

**Supplemental Material for Chapter 3:**  
**Use of Oral Diabetes Medications and the Risk of Incident Dementia in US veterans aged  $\geq$**   
**60 years with Type 2 Diabetes**

\*The corresponding work has been accepted by BMJ Open.

**Table S1. Outcome definition and baseline covariates extraction.**

	<b>Extraction start point</b>	<b>Extraction end point</b>	<b>Aggregation method</b>	<b>ICD-9 and ICD-10 code</b>
<b>Outcomes</b>				
All-cause dementia	Index date	First diagnosis record of the outcome or date of censoring	Date of the first diagnosis record of the outcome	ICD-9: 290.x, 294.1, 294.8, 331.0–331.1, 331.82; or ICD-10: G30, G31.0, G31.83, F00, F01, F02, F03, or F05.1
Alzheimer’s disease	Index date	First diagnosis record of the outcome or date of censoring	Date of the first diagnosis record of the outcome	ICD-9 331.0, 290.0-290.3; ICD-10 G30.9
Vascular dementia	Index date	First diagnosis record of the outcome or date of censoring	Date of the first diagnosis record of the outcome	ICD-9 290.4; ICD-10 F01.50, or F01.51
Stroke	Index date	First diagnosis record of the outcome or date of censoring	Date of the first diagnosis record of the outcome	ICD-9: 430-434, 436, 438; ICD-10: I61-I63
Atherosclerosis of arteries	Index date	First diagnosis record of the outcome or date of censoring	Date of the first diagnosis record of the outcome	ICD-9: 440; ICD-10: I70
MI	Index date	First diagnosis record of the outcome or date of censoring	Date of the first diagnosis record of the outcome	ICD-9: 410; ICD-10: I21, I22
Cancer	Index date	First diagnosis record of the outcome or date of censoring	Date of the first diagnosis record of the outcome	ICD-9 140-239; ICD-10 C00-D48
<b>Covariates</b>				
Sex	5 years before baseline	December 2019	Mode of reported sex	-
Age at baseline	-	December 2019	Mean age calculated from all reported and valid dates of birth	-
Race	-	December 2019	Mode of reported race; Due to the small numbers of racial minorities, race was aggregated as White, Black, and Other.	-
Baseline statin use	1.5 years before baseline	Baseline	Coded as users if had >2 statin prescriptions, as non-users otherwise.	-
Elixhauser-based comorbidities <sup>a</sup>				

Coagulopathy	1.5 years before baseline	Baseline	A binary index: coded as 1 if a diagnostic record existed, otherwise, coded as 0.	Used Quan et al.'s list. <sup>1</sup>
Congestive heart failure	1.5 years before baseline	Baseline	A binary index: coded as 1 if a diagnostic record existed, otherwise, coded as 0.	Used Quan et al.'s list. <sup>1</sup>
Drug abuse	1.5 years before baseline	Baseline	A binary index: coded as 1 if a diagnostic record existed, otherwise, coded as 0.	Used Quan et al.'s list. <sup>1</sup>
Hypertension	1.5 years before baseline	Baseline	A binary index: coded as 1 if a diagnostic record existed, otherwise, coded as 0.	Used Quan et al.'s list. <sup>1</sup>
Hypothyroidism	1.5 years before baseline	Baseline	A binary index: coded as 1 if a diagnostic record existed, otherwise, coded as 0.	Used Quan et al.'s list. <sup>1</sup>
Neurological diseases	1.5 years before baseline	Baseline	A binary index: coded as 1 if a diagnostic record existed, otherwise, coded as 0.	Used Quan et al.'s list. <sup>1</sup>
Peripheral vascular disorder	1.5 years before baseline	Baseline	A binary index: coded as 1 if a diagnostic record existed, otherwise, coded as 0.	Used Quan et al.'s list. <sup>1</sup>
Psychoses	1.5 years before baseline	Baseline	A binary index: coded as 1 if a diagnostic record existed, otherwise, coded as 0.	Used Quan et al.'s list. <sup>1</sup>
Valvular diseases	1.5 years before baseline	Baseline	A binary index: coded as 1 if a diagnostic record existed, otherwise, coded as 0.	Used Quan et al.'s list. <sup>1</sup>
No. Other comorbidities <sup>b</sup>	1.5 years before baseline	Baseline	Binary indices were created for each comorbidity. Then sum of the indices was calculated.	Used Quan et al.'s list. <sup>1</sup>
No. Diabetic Complications <sup>c</sup>	1.5 years before baseline	Baseline	Binary indices were created for each complication. Then sum of the indices was calculated.	Used Young et al.'s ICD-9 list <sup>2</sup> . Used Glasheen et al.'s ICD-10 list. <sup>3</sup>
<b>Biomarkers<sup>d</sup></b>				
HbA1c	1.5 years before baseline	Baseline	The latest measure as of baseline	-
BMI	1.5 years before baseline	Baseline	The latest measure as of baseline	-
SBP	1.5 years before baseline	Baseline	The latest measure as of baseline	-
DBP	1.5 years before baseline	Baseline	The latest measure as of baseline	-
HDL	1.5 years before baseline	Baseline	The latest measure as of baseline	-

LDL	1.5 years before baseline	Baseline	The latest measure as of baseline	-
Triglycerides	1.5 years before baseline	Baseline	The latest measure as of baseline	-
Total cholesterol	1.5 years before baseline	Baseline	The latest measure as of baseline	-

<sup>a</sup> Comorbidity conditions other than diabetic complications were selected based on the Elixhauser comorbidities.<sup>4</sup>

<sup>b</sup> The number of other Elixhauser-based comorbidities (include AIDS/HIV, alcohol abuse, deficiency anemia, arthritis, blood loss anemia, chronic lung disease, liver disease, lymphoma, metastatic cancer, paralysis, pulmonary circulation disorder, renal failure, solid tumor without metastasis, peptic ulcer diseases, weight loss) was summed together to be used a continuous variable.<sup>4</sup>

<sup>c</sup> Diabetic complications were selected based on the Diabetes Complications Severity Index.<sup>2</sup>

<sup>d</sup> Baseline biomarkers (except for HbA1c) were imputed by the Markov chain Monte Carlo method. Distributions of covariates remain unchanged after imputation.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; ICD-9, International Classification of Diseases Ninth Revision; ICD-10, International Classification of Diseases Tenth Revision; LDL, low-density lipoprotein cholesterol; MI, myocardial ischemic; NA, not applicable; SBP, Systolic blood pressure.

**Table S2. Standardized mean differences between metformin monotherapy group and other groups with IPTW.**

Covariates	Weighted SMDs				
	SU monotherapy	TZD monotherapy	MET and SU	MET and TZD	SU and TZD
Male	0·01	-0·01	-0·01	-0·05	-0·05
Age at baseline	0·01	-0·07	-0·02	-0·13	0·05
Race					
White	0·01	-0·03	-0·01	-0·07	0·02
Black	-0·01	0·07	0·01	0·04	-0·05
Other	-0·01	-0·04	0·01	0·05	0·03
Annual income					
<\$15 000	0·01	0·01	0·01	0·04	0·03
\$15 000 - \$40 000	-0·01	0·07	0·01	0·03	-0·04
>\$40 000	-0·01	-0·09	-0·01	-0·07	0·02
Categorized BMI					
< 18·5 kg/m <sup>2</sup>	-0·01	0·01	0·01	0·03	-0·02
18·5–25 kg/m <sup>2</sup>	0·01	0·03	0·01	0·03	0·03
25–30 kg/m <sup>2</sup>	0·01	-0·01	0·01	-0·01	0·09
> 30 kg/m <sup>2</sup>	-0·01	-0·02	-0·01	-0·01	-0·10
Baseline statins use	-0·01	-0·18	0·01	-0·05	-0·05
Calendar year of baseline	-0·02	-0·23	0·01	-0·11	0·12
Elixhauser-based comorbidities <sup>b</sup>					
Coagulopathy	0·01	-0·04	0·01	-0·02	-0·03
Congestive heart failure	-0·01	-0·09	-0·01	-0·04	-0·08
Drug abuse	-0·01	0·05	-0·01	0·08	-0·02
Hypertension	0·01	0·04	0·01	0·04	0·03
Hypothyroidism	0·01	-0·02	-0·01	0·03	-0·01
Neurological diseases	-0·01	0·01	0·01	0·01	0·09
Peripheral vascular disorder	-0·01	0·02	0·01	0·08	-0·04
Psychoses	-0·01	-0·06	0·01	-0·03	-0·05
Valvular diseases	-0·01	-0·01	0·01	-0·01	-0·01
Depression	-0·01	-0·07	-0·01	-0·08	0·08
No. other comorbidities, mean (SD) <sup>c</sup>	-0·01	0·09	-0·01	-0·06	0·13
No. diabetes complications, mean (SD) <sup>d</sup>	-0·01	0·05	-0·01	-0·01	0·06
Biomarkers					
HbA1c, mean (SD), %	-0·03	-0·33	0·19	-0·13	-0·28
SBP, mean (SD), mm Hg	0·01	-0·04	0·02	0·01	0·01
DBP, mean (SD), mm Hg	0·01	0·01	0·02	0·09	-0·02
HDL, mean (SD), mg/dL	0·01	-0·04	0·01	-0·06	0·03
LDL, mean (SD), mg/dL	0·01	0·06	0·01	-0·01	0·08

<b>Covariates</b>	<b>Weighted SMDs</b>				
	<b>SU monotherapy</b>	<b>TZD monotherapy</b>	<b>MET and SU</b>	<b>MET and TZD</b>	<b>SU and TZD</b>
Triglycerides, mean (SD), mg/dL	-0·01	0·01	0·01	0·03	0·01
Total cholesterol, mg/dL	0·01	0·04	0·01	0·01	0·09

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; IPTW, inverse probability treatment weighting; LDL, low-density lipoprotein cholesterol; MET, metformin; SBP, Systolic blood pressure; SMD, standardized mean differences; SU, sulfonylurea; TZD, thiazolidinedione.

**Table S3. Baseline characteristics and the rate of the outcomes stratified by types of treatment with IPTW. <sup>a</sup>**

	<b>MET monotherapy (n = 296201)</b>	<b>SU monotherapy (n = 125870)</b>	<b>TZD monotherapy (n = 5432)</b>	<b>MET and SU (n = 122928)</b>	<b>MET and TZD (n = 4132)</b>	<b>SU and TZD (n = 4543)</b>
Male (%)	284723 (96)	123459 (98)	5312 (98)	119750 (97)	4028 (97)	4484 (99)
Age at baseline	65 (8·1)	68·6 (9·7)	69·6 (9·2)	64 (8·1)	64·5 (8·3)	69·4 (9·1)
Race						
White	222 797 (75)	100 281 (80)	4646 (86)	94 218 (77)	3534 (86)	3837 (84)
Black	35 669 (12)	16 083 (13)	459 (8·4)	14 057 (11)	327 (7·9)	508 (11)
Other	37 735 (13)	9506 (7·6)	327 (6)	14 653 (12)	271 (6·6)	198 (4·4)
Annual income						
<\$15 000	72 115 (24)	33 549 (27)	1388 (26)	29 968 (24)	916 (22)	1109 (24)
\$15 000 - \$40 000	157 028 (53)	66 979 (53)	2591 (48)	65 057 (53)	2149 (52)	2268 (50)
>\$40 000	67 058 (23)	25 342 (20)	1453 (27)	27 903 (23)	1067 (26)	1166 (26)
Categorized BMI						
< 18·5 kg/m <sup>2</sup>	228 (0·1)	200 (0·2)	7 (0·1)	108 (0·1)	1 (0)	4 (0·1)
18·5–25 kg/m <sup>2</sup>	17 035 (5·8)	11 749 (9·3)	511 (9·4)	7582 (6·2)	278 (6·7)	321 (7·1)
25–30 kg/m <sup>2</sup>	85 304 (29)	43 731 (35)	1915 (35)	34 709 (28)	1256 (30)	1492 (33)
> 30 kg/m <sup>2</sup>	19 3634 (65)	70 190 (56)	2999 (55)	80 529 (66)	2597 (63)	2726 (60)
Baseline statin use (%)	12 9763 (44)	53 737 (43)	2406 (44)	55 282 (45)	2006 (49)	2409 (53)
Calendar year of baseline						
2002 to 2005	40 207 (14)	48 441 (38)	2303 (42)	34 316 (28)	1594 (39)	2415 (53)
2006 to 2010	100 749 (34)	48 754 (39)	2500 (46)	43 270 (35)	2193 (53)	1807 (40)
2011 to 2015	107 799 (36)	22 643 (18)	465 (8·6)	34 603 (28)	226 (5·5)	274 (6)

	<b>MET monotherapy (n = 296201)</b>	<b>SU monotherapy (n = 125870)</b>	<b>TZD monotherapy (n = 5432)</b>	<b>MET and SU (n = 122928)</b>	<b>MET and TZD (n = 4132)</b>	<b>SU and TZD (n = 4543)</b>
2016 to 2019	47 446 (16)	6032 (4·8)	164 (3)	10 739 (8·7)	119 (2·9)	47 (1)
<b>Elixhauser-based comorbidities<sup>b</sup></b>						
Coagulopathy	4440 (1·5)	3043 (2·4)	88 (1·6)	1694 (1·4)	48 (1·2)	52 (1·1)
Congestive heart failure	13 400 (4·5)	13 270 (11)	308 (5·7)	6057 (4·9)	116 (2·8)	358 (7·9)
Drug abuse	15 006 (5·1)	4608 (3·7)	83 (1·5)	5188 (4·2)	69 (1·7)	67 (1·5)
Hypertension	235 789 (80)	102 587 (82)	4431 (82)	96 414 (78)	3174 (77)	3743 (82)
Hypothyroidism	21 623 (7·3)	9249 (7·3)	441 (8·1)	7262 (5·9)	265 (6·4)	312 (6·9)
Neurological diseases	5106 (1·7)	2151 (1·7)	49 (0·9)	1648 (1·3)	43 (1)	42 (0·9)
Peripheral vascular disorder	18 680 (6·3)	10 630 (8·4)	393 (7·2)	7180 (5·8)	211 (5·1)	348 (7·7)
Psychoses	9317 (3·1)	3828 (3)	96 (1·8)	3368 (2·7)	60 (1·5)	85 (1·9)
Valvular diseases	7452 (2·5)	4753 (3·8)	165 (3)	2719 (2·2)	81 (2)	137 (3)
Depression	81 528 (28)	25 854 (21)	902 (17)	28 314 (23)	823 (20)	614 (14)
No other comorbidities <sup>c</sup>	1·5 (0·8)	1·6 (0·8)	1·5 (0·7)	1·5 (0·7)	1·4 (0·6)	1·4 (0·7)
No. diabetes complications <sup>d</sup>	0·9 (0·9)	1·1 (0·9)	1 (0·9)	0·8 (0·9)	0·7 (0·8)	1 (0·9)
<b>Biomarkers<sup>b</sup></b>						
HbA1c, %	6·6 (0·8)	6·7 (1)	6·5 (0·8)	7·4 (1·3)	6·8 (1)	7·1 (1·1)
SBP, mm Hg	134 (12·7)	137 (14·6)	136·5 (14·9)	137 (14·3)	136 (14·2)	139 (15·8)
DBP, mm Hg	77 (8·3)	75 (9)	73 (8·9)	78 (8·7)	76 (8·7)	74 (9·2)
HDL, mg/dL	42 (8·4)	41 (8·1)	43 (8·4)	41 (7·9)	43 (8·1)	41 (7·4)
LDL, mg/dL	100 (28·8)	101 (28·8)	99 (28·2)	101 (29·7)	99 (28·3)	101 (28·8)
Triglycerides, mg/dL	173 (82)	178 (83·3)	175 (80·9)	187 (88)	178 (83·1)	189 (84·3)



	<b>MET monotherapy (n = 296201)</b>	<b>SU monotherapy (n = 125870)</b>	<b>TZD monotherapy (n = 5432)</b>	<b>MET and SU (n = 122928)</b>	<b>MET and TZD (n = 4132)</b>	<b>SU and TZD (n = 4543)</b>
Total cholesterol, mg/dL	175 (34.9)	176 (35.2)	176 (34.8)	178 (36.6)	176 (35.3)	179 (36.5)
Outcome rates, cases per 1000 person-years (No. events)						
All-cause dementia	6.2 (11521)	12.9 (11689)	9.9 (450)	7.5 (6725)	6.3 (247)	13.4 (493)
AD	0.6 (1169)	1.3 (1200)	1.2 (62)	0.7 (634)	0.5 (22)	1.4 (55)
VaD	0.5 (949)	1.0 (922)	0.4 (19)	0.7 (611)	0.3 (11)	0.8 (30)

<sup>a</sup> Data are presented as number (percentage) of patients.

<sup>b</sup> Data are presented as mean (SD) of biomarker measures.

<sup>c</sup> Comorbidity conditions other than diabetes complications were selected based on Elixhauser comorbidities.<sup>27</sup>

<sup>d</sup> The number of other comorbidities (include AIDS/HIV, alcohol abuse, deficiency anemia, arthritis, blood loss anemia, chronic lung disease, liver disease, lymphoma, metastatic cancer, paralysis, pulmonary circulation disorder, renal failure, solid tumor without metastasis, peptic ulcer diseases, weight loss) was summed together to be a continuous variable.

<sup>e</sup> Diabetes complications were selected based on the Diabetes Complications Severity Index.<sup>23</sup>

Abbreviations: AD, Alzheimer's disease; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MET, metformin; SBP, systolic blood pressure; SD, standard deviation; SU, sulfonylureas; TZD, thiazolidinedione; VaD, vascular dementia.

SI conversion factors: to convert HbA1c to proportion of total hemoglobin, multiply by 0.01; HDL, LDL, and total cholesterol to mmol/L, multiply by 0.0259; and triglycerides to mmol/L, multiply by 0.0113.

**Table S4. Follow-up time and censoring reasons, after one year of treatment.<sup>a</sup>**

One-year treatment	Follow-up time, year <sup>b</sup>	Censoring reasons among participants who did not develop any dementia		
		Death	Reached Dec 12, 2019	Lost to follow-up
MET	6.3 (3.9)	43164 (15.16)	58917 (20.7)	182599 (64.14)
SU	7.2 (4.2)	42167 (36.93)	13142 (11.51)	58872 (51.56)
TZD	8.4 (4.3)	1954 (39.22)	653 (13.11)	2375 (47.67)
MET and SU	7.3 (4.2)	25269 (21.75)	20762 (17.87)	70172 (60.39)
MET and TZD	9.5 (4.1)	1010 (26)	652 (16.78)	2223 (57.22)
SU and TZD	8.1 (4.3)	1876 (46.32)	387 (9.56)	1787 (44.12)

<sup>a</sup> Data presented as count (percentage).

<sup>b</sup> Data presented as mean (standard deviation).

Abbreviations: MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione.

**Table S5. Risk of vascular diseases and cancer after one-year treatment compared with metformin monotherapy.**

	MI or AOA			Metastatic Cancer (negative control outcome)		
	No. Events	Unadjusted HR (95% CI)	Adjusted HR (95% CI) <sup>a</sup>	No. Events	Unadjusted HR (95% CI)	Adjusted HR (95% CI) <sup>a</sup>
SU (n=125870)	16439	<b>1.07 (1.05, 1.09)</b>	<b>1.07 (1.04, 1.09)</b>	32860	1.01 (0.99–1.02)	1.01 (0.99–1.02)
TZD (n=5432)	541	<b>0.85 (0.83, 0.87)</b>	<b>0.84 (0.82, 0.86)</b>	1340	0.93 (0.89–0.95)	0.98 (0.95–1.01)
MET and SU (n=122928)	15650	<b>1.06 (1.04, 1.08)</b>	<b>1.09 (1.07, 1.11)</b>	26170	1.00 (0.99–1.02)	0.99 (0.97–1.00)
MET and TZD (n=4132)	511	<b>0.96 (0.94, 1.01)</b>	0.95 (0.93, 1.02)	961	<b>0.93 (0.91–0.94)</b>	<b>0.90 (0.89–0.92)</b>
SU and TZD (n=4543)	655	<b>1.14 (1.12, 1.17)</b>	<b>1.20 (1.17, 1.22)</b>	1132	<b>0.94 (0.93–0.96)</b>	0.97 (0.96–1.01)

Bold font represents estimated hazard ratios were statistically different from zero with p-value < 0.05.

<sup>a</sup> Models were adjusted for age, calendar year of individual baseline, statin use, HbA1c, systolic blood pressure, and diastolic blood pressure at baseline.

Abbreviations: AOA, atherosclerosis of arteries; CI, confidence interval; HbA1c, glycosylated hemoglobin; HR, hazard ratio; MET, metformin; MI, myocardial ischemic; SU, sulfonylurea; TZD, thiazolidinedione.

**Table S6. Estimated hazard ratio and their 95% CI of all-cause dementia defined by both ICD codes and anti-dementia medications, compared with metformin monotherapy.**

	<b>Unadjusted HR (95% CI)</b>	<b>Adjusted HR (95% CI)<sup>a</sup></b>
<b>Primary analysis: one-year exposure</b>		
SU	<b>1·12 (1·09–1·14)</b>	<b>1·11 (1·08–1·13)</b>
TZD	<b>0·85 (0·82–0·88)</b>	<b>0·84 (0·81–0·86)</b>
MET and SU	<b>1·16 (1·13–1·19)</b>	<b>1·13 (1·10–1·16)</b>
MET and TZD	<b>0·95 (0·92–0·98)</b>	<b>0·90 (0·87–0·93)</b>
SU and TZD	<b>1·09 (1·05–1·12)</b>	1·03 (0·99–1·07)
<b>Exploratory analysis: two-year exposure</b>		
SU	<b>1·17 (1·14–1·21)</b>	<b>1·13 (1·10–1·17)</b>
TZD	<b>0·66 (0·64–0·69)</b>	<b>0·69 (0·66–0·72)</b>
MET and SU	<b>0·90 (0·87–0·93)</b>	<b>0·93 (0·90–0·96)</b>
MET and TZD	<b>0·72 (0·69–0·75)</b>	<b>0·74 (0·71–0·78)</b>
SU and TZD	<b>0·89 (0·85–0·92)</b>	<b>0·92 (0·88–0·95)</b>

Bold font represents estimated hazard ratios were statistically different from with p-value < 0.05.

<sup>a</sup> Models were adjusted for age, calendar year of individual baseline, statin use, HbA1c, systolic blood pressure, diastolic blood pressure, and the history of congestive heart failure at baseline.

Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; HR, hazard ratio; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione.

**Table S7. Estimated hazard ratio (95% CI) comparing ADM treatment with metformin monotherapy for all-cause dementia onset among T2D patients without CHF, MI, or ATH diseases at baseline**

	No CHF history		No MI or AOA history	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI) <sup>a</sup>	Unadjusted HR (95% CI)	Adjusted HR (95% CI) <sup>a</sup>
<b>Primary analysis: one-year exposure</b>				
SU	<b>1.15 (1.11–1.18)</b>	<b>1.14 (1.11–1.17)</b>	<b>1.13 (1.10, 1.16)</b>	<b>1.13 (1.10, 1.16)</b>
TZD	<b>0.83 (0.80–0.86)</b>	<b>0.80 (0.77–0.83)</b>	<b>0.77 (0.74, 0.80)</b>	<b>0.77 (0.73, 0.80)</b>
MET and SU	<b>1.18 (1.14–1.21)</b>	<b>1.15 (1.11–1.18)</b>	<b>1.15 (1.11–1.18)</b>	<b>1.15 (1.11–1.19)</b>
MET and TZD	<b>0.98 (0.94–1.02)</b>	<b>0.93 (0.90–0.97)</b>	<b>0.89 (0.86, 0.92)</b>	<b>0.89 (0.86, 0.92)</b>
SU and TZD	<b>1.13 (1.09–1.17)</b>	<b>1.06 (1.02–1.10)</b>	<b>1.06 (1.02, 1.09)</b>	<b>1.06 (1.01, 1.09)</b>
<b>Exploratory analysis: two-year exposure</b>				
SU	<b>1.19 (1.16–1.23)</b>	<b>1.16 (1.12–1.20)</b>	<b>1.20 (1.16, 1.24)</b>	<b>1.17 (1.13, 1.21)</b>
TZD	<b>0.62 (0.59–0.65)</b>	<b>0.65 (0.62–0.68)</b>	<b>0.62 (0.59, 0.65)</b>	<b>0.65 (0.62, 0.68)</b>
MET and SU	<b>0.90 (0.87–0.93)</b>	<b>0.94 (0.91–0.97)</b>	<b>0.91 (0.88, 0.94)</b>	<b>0.94 (0.91, 0.97)</b>
MET and TZD	<b>0.70 (0.67–0.73)</b>	<b>0.72 (0.69–0.76)</b>	<b>0.68 (0.65, 0.72)</b>	<b>0.71 (0.67, 0.74)</b>
SU and TZD	<b>0.89 (0.85–0.93)</b>	<b>0.94 (0.91–0.98)</b>	<b>0.89 (0.85, 0.93)</b>	<b>0.92 (0.88, 0.96)</b>

Bold font represents estimated hazard ratios were statistically different from with p-value < 0.05.

<sup>a</sup> Models were adjusted for age, calendar year of individual baseline, statin use, HbA1c, systolic blood pressure, and diastolic blood pressure at baseline.

Abbreviations: AOA, atherosclerosis of arteries; CHF, congestive heart failure; CI, confidence interval; HbA1c, glycated hemoglobin; HR, hazard ratio; MET, metformin; MI, myocardial ischemic; SU, sulfonylurea; TZD, thiazolidinedione.

**Table S8. Association between days of supply categories of SU or TZD uses and the onset of all-cause dementia compared with metformin monotherapy.**

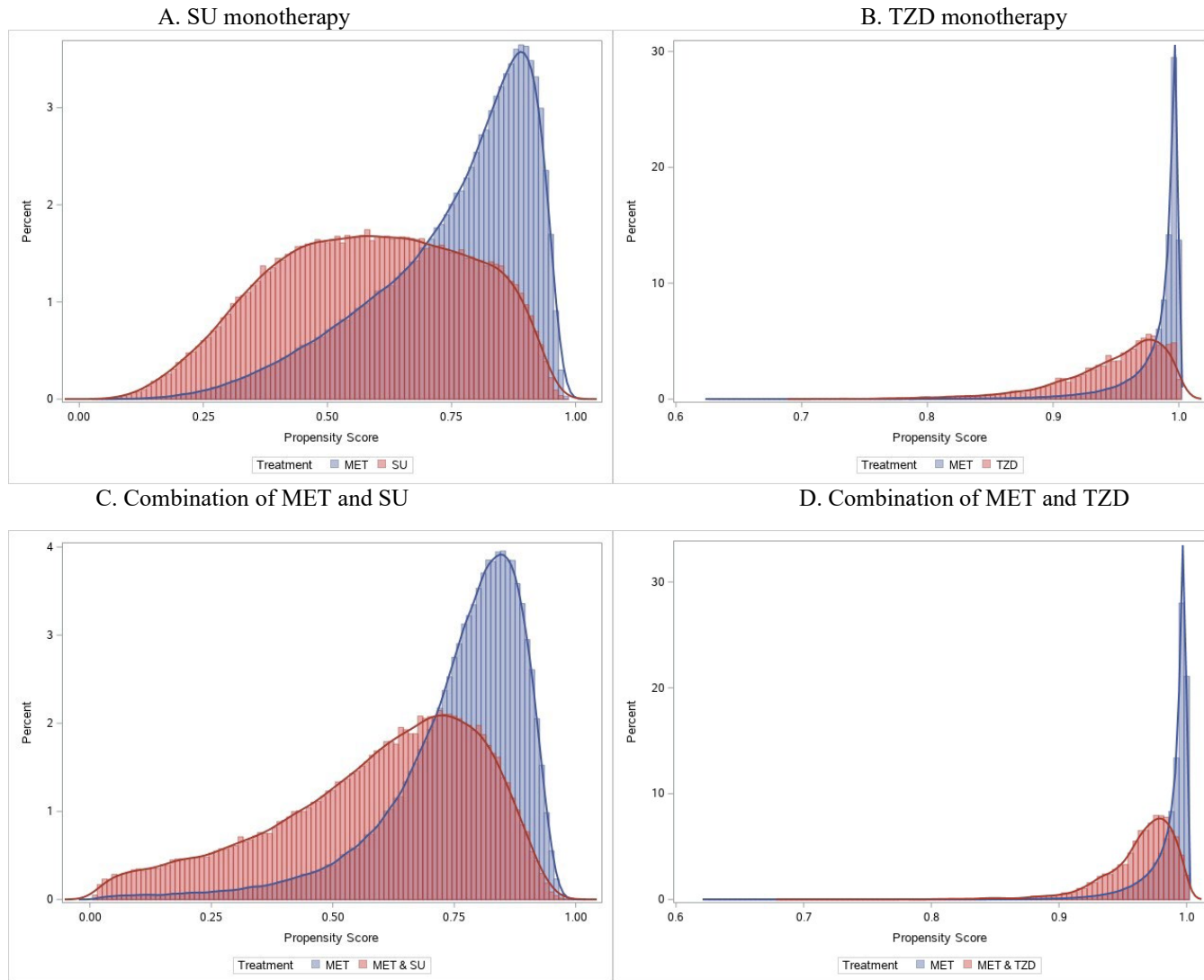
<b>Baseline-adjusted HR (95% CI)<sup>b</sup></b>				
<b>Primary analysis: one-year exposure</b>				
<b>Treatment<sup>a, b</sup></b>	<b>SU supply days during the exposure window</b>		<b>TZD supply days during the exposure window</b>	
	<b>1/3 to 2/3</b>	<b>&gt;2/3</b>	<b>1/3 to 2/3</b>	<b>&gt;2/3</b>
SU	0.99 (0.93–1.07)	1.13 (1.10–1.16)	-	-
TZD	-	-	0.79 (0.71–0.89)	0.78 (0.75–0.81)
MET and SU	1.15 (1.08–1.23)	1.14 (1.11–1.18)	-	-
MET and TZD	-	-	1.04 (0.95–1.13)	0.89 (0.85–0.92)
<b>Exploratory analysis: two-years exposure</b>				
<b>Treatment<sup>a, b</sup></b>	<b>SU supply days during the exposure window</b>		<b>TZD supply days during the exposure window</b>	
	<b>1/3 to 2/3</b>	<b>&gt;2/3</b>	<b>1/3 to 2/3</b>	<b>&gt;2/3</b>
SU	1.07 (0.99–1.17)	1.15 (1.11–1.19)	-	-
TZD	-	-	0.79 (0.7–0.9)	0.64 (0.61–0.67)
MET and SU	0.82 (0.75–0.9)	0.92 (0.89–0.96)	-	-
MET and TZD	-	-	0.79 (0.71–0.88)	0.67 (0.64–0.7)

<sup>a</sup> The dual therapy of SU and TZD was not assessed.

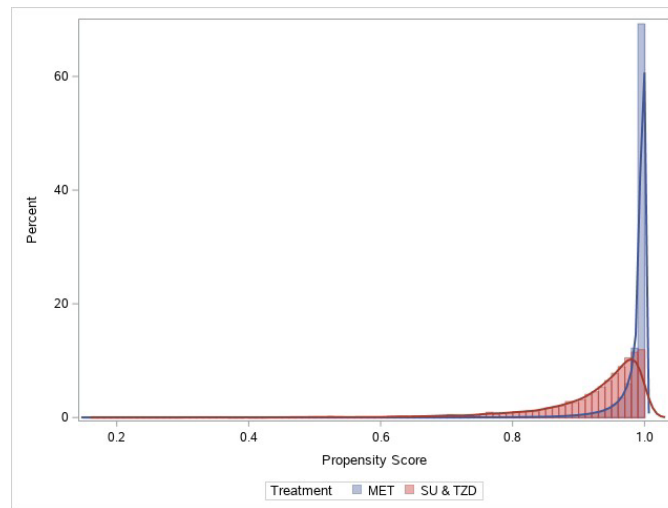
<sup>b</sup> Models were adjusted for age, calendar year of individual baseline, statin use, HbA1c, systolic blood pressure, diastolic blood pressure, and the history of congestive heart failure at baseline, as these variables remained unbalanced after matching in at least one comparison.

Abbreviations: CI, confidence interval; HbA1c, glycosylated hemoglobin; HR, hazard ratio; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione.

**Figure S1. The distributions of unadjusted propensity scores across treatment groups compared with the Metformin monotherapy group.**



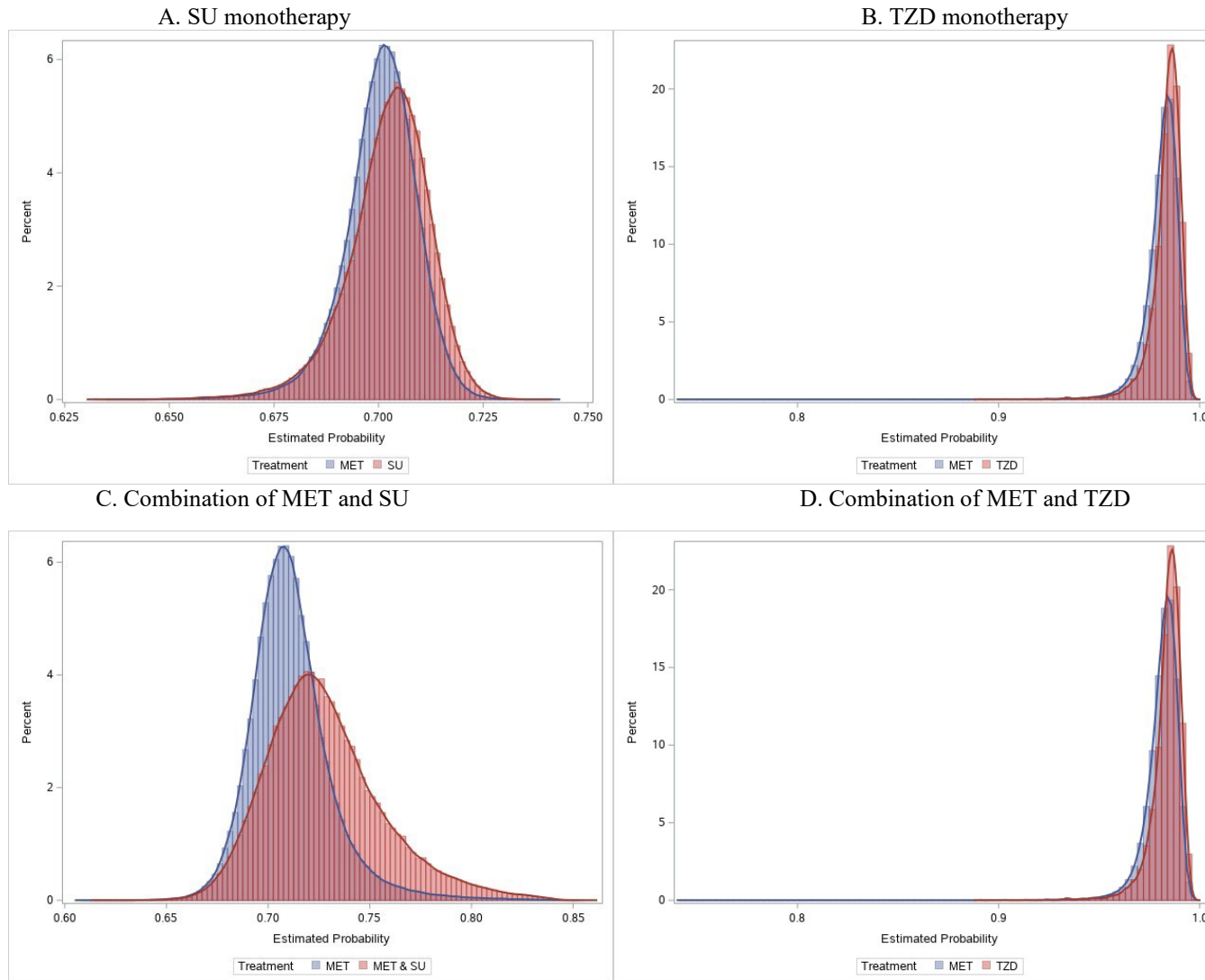
### E. Combination of SU and TZD



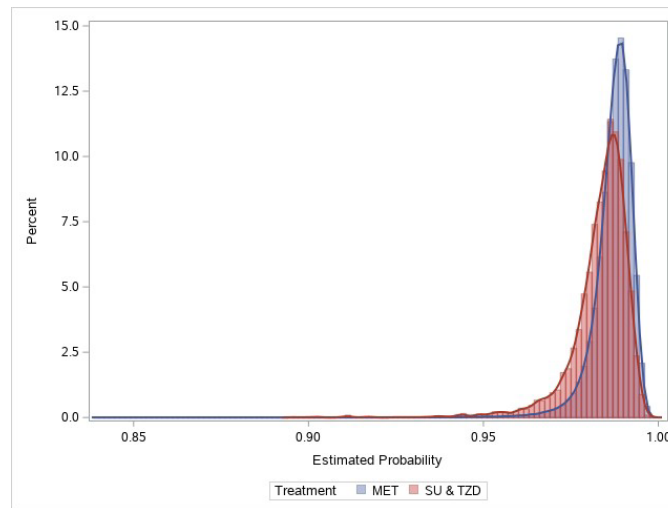
Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; HR, hazard ratio; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione.



**Figure S2. The distributions of the stabilized propensity scores across treatment groups compared with Metformin monotherapy group.**

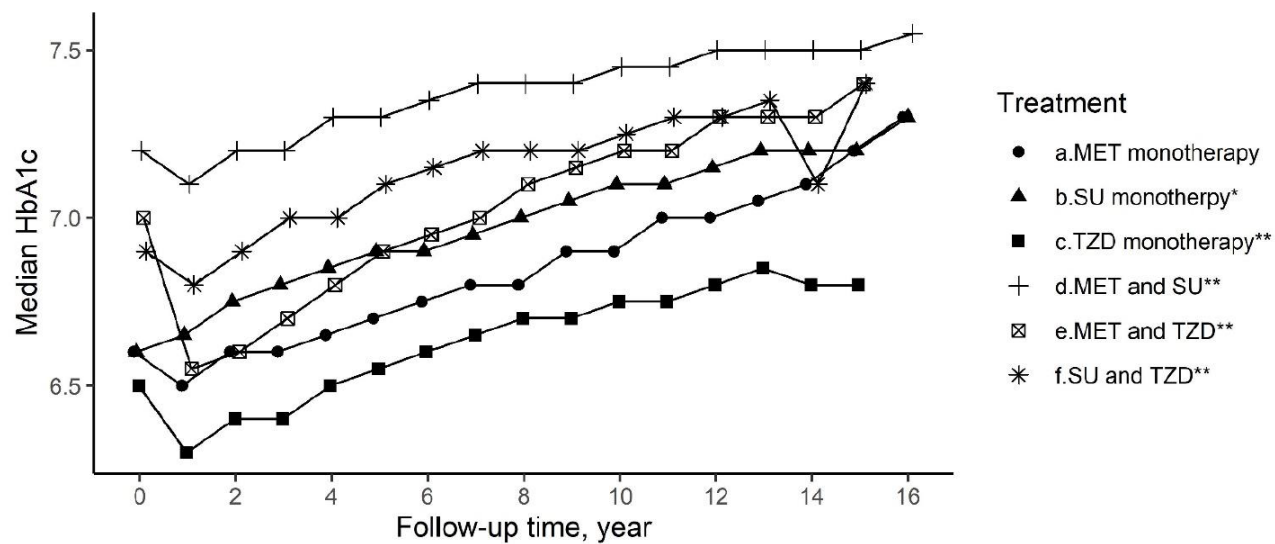


### E. Combination of SU and TZD



Abbreviations: CI, confidence interval; HbA<sub>1c</sub>, glycated hemoglobin; HR, hazard ratio; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione.

Figure S3. HbA1c median profile plots across treatment groups during the follow-up period after one year of treatment.



Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; HR, hazard ratio; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione.  
 \* 0.01 < P < 0.05; \*\* P < 0.01

## Reference

1. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43(11):1130-1139.
2. Young BA, Lin E, Von Korff M, et al. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. *Am J Manag Care*. 2008;14(1):15-23.
3. Glasheen WP, Renda A, Dong Y. Diabetes Complications Severity Index (DCSI)-Update and ICD-10 translation. *J Diabetes Complications*. 2017;31(6):1007-1013.
4. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Medical care*. 1998;8-27.