0001	0.23(0.21-0.25)	<0.0001
CRC-specific mortality[c]						
Metformin nonuser	reference		reference		reference	
DDD≤180	0.86(0.80-0.91)	<0.0001	0.91(0.85-0.98)	0.0087	1.06(0.99-1.13)	0.0995
180<DDD≤365	0.41(0.38-0.45)	<0.0001	0.44(0.40-0.48)	<0.0001	0.49(0.45-0.54)	<0.0001
DDD>365	0.19(0.17-0.21)	<0.0001	0.20(0.18-0.22)	<0.0001	0.23(0.21-0.25)	<0.0001

Abbreviation: CRC, colorectal cancer; IPTW, inverse probability of treatment weighting; DDD, defined daily dose

[a]Covariates adjusted for in multivariate time-dependent Cox regression analyses include age, sex, monthly income, enrolle category, diebetes duration, adapted diabetes complications severity Index, antidiabetic medications 1 year before diagnosis, year of diagnosis, primary site, grade, stage, treatment type, comorbidities, prediagnostic metformin use, and use of medications after CRC diagnosis (aspirin, statin, and beta-blocker).

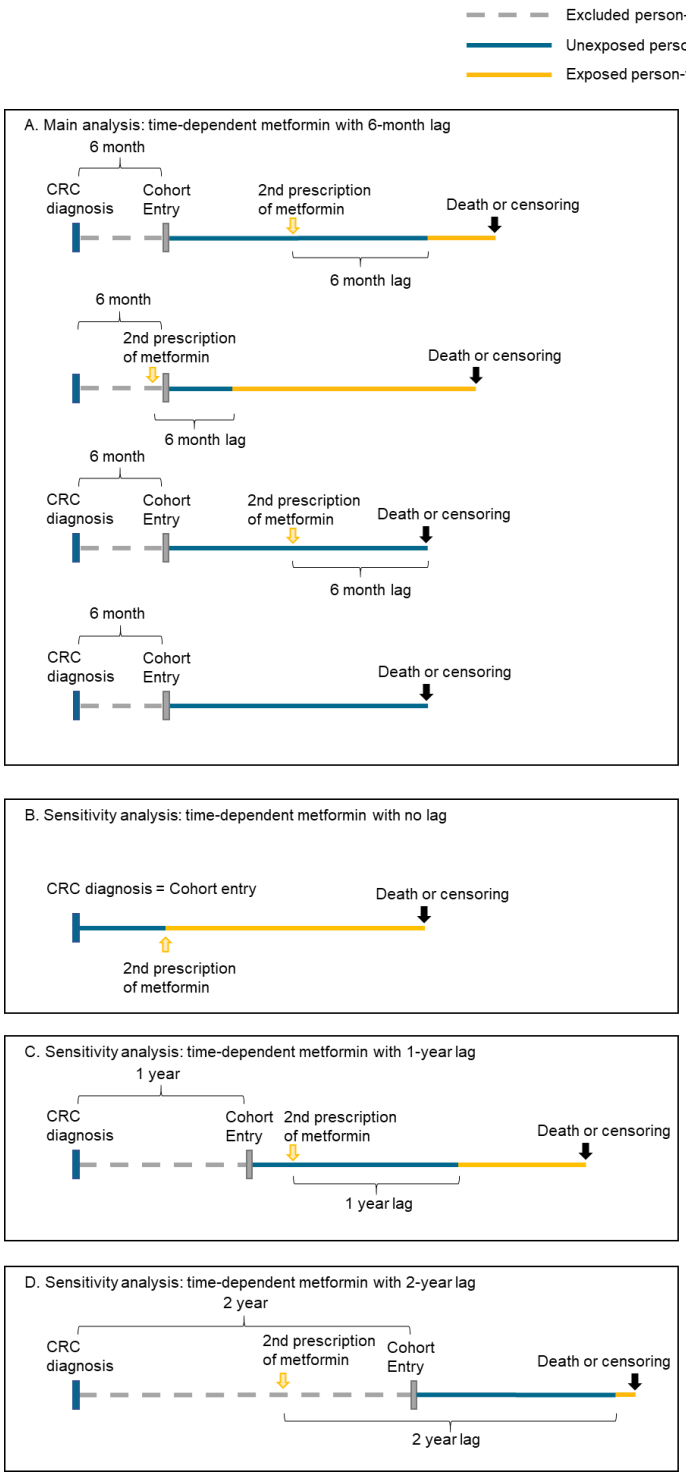
[b]Covariates at baseline adjusted for in inverse probability of treatment weighting using propensity score include age, sex, monthly income, enrolle category, diebetes duration, adapted diabetes complications severity Index, antidiabetic medications 1 year before diagnosis, year of diagnosis, primary site, grade, stage, treatment type, comorbidities, prediagnostic metformin use, and use of aspirin, statin, and beta-blocker.

Supplementary Table S7. Adjusted Hazard Ratios and E-Values for All-Cause Mortality and Colorectal Cancer (CRC)-Specific Mortality Among Diabetic Patients with Newly Diagnosed Colorectal Cancer: Postdiagnostic Metformin Users vs Nonusers[a]

	Multivariable time-dependent analyses		After Stabilized Inverse Probability of Treatment Weighting[b]	
	Hazard Ratio(95% CI)	E-Value(95 % Lower limit[c])	Hazard Ratio(95% CI)	E-Value(95 % Lower limit)
All-cause Mortality				
Overall	0.42 (0.40-0.44)	3.03 (2.91)	0.56 (0.53-0.59)	2.34 (2.24)
Without prediagnostic metformin use	0.41 (0.38-0.47)	3.09 (2.75)	0.50 (0.44-0.57)	2.60 (2.31)
With prediagnostic metformin use	0.42 (0.40-0.44)	3.03 (2.91)	0.56 (0.53-0.59)	2.35 (2.24)
CRC-specific Mortality				
Overall	0.41 (0.39-0.44)	3.09 (2.91)	0.58 (0.55-0.61)	2.27 (2.16)
Without prediagnostic metformin use	0.40 (0.34-0.48)	3.16 (2.70)	0.52 (0.44-0.61)	2.51 (2.16)
With prediagnostic metformin use	0.42 (0.39-0.45)	3.03 (2.86)	0.58 (0.54-0.62)	2.27 (2.13)

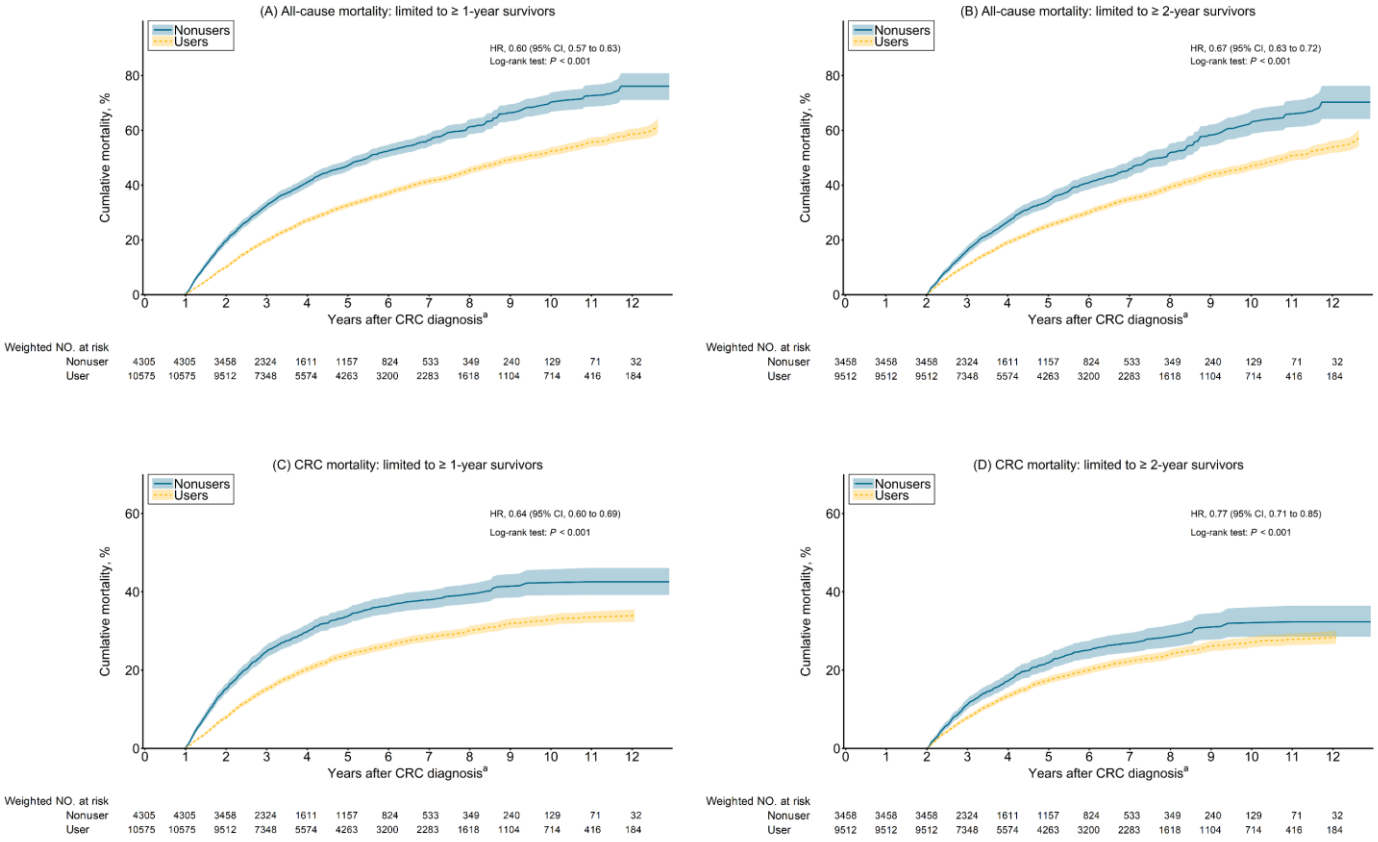
[a]The reference group is postdiagnostic metformin nonusers
[b]The covariates in Table 1 were included in the generalized boosting method to obtain stabilized inverse probability of treatment weighting
[c]The limit of the confidence interval closest to the null

Supplementary Figure S1. Study Design Using Exposure-Lagging Analyses



Panel A shows the main analysis. The cohort entry (start of follow-up) was defined as the point 6 months after colorectal cancer diagnosis. The dashed gray line indicates person-time between colorectal cancer diagnosis and cohort entry, which is not included in the analysis. Exposure was lagged by 6 months after the second prescription of metformin. The time between cohort entry and the end of the lag period is counted as unexposed person-time and is indicated by the solid blue line. The time after the end of the 6-month lag period is counted as exposed person-time and is indicated by the solid orange line. When events occurred during the 6-month lag period, patients were considered metformin nonusers. The time after cohort entry was counted as unexposed person-time for metformin nonusers. Panel B shows the sensitivity analysis with no lag. The time after colorectal cancer diagnosis was counted as unexposed person-time until the second metformin prescription, after which it was counted as exposed person-time. Panels C and D show the sensitivity analysis with 1-year and 2-year lags, respectively. Person-time and events were defined as in the main

Supplementary Figure S2. Conditional Landmark Analyses of Mortality Among Diabetic Patients with Colorectal Cancer with vs without Postdiagnostic Metformin After Stabilized Inverse Probability of Treatment Weighting

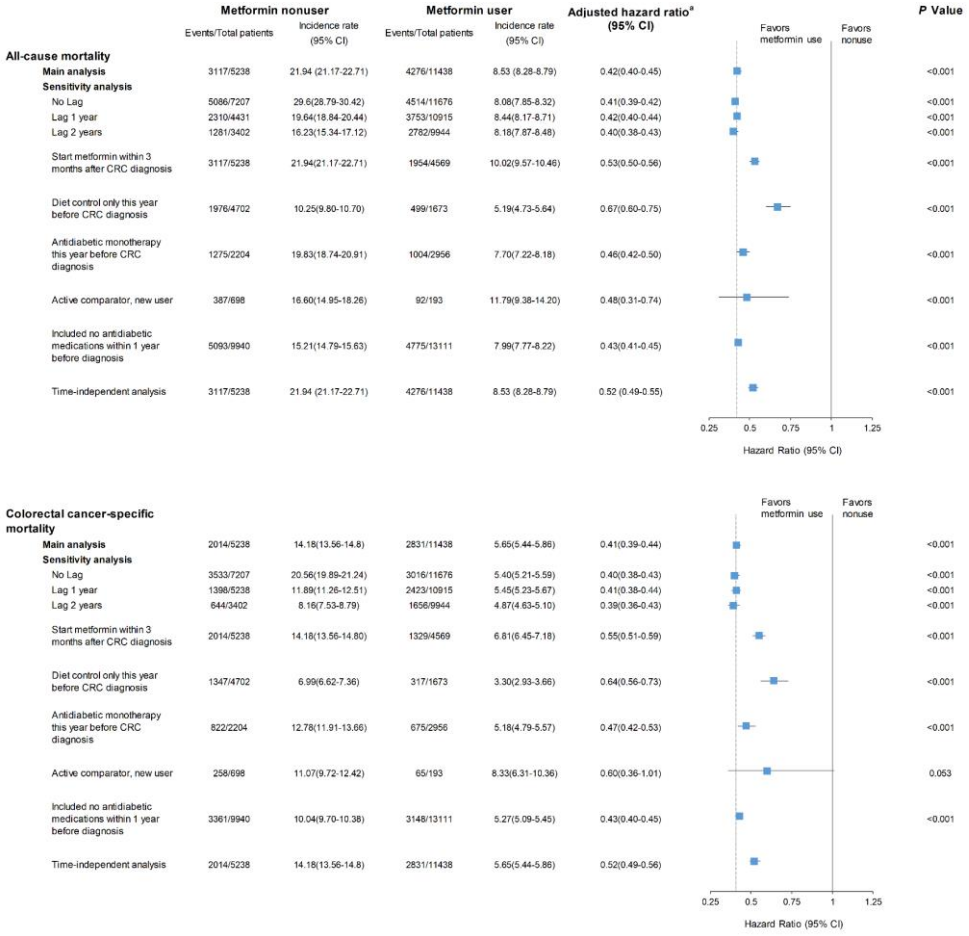


Abbreviations: CRC, colorectal cancer

[a] followed-up starting from 6 months after CRC diagnosis

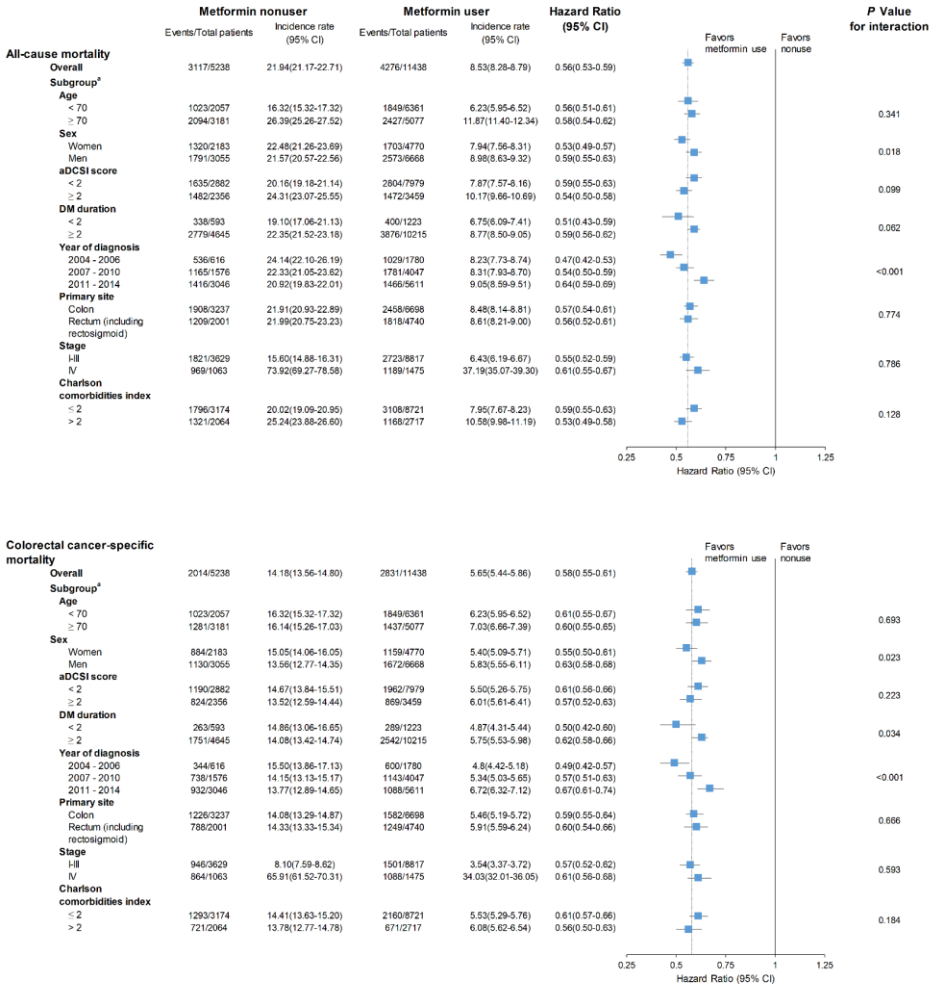
[b] death from causes other than CRC considered as a competing risk event

Supplementary Figure S3. Association of Metformin Use with All-Cause /CRC-Specific Mortality in a Time-Dependent Multivariate Cox Regression Model: Sensitivity Analysis.



[a]Data markers indicate hazard ratios adjusted for age, sex, monthly income, enrollee category, diabetes duration, adapted diabetes complication severity index, antidiabetic medications within 1 year before diagnosis, year of diagnosis, primary site, grade, stage, treatment type, comorbidities, prediagnostic metformin, aspirin, statin, and beta-blockers.

Supplementary Figure S4. Association of Metformin Use and All-Cause /CRC-Specific Mortality after stabilized IPTW: Subgroup Analysis



Propensity score was reestimated and the inverse probability of treatment weights was regenerated for each subgroup.