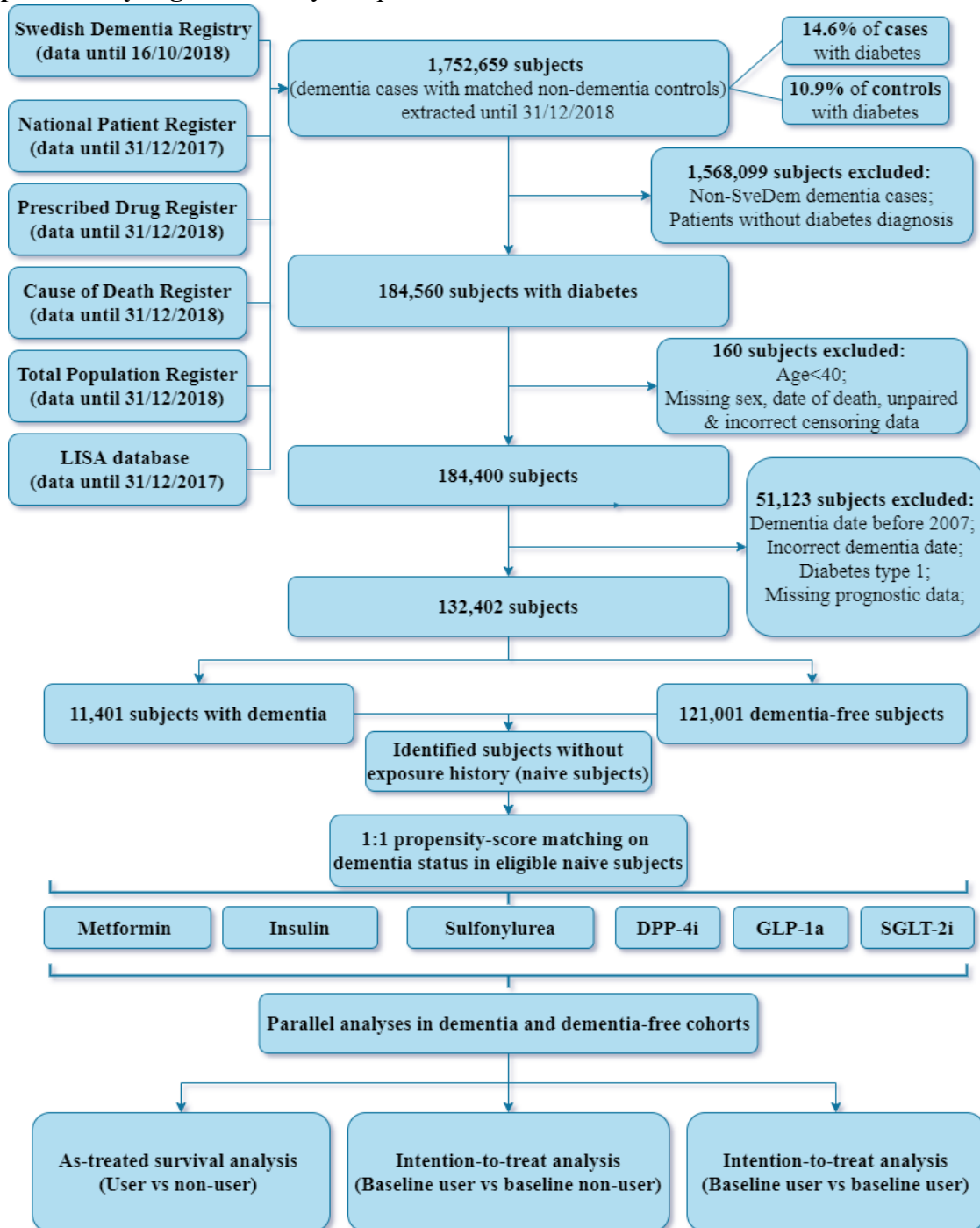# Supplementary Material

Glucose-Lowering Medications and Post-Dementia Survival in Patients with Diabetes and Dementia

Supplementary Figure 1. Study sample selection

DPP4i, dipeptidyl-peptidase-4 inhibitors; GLP-1a, glucagon-like peptide-1 analogues; SGLT-2i, sodium-glucose cotransporter-2 inhibitors

Supplementary List 1. Sampling controls from the Total Population Register, ICD-10 codes for inclusion and exclusion criteria for dementia cases and matching process on dementia status.

Dementia-free controls were sampled from the Total Population Register. The exclusion criteria for dementia-free controls in the original data extraction were as follows:

a. Dementia diagnosis recorded in SveDem

b. ICD-10 codes F00-F03, G30, G31 (see inclusionary codes below) recorded by the Swedish National Patient Register (Patient Register) or Swedish Cause of Death Register (Death Register);

c. ATC code N06D (anti-dementia drugs) recorded by the Swedish Prescribed Drug Register (Drug Register).

In addition, subjects with record of ICD-10 codes F05-F09, G32 (see exclusionary codes below) were not considered as controls (nor as dementia cases). Overall, up to four dementia-free controls per one dementia case were matched on birth year (±3 years), sex, and the county of residence and assigned an index date matching with the dementia diagnosis date (1,328,035 controls matched with 424,624 cases in total). Out of this original data, we selected only subjects diagnosed with diabetes with and without dementia diagnosis, where dementia diagnosis originated only from SveDem (184,560 subjects in total). After excluding subjects with incorrect or missing data and patients with type 1 diabetes, the cohort consisted of 132,402 subjects with diabetes, of which 11,401 (8.6%) had diagnosis of dementia and 121,001 (91.4%) were dementia-free (Supplementary Figure 1).

Inclusionary codes for dementia

    a. F00 Dementia in Alzheimer disease

    b. F01 Vascular dementia

    c. F02 Dementia in other diseases classified elsewhere

    d. F03 Unspecified dementia

    e. G30 Alzheimer disease

    f. Other degenerative diseases of nervous system, not elsewhere classified

Exclusionary codes for dementia

    a.   F05 Delirium, not induced by alcohol and other psychoactive substances

    b.   F06 Other mental disorders due to brain damage and dysfunction and to physical diseases

    c.   F07 Personality and behavioral disorders due to brain disease, damage and dysfunction

    d.   F09 Unspecified organic or symptomatic mental disorder

    e.   G32 Other degenerative disorders of nervous system in diseases classified elsewhere

Propensity-score matching on dementia status

From the whole cohort of 132,402 subjects, we sampled PS-matched pairs of dementia – dementia-free subjects and then analyzed the associations between GLD use and mortality within the PS-matched dementia and dementia-free cohorts in parallel analytical branches (dementia and dementia-free were analyzed separately and not directly compared).

    a.   Only subjects eligible to be new users were considered for matching (e.g., only subjects who had no history of insulin usage prior to the one-year interval before index date).

    b.   The 1:1 nearest-neighbor matching with 0.1 caliper of the logit of the propensity score combined with exact matching on the index year (year of the index date) was used to create the dementia – dementia-free pairs. Baseline characteristics used to generate PS included age, sex, Charlson comorbidity score, renal disease, diabetes type, diabetes duration, income category, use of statins, antihypertensive, diuretic, antithrombotic, antipsychotic and antidepressant drugs and other GLD (dispensed prior to and including the index date).

    c.   In total, 3,962 dementia – dementia-free PS-matched pairs were identified for new-user analysis of metformin; 7,489 pairs for new-user analysis of insulin; 7,686 sulfonylurea; 10,756 for DPP-4i; 11,243 for GLP-1a; 11,333 for SGLT-2i; 407 for new-users of insulin versus new-users of sulfonylurea; 291 for DPP-4i versus sulfonylurea; 551 for DPP-4i versus insulin

    d.   Overall, $\geq 96\%$ of the original eligible dementia subjects were retained for each medication analysis and all standardized mean differences were below 0.1 (balance between dementia cohorts is not shown).


The PS-matched dementia and dementia-free cohorts were subsequently separated and analyzed in parallel. Inverse-probability weighting and propensity-score matching on exposure were used to adjust for confounding between exposure groups.

Supplementary Table 1. Baseline characteristics of the whole cohort by dementia status

Patients with diabetes (132,402)		Dementia 11,401 subjects	Dementia-free 121,001 subjects	p
Age, y		79.7 (7.1)	80.6 (7.2)	<0.001
Females		5,556 (48.7%)	61,163 (50.5%)	<0.001
Cohabitation	Living alone	4,730 (41.5%)		
	Living with another adult	5,609 (49.2%)	n/a	
	Institutionalized	1,062 (9.3%)		
Dementia type	Alzheimer's disease	2,606 (22.9%)		
	Mixed-pathology dementia	2,498 (21.9%)		
	Vascular dementia	3,151 (27.6%)		
	Lewy body dementia	272 (2.4%)	n/a	
	Frontotemporal dementia	132 (1.2%)		
	Unspecified dementia	2,482 (21.8%)		
	Other dementia	260 (2.3%)		
Mini-Mental State Examination, points		21 (6)	n/a	
Charlson comorbidity score		2 (2)	1 (2)	<0.001
Renal disease		773 (6.8%)	9,002 (7.4%)	0.01
Diabetes type	Type 2	7,177 (63.0%)	71,545 (59.1%)	<0.001
	Other/unspecified	4,224 (37.0%)	49,456 (40.9%)	
Diabetes duration, years		7.5 (6)	6.5 (6)	<0.001
Antihypertensives		9,097 (79.8%)	97,068 (80.2%)	0.27
Diuretics		5,527 (48.5%)	68,429 (56.6%)	<0.001
Statins		7,707 (67.6%)	73,904 (61.1%)	<0.001
Antithrombotic drugs		8,478 (74.4%)	86,260 (71.3%)	<0.001
Antipsychotics		791 (6.9%)	3,791 (3.1%)	<0.001
Antidepressants		4,168 (36.6%)	24,983 (20.6%)	<0.001
Cholinesterase inhibitors		1,188 (10.4%)	n/a	
Other GLDs				
Income category	Low	3,337 (29.6%)	40,174 (33.2%)	
	Middle	3,906 (34.3%)	39,787 (32.9%)	<0.001
	High	4,118 (36.1%)	41,040 (33.9%)	
Mortality		5,915 (51.9%)	56,378 (46.6%)	<0.001

Age is described as mean (SD). Charlson comorbidity index, Diabetes duration, and Mini-Mental State Examination are described as median (IQR). All other variables are described as n (%). Dementia with Lewy bodies and Parkinson's disease dementia were merged into one group "Lewy body dementia".

Supplementary Figure 2. Exposure-time assignment in the as-treated analytical cohorts
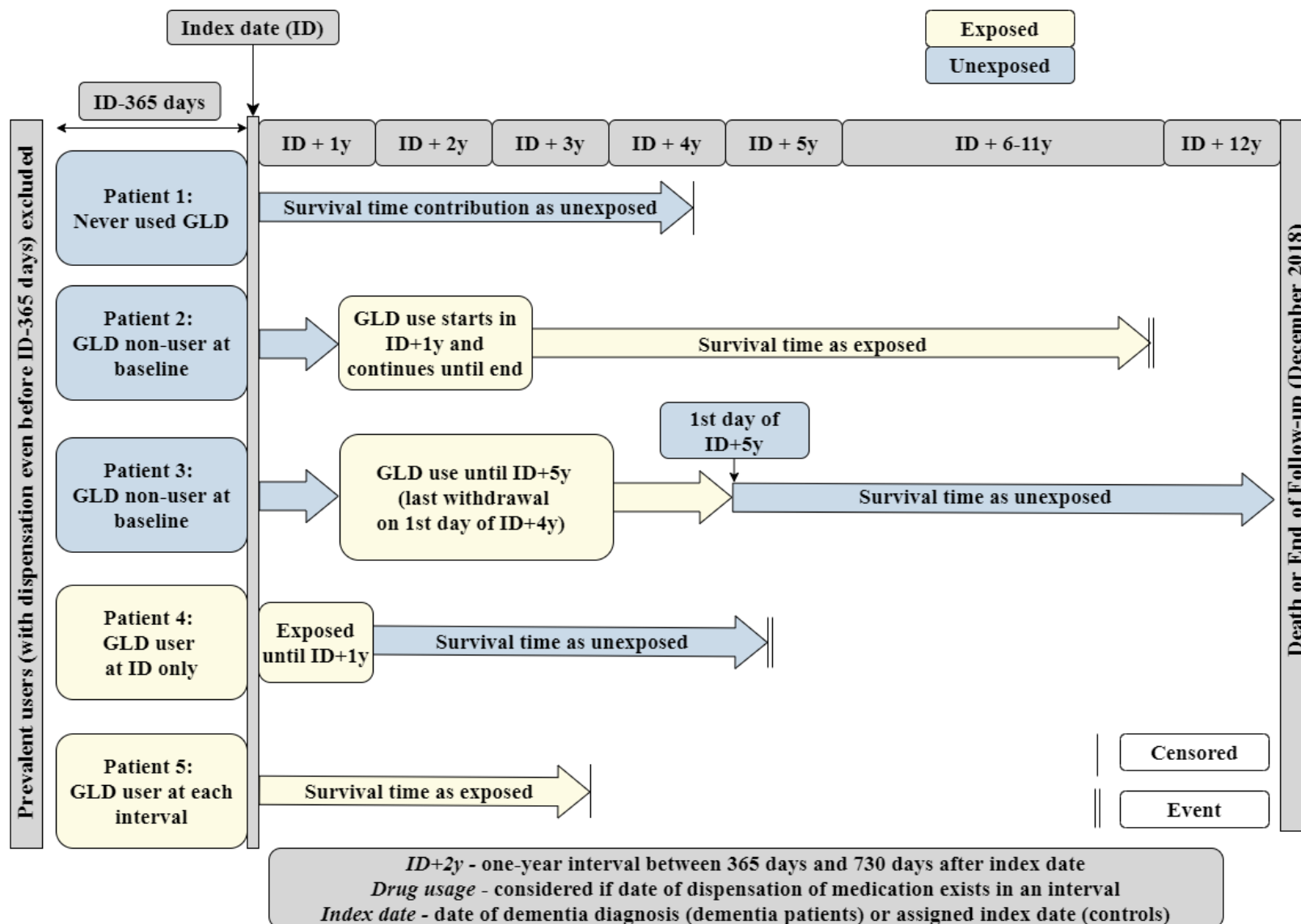
GLD, glucose-lowering drug

Supplementary Algorithm 1. Diabetes types according to Patient and Drug Register

Type 1 diabetes was assigned if:

1. Patient had ICD-10 code E10 in the Patient Register, no other ICD-10 code relevant to diabetes (E11-E14) and had been on insulin-only antidiabetic treatment as recorded in the Drug Register. ("Definite type 1")

2. Patient had ICD-10 code E10 in the Patient Register, as well as other relevant ICD-10 diabetes code (E11-E14), the ICD-10 code E10 was recorded prior to the other diabetes codes, and patient had been on insulin-only antidiabetic treatment as recorded in the Drug Register. ("Probable type 1")

Type 2 diabetes was assigned if:

1. Patient had ICD-10 code E11 in the Patient Register and no other relevant ICD-10 diabetes code was recorded. ("Definite type 2")

2. Patient had ICD-10 code E11 in the Patient Register as well as relevant ICD-10 diabetes codes for type 1 and other/unspecified diabetes, and ICD-10 code E11 was recorded prior to the other diabetes codes. ("Probable type 2")

3. Patient had ICD-10 code E11 in the Patient Register as well as relevant ICD-10 diabetes codes for type 1 diabetes (E10), and ICD-10 code E11 was recorded prior to the ICD-10 code E10, and patient was not on insulin treatment as recorded in the Drug Register. ("Probable type 2")

4. Patient had ICD-10 code E11 in the Patient Register as well as relevant ICD-10 diabetes codes for other/unspecified diabetes (E12-E14), and ICD-10 code E11 was recorded prior to the other diabetes codes. ("Probable type 2")

Other/unspecified diabetes was assigned if:

1. Patient had not fulfilled criteria for type 1 or type 2 diabetes.

Using the algorithm, we excluded patients with type 1 diabetes (both "definite" and "probable") and arrived at the total cohort (132,402 subjects). Then, 78,722 (59.5%) patients were assigned with type 2 diabetes diagnosis (51.4% "Definite type 2"; 8.1% "Probable type 2") and 53,680 (40.5%) were diagnosed with other/unspecified diabetes.

Supplementary Table 2. Baseline differences in PS-matched intention-to-treat user versus non-user cohorts of individual glucose-lowering drugs by dementia status.

	Dementia cohort – baseline exposure PS-matched user versus non-user intention-to-treat cohorts											
	Metformin Yes (n=478)	**Metformin No (478)**	**p**	**SMD**	**Insulin Yes (496)**	**Insulin No (496)**	**p**	**SMD**	**SU Yes (190)**	**SU No (190)**	**p**	**SMD**
Age, y	79.5 (6.9)	78.7 (7.9)	0.09	0.10	80.2 (7.6)	79.8 (7.2)	0.37	0.06	79.3 (7.1)	79.6 (7.2)	0.69	-0.04
Female	248 (51.9%)	240 (50.2%)	0.61	-0.04	255 (51.4%)	245 (49.4%)	0.53	-0.04	102 (53.7%)	96 (50.5%)	0.54	-0.06
MMSE	21 (6)	21 (7)	0.83	0.01	21 (6)	21 (6)	0.75	0.02	21 (6)	21 (6)	0.90	0.01
Living alone	184 (38.5%)	179 (37.4%)	0.11	-0.08	208 (41.9%)	172 (34.7%)	0.02	-0.08	77 (40.5%)	76 (40.0%)	0.52	0.04
Institutionalized	36 (7.5%)	55 (11.5%)			65 (13.1%)	57 (11.5%)			20 (10.5%)	14 (7.4%)		
Diabetes duration, y	0.81 (5.9)	2.4 (5.4)	<0.001	-0.09	6.3 (7.2)	6.5 (5.7)	0.56	-0.02	3.3 (6.6)	3.8 (5.4)	0.42	-0.03
Charlson comorbidity index	2 (2)	2 (2)	0.20	-0.06	2 (2)	2 (2)	0.20	0.02	2 (2)	2 (2)	0.61	0.05
Renal disease	8 (1.7%)	14 (2.9%)	0.20	-0.10	47 (9.5%)	43 (8.7%)	0.66	0.03	11 (5.8%)	8 (4.2%)	0.48	0.06
Antihypertensives	355 (74.3%)	356 (74.5%)	0.94	-0.00	403 (81.3%)	417 (84.1%)	0.24	-0.07	144 (75.8%)	139 (73.2%)	0.57	0.06
Diuretics	221 (46.2%)	208 (43.5%)	0.40	0.05	276 (55.6%)	258 (52.0%)	0.25	0.07	90 (47.4%)	86 (45.3%)	0.68	0.04
Statins	289 (60.5%)	295 (61.7%)	0.69	-0.03	331 (66.7%)	329 (66.3%)	0.89	0.01	123 (64.7%)	121 (63.7%)	0.83	0.02
Antithrombotic drugs	326 (68.2%)	306 (64.0%)	0.17	0.09	366 (73.8%)	360 (72.6%)	0.67	0.03	133 (70.0%)	132 (69.5%)	0.91	0.01
Antipsychotics	24 (5.0%)	21 (4.4%)	0.65	0.03	35 (7.1%)	33 (6.7%)	0.80	0.02	8 (4.2%)	9 (4.7%)	0.80	-0.03
Antidepressants	162 (33.9%)	157 (32.8%)	0.73	0.02	165 (33.3%)	155 (31.3%)	0.50	0.04	57 (30.0%)	59 (31.1%)	0.82	-0.02
Cholinesterase inhibitors	51 (10.7%)	43 (9.0%)	0.39	0.05	39 (7.9%)	44 (8.9%)	0.57	-0.04	22 (11.6%)	24 (12.6%)	0.75	-0.03
Metformin					375 (75.6%)	374 (75.4%)	0.94	0.01	130 (68.4%)	136 (71.6%)	0.50	-0.07
Other non-metformin GLDs	168 (35.1%)	173 (36.2%)	0.74	-0.02	267 (53.8%)	279 (56.3%)	0.44	-0.05	45 (23.7%)	45 (23.7%)	1.00	0.00
Income category — Low	148 (31.0%)	147 (30.8%)	0.88	-0.02	157 (31.7%)	160 (32.3%)	0.44	-0.03	65 (34.2%)	76 (40.0%)	0.51	0.10
Income category — High	180 (37.7%)	187 (39.1%)			165 (33.3%)	180 (36.3%)			54 (28.4%)	49 (25.8%)		

	DPP-4i Yes (230)	**DPP-4i No (230)**	**p**	**SMD**	**GLP-1a Yes (39)**	**GLP-1a No (155)**	**p**	**SMD**	**SGLT-2i Yes (51)**	**SGLT-2i No (201)**	**p**	**SMD**
Age, y	79.7 (7.0)	79.5 (7.0)	0.75	0.03	76.1 (6.7)	76.7 (7.7)	0.64	-0.07	75.7 (6.3)	76.1 (7.8)	0.75	-0.03
Female	103 (44.8%)	101 (43.9%)	0.85	0.02	20 (51.3%)	71 (45.8%)	0.54		24 (47.1%)	106 (52.7%)	0.47	
MMSE	21 (6.3)	21 (7)	0.80	-0.01	22 (8)	21 (6)	0.15		23 (6)	22 (4)	0.02	
Living alone	96 (41.7%)	82 (35.7%)	0.28	-0.07	17 (43.6%)	67 (43.2%)	0.57		19 (37.3%)	84 (41.8%)	0.77	0.05
Institutionalized	27 (11.7%)	24 (10.4%)			5 (12.8%)	12 (7.7%)			4 (7.8%)	18 (9.0%)		
Diabetes duration, y	9.0 (7.1)	8.2 (6.7)	0.44	0.07	12.2 (3.7)	11.6 (4.8)	0.94	-0.01	10.8 (6.9)	10.3 (6.3)	0.89	-0.01
Charlson comorbidity index	2 (2.3)	2 (2)	0.28	0.10	2 (2)	3 (3)	0.36		2 (2)	2 (2)	0.92	
Renal disease	30 (13.0%)	30 (13.0%)	1.00	0.00	5 (12.8%)	15 (9.7%)	0.56		1 (2.0%)	16 (8.0%)	0.11	
Antihypertensives	196 (85.2%)	190 (82.6%)	0.45	0.07	33 (84.6%)	139 (89.7%)	0.37		42 (82.4%)	166 (82.6%)	0.97	
Diuretics	125 (54.3%)	125 (53.9%)	0.93	0.01	26 (66.7%)	80 (51.6%)	0.09		20 (39.2%)	96 (47.8%)	0.27	
Statins	179 (77.8%)	174 (75.7%)	0.58	0.05	34 (87.2%)	129 (83.2%)	0.55		38 (74.5%)	147 (73.1%)	0.84	0.02
Antithrombotic drugs	177 (77.0%)	175 (76.1%)	0.83	0.02	27 (69.2%)	124 (80.0%)	0.15		40 (78.4%)	147 (73.1%)	0.44	
Antipsychotics	16 (7.0%)	19 (8.3%)	0.60	-0.05	5 (12.8%)	7 (4.5%)	0.05		4 (7.8%)	13 (6.5%)	0.73	
Antidepressants	73 (31.7%)	63 (27.4%)	0.31	0.09	18 (46.2%)	61 (39.4%)	0.44		20 (39.2%)	78 (38.8%)	0.96	
Cholinesterase inhibitors	27 (11.7%)	28 (12.2%)	0.89	-0.01	5 (12.8%)	19 (12.3%)	0.92	0.02	5 (9.8%)	23 (11.4%)	0.74	
Metformin	182 (79.1%)	179 (77.8%)	0.73	0.03	37 (94.9%)	123 (79.4%)	0.02		49 (96.1%)	157 (78.1%)	0.003	

	Metformin Yes	Metformin No	p	SMD	Insulin Yes	Insulin No	p	SMD	SU Yes	SU No	p	SMD
Other non-metformin GLDs	159 (69.1%)	159 (69.1%)	1.00	0.00	38 (97.4%)	152 (98.1%)	0.60	-0.04	44 (86.3%)	144 (71.6%)	0.03	
Income category Low	72 (31.3%)	67 (29.1%)	0.68	-0.01	5 (12.8%)	36 (23.2%)	0.07		14 (27.5%)	65 (32.3%)	0.48	-0.01
High	82 (35.7%)	78 (33.9%)			10 (25.6%)	55 (35.5%)			17 (33.3%)	75 (37.3%)		

Dementia-free cohort - baseline exposure PS-matched user versus non-user intention-to-treat cohorts

	Metformin Yes (326)	Metformin No (326)	p	SMD	Insulin Yes (481)	Insulin No (481)	p	SMD	SU Yes (169)	SU No (169)	p	SMD
Age, y	78.6 (6.0)	77.8 (8.1)	0.15	0.11	80.9 (6.8)	81.0 (6.5)	0.95	-0.01	77.4 (7.4)	77.3 (8.1)	0.93	0.01
Female	163 (50.0%)	161 (49.4%)	0.88	-0.01	237 (49.3%)	231 (48.0%)	0.70	-0.02	89 (52.7%)	97 (57.4%)	0.39	0.09
Diabetes duration, y	0.89 (4.6)	2.51 (4.3)	<0.001	-0.11	6.2 (7.0)	5.9 (5.9)	0.88	0.02	4.1 (5.6)	3.7 (4.7)	0.63	-0.01
Charlson comorbidity index	2 (3)	1 (2)	0.27	0.09	2 (3)	2 (3)	0.29	0.02	2 (3)	2 (3)	0.38	0.07
Renal disease	4 (1.2%)	7 (2.1%)	0.36	-0.10	48 (10.0%)	36 (7.5%)	0.17	0.08	4 (2.4%)	4 (2.4%)	0.64	0.00
Antihypertensives	245 (75.2%)	239 (73.3%)	0.59	0.04	387 (80.5%)	388 (80.7%)	0.94	-0.01	124 (73.4%)	118 (69.8%)	0.47	0.08
Diuretics	143 (43.9%)	149 (45.7%)	0.64	-0.04	273 (56.8%)	265 (55.1%)	0.60	0.03	77 (45.6%)	72 (42.6%)	0.58	0.06
Statins	205 (62.9%)	223 (68.4%)	0.14	-0.11	320 (66.5%)	308 (64.0%)	0.42	0.05	118 (69.8%)	113 (66.9%)	0.56	0.06
Antithrombotic drugs	220 (67.5%)	215 (66.0%)	0.68	0.03	372 (77.3%)	365 (75.9%)	0.59	0.03	111 (65.7%)	110 (65.1%)	0.91	0.01
Antipsychotics	12 (3.7%)	14 (4.3%)	0.69	-0.03	31 (6.4%)	36 (7.5%)	0.53	-0.04	12 (7.1%)	10 (5.9%)	0.66	0.05
Antidepressants	93 (28.5%)	96 (29.4%)	0.80	-0.02	185 (38.5%)	186 (38.7%)	0.95	-0.01	55 (32.5%)	56 (33.1%)	0.91	-0.01
Metformin					352 (73.2%)	350 (72.8%)	0.89	0.01	126 (74.6%)	129 (76.3%)	0.71	-0.04
Other non-metformin GLDs	107 (32.8%)	117 (35.9%)	0.41	-0.07	254 (52.8%)	263 (54.7%)	0.56	-0.04	46 (27.2%)	47 (27.8%)	0.90	-0.01
Income category Low	81 (24.8%)	82 (25.2%)	0.51	-0.04	154 (32.0%)	149 (31.0%)	0.59	0.01	47 (27.8%)	41 (24.3%)	0.26	0.01
High	139 (42.6%)	151 (46.3%)			159 (33.1%)	149 (31.0%)			75 (44.4%)	67 (39.6%)		

	DPP-4i Yes (233)	DPP-4i No (233)	p	SMD	GLP-1a Yes (35)	GLP-1a No (137)	p	SMD	SGLT-2i Yes (45)	SGLT-2i No (180)	p	SMD
Age, y	78.6 (7.3)	78.0 (7.8)	0.42	0.08	73.2 (7.7)	73.2 (8.1)	0.99	0.04	75.5 (7.1)	75.7 (7.3)	0.90	-0.02
Female	113 (48.5%)	116 (49.8%)	0.78	-0.03	15 (42.9%)	83 (60.6%)	0.06		23 (51.1%)	101 (56.1%)	0.55	
Diabetes duration, y	8.7 (5.0)	8.1 (6.8)	0.70	0.01	10.2 (6.6)	9.4 (5.8)	0.60	0.08	10.9 (5.7)	10.2 (5.9)	0.74	-0.01
Charlson comorbidity index	2 (3)	2 (3.5)	0.88	-0.03	1 (2)	1 (3)	0.20		1 (2)	2 (3)	0.01	
Renal disease	23 (9.9%)	25 (10.7%)	0.76	-0.03	1 (2.9%)	7 (5.1%)	0.49		0 (0.0%)	11 (6.1%)	0.08	
Antihypertensives	206 (88.4%)	203 (87.1%)	0.67	0.04	34 (97.1%)	109 (79.6%)	0.01		38 (84.4%)	155 (86.1%)	0.78	
Diuretics	111 (47.6%)	100 (42.9%)	0.31	0.09	12 (34.3%)	44 (32.1%)	0.81		16 (35.6%)	80 (44.4%)	0.28	
Statins	177 (76.0%)	172 (73.8%)	0.59	0.05	30 (85.7%)	101 (73.7%)	0.14		38 (84.4%)	154 (85.6%)	0.85	-0.03
Antithrombotic drugs	186 (79.8%)	179 (76.8%)	0.43	0.07	20 (57.1%)	101 (73.7%)	0.06		28 (62.2%)	140 (77.8%)	0.03	
Antipsychotics	5 (2.1%)	6 (2.6%)	0.76	-0.03	1 (2.9%)	6 (4.4%)	0.57		1 (2.2%)	15 (8.3%)	0.15	
Antidepressants	85 (36.5%)	91 (39.1%)	0.57	-0.05	10 (28.6%)	40 (29.2%)	0.94		17 (37.8%)	67 (37.2%)	0.95	
Metformin	205 (88.0%)	202 (86.7%)	0.68	0.04	33 (94.3%)	95 (69.3%)	0.003		44 (97.8%)	132 (73.3%)	<0.001	
Other non-metformin GLDs	153 (65.7%)	153 (65.7%)	1.00	0.00	30 (85.7%)	88 (64.2%)	0.02		37 (82.2%)	119 (66.1%)	0.04	
Income category Low	58 (24.9%)	57 (24.5%)	0.96	-0.02	8 (22.9%)	27 (19.7%)	0.92	-0.08	7 (15.6%)	40 (22.2%)	0.56	0.09
High	97 (41.6%)	100 (42.9%)			19 (54.3%)	77 (56.2%)			20 (44.4%)	79 (43.9%)		

DPP-4i, dipeptidyl-peptidase-4 inhibitors; GLP-1a, glucagon-like peptide-1 agonists; GLD, glucose-lowering drugs; MMSE, Mini-Mental State Examination; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SU, sulfonylureas. p-values refer to the exposure "Yes" versus exposure "No" comparisons. Due to space constraints are the distributions of dementia diagnoses summarized in Supplementary Table 3. Age is described as mean (SD). Charlson comorbidity index, Diabetes duration, and MMSE are described as median (IQR); all other variables are described as n (%).

Supplementary Table 3. Baseline differences in the PS-matched comparative user versus user cohorts

Dementia		Insulin (135)	Sulfonylurea (135)	p	SMD	DPP-4i (81)	Sulfonylurea (81)	p	SMD	DPP-4i (123)	Insulin (123)	p	SMD
Age, y		80.4 (7.7)	80.1 (6.5)	0.72	0.04	79.3 (6.5)	78.7 (7.2)	0.58	0.09	79.8 (6.6)	79.5 (7.4)	0.76	0.04
Female		68 (50.4%)	72 (53.3%)	0.63		41 (50.6%)	44 (54.3%)	0.64		68 (55.3%)	61 (49.6%)	0.37	
MMSE		22 (6)	20 (6)	0.32	0.04	21 (8)	21 (6.5)	0.75	0.06	21 (7)	21 (6)	0.84	-0.02
Living alone		61 (45.2%)	53 (39.3%)	0.05	0.02	31 (38.3%)	29 (35.8%)	0.74	-0.09	47 (38.2%)	49 (39.8%)	0.89	0.05
Institutionalized		23 (17.0%)	13 (9.6%)			7 (8.6%)	10 (12.3%)			12 (9.8%)	10 (8.1%)		
Diabetes duration, y		3.1 (6.1)	3.1 (6.7)	0.76	0.01	4.6 (6.9)	4.6 (8.4)	0.99		2 (2)	2 (2)	0.79	-0.09
Charlson comorbidity index		2 (2)	2 (2)	0.75	0.04	2 (2)	2 (2)	0.84	0.10	6.2 (6.6)	6.8 (5.7)	0.43	-0.01
Renal disease		13 (9.6%)	9 (6.7%)	0.37	0.10	6 (7.4%)	4 (4.9%)	0.51	0.07	11 (8.9%)	10 (8.1%)	0.82	0.03
Antihypertensives		105 (77.8%)	108 (80.0%)	0.66	-0.06	69 (85.2%)	67 (82.7%)	0.67		102 (82.9%)	98 (79.7%)	0.51	
Diuretics		70 (51.9%)	65 (48.1%)	0.54		43 (53.1%)	49 (60.5%)	0.34		60 (48.8%)	67 (54.5%)	0.37	
Statins		76 (56.3%)	83 (61.5%)	0.39	-0.10	55 (67.9%)	56 (69.1%)	0.87	-0.03	94 (76.4%)	92 (74.8%)	0.77	0.04
Antithrombotic drugs		95 (70.4%)	94 (69.6%)	0.89	0.02	55 (67.9%)	63 (77.8%)	0.16		90 (73.2%)	88 (71.5%)	0.78	
Antipsychotics		8 (5.9%)	6 (4.4%9)	0.58	0.06	4 (4.9%)	4 (4.9%)	1.00		9 (7.3%)	5 (4.1%)	0.27	
Antidepressants		37 (27.4%)	41 (30.4%)	0.59	-0.06	23 (28.4%)	24 (29.6%)	0.86		35 (28.5%)	39 (31.7%)	0.58	
Cholinesterase inhibitors		9 (6.7%)	10 (7.4%)	0.81	-0.03	8 (9.9%)	6 (7.4%)	0.58	0.09	13 (10.6%)	11 (8.9%)	0.67	0.05
Metformin		95 (70.4%)	92 (68.1%)	0.69	0.05	59 (72.8%)	57 (70.4%)	0.73		97 (78.9%)	100 (81.3%)	0.63	
Other non-metformin GLDs		18 (12.6%)	15 (11.%)	0.71	0.05	21 (25.9%)	22 (27.2%)	0.86		58 (47.2%)	58 (47.2%)	1.00	
Income category	Low	40 (29.6%)	39 (28.9%)	0.97	0.00	28 (34.6%)	28 (34.6%)	0.15	0.10	39 (31.7%)	41 (33.3%)	0.86	0.00
	High	43 (31.9%)	42 (31.1%)			32 (39.5%)	22 (27.2%)			42 (34.1%)	44 (35.8%)		

| Dementia-free		Insulin (139)	Sulfonylurea (139)	p	SMD	DPP-4i (81)	Sulfonylurea (81)	p	SMD	DPP-4i (152)	Insulin (152)	p	SMD
Age, y		79.2 (6.2)	79.3 (7.0)	0.87	-0.02	78.4 (8.0)	78.2 (9.2)	0.87	0.03	79.5 (7.1)	79.5 (7.4)	0.97	0.01
Female		77 (55.4%)	79 (56.8%)	0.81	0.03	43 (53.1%)	40 (49.4%)	0.64		76 (50.0%)	74 (48.7%)	0.82	-0.03
Diabetes duration, y		3.4 (7.1)	4.0 (6.0)	0.75	-0.02	4.9 (6.7)	4.8 (5.3)	0.68	-0.07	6.6 (7.3)	7.2 (4.9)	0.87	0.07
Charlson comorbidity index		2 (2)	1 (3)	0.50	0.06	2 (3)	2 (3)	0.89	0.05	2 (3)	2 (2)	0.64	-0.03
Renal disease		6 (4.3%)	5 (3.6%)	0.76	0.02	5 (6.2%)	3 (3.7%)	0.47	0.07	14 (9.2%)	15 (9.9%)	0.85	-0.03
Antihypertensives		110 (79.1%)	107 (77.0%)	0.66	0.05	66 (81.5%)	66 (81.5%)	1.00	0.00	131 (86.2%)	128 (84.2%)	0.63	0.06
Diuretics		71 (51.1%)	74 (53.2%)	0.72	-0.04	35 (43.2%)	39 (48.1%)	0.53		74 (48.7%)	73 (48.0%)	0.91	0.01
Statins		88 (63.3%)	89 (64.0%)	0.90	-0.01	59 (72.8%)	57 (70.4%)	0.73	0.06	123 (80.9%)	129 (84.9%)	0.36	-0.10
Antithrombotic drugs		101 (72.7%)	99 (71.2%)	0.79	0.03	60 (74.1%)	62 (76.5%)	0.72	-0.06	112 (73.7%)	118 (77.6%)	0.42	-0.09
Antipsychotics		8 (5.8%)	6 (4.3%)	0.58	0.07	1 (1.2%)	2 (2.5%)	0.56	-0.10	6 (3.9%)	4 (2.6%)	0.52	0.07
Antidepressants		42 (30.2%)	43 (30.9%)	0.90	-0.02	24 (29.6%)	21 (25.9%)	0.60	0.08	50 (32.9%)	54 (35.5%)	0.63	-0.06
Metformin		104 (74.8%)	99 (71.2%)	0.50	0.08	62 (76.5%)	62 (76.5%)	1.00	0.00	133 (87.5%)	129 (84.9%)	0.51	0.08
Other non-metformin GLDs		19 (13.7%)	16 (11.5%)	0.59	0.06	26 (32.1%)	26 (32.1%)	1.00	0.00	64 (42.1%)	65 (42.8%)	0.91	-0.01
Income category	Low	45 (32.4%)	46 (33.1%)	0.72	-0.04	26 (32.1%)	20 (24.7%)	0.53	-0.10	41 (27.0%)	35 (23.0%)	0.70	-0.09
	High	43 (30.9%)	48 (34.5%)			30 (37.0%)	31 (38.3%)			54 (35.5%)	59 (38.8%)		

DPP-4i, dipeptidyl-peptidase-4 inhibitors; GLDs, glucose-lowering drugs; MMSE, Mini-Mental State Examination; SMD, standardized mean differences

Supplementary Table 4. Central tendency and spread of stabilized inverse-probability of treatment and censoring weights in patients with diabetes by dementia status
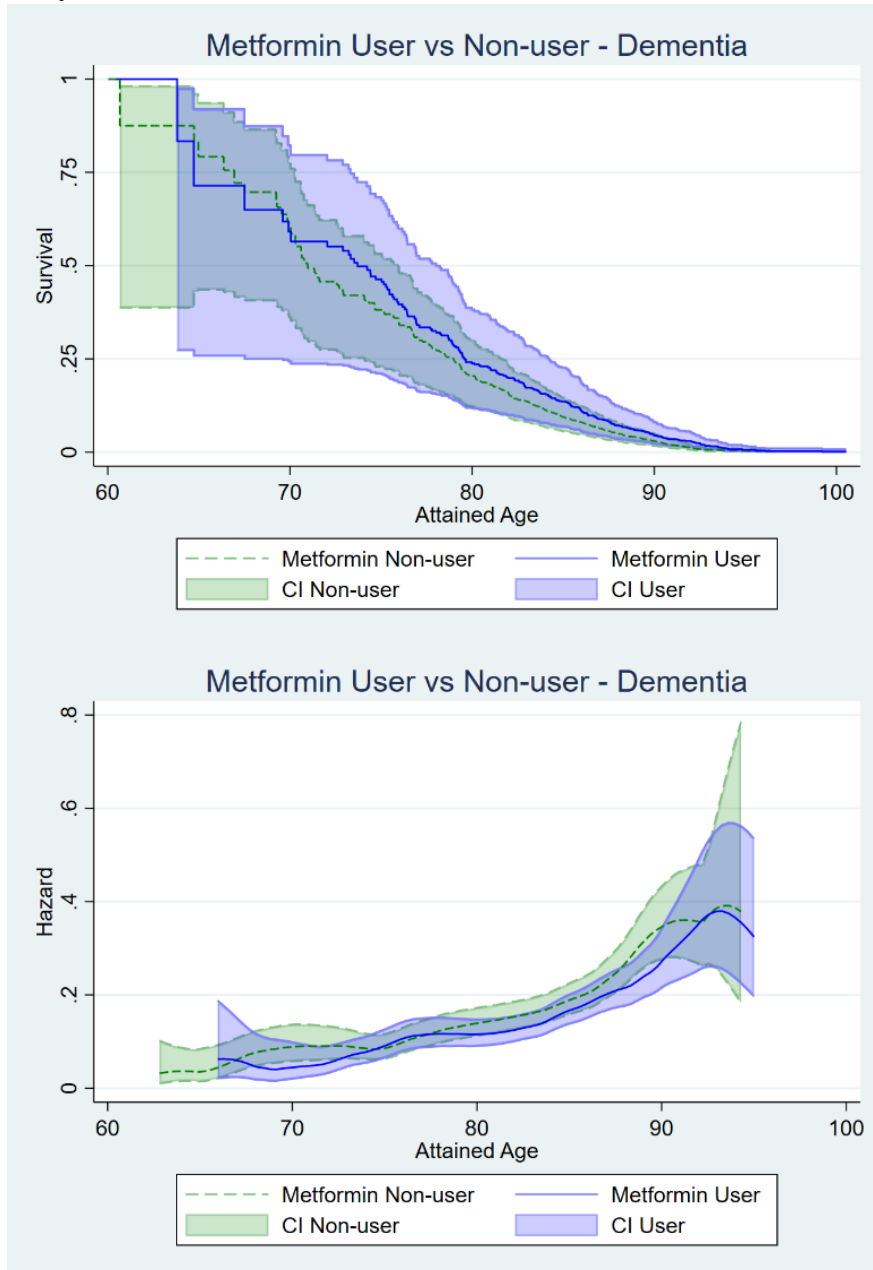
IPTCW in patients with dementia			
	Mean	SD	Smallest	Largest
Metformin	1.00	0.54	0.30	51.1
Insulin	1.00	0.16	0.16	5.7
SU	1.00	0.10	0.34	5.3
DPP-4i	1.00	0.11	0.30	6.2
GLP-1a	1.00	0.15	0.20	23.2
SGLT-2i	1.00	0.22	0.17	29.5

IPTCW in dementia-free subjects			
	Mean	SD	Smallest	Largest
Metformin	1.00	0.23	0.21	20.7
Insulin	1.00	0.20	0.06	10.5
SU	1.00	0.11	0.29	8.00
DPP-4i	1.00	0.1	0.22	4.4
GLP-1a	1.00	0.12	0.20	8.6
SGLT-2i	1.00	0.15	0.01	15.1

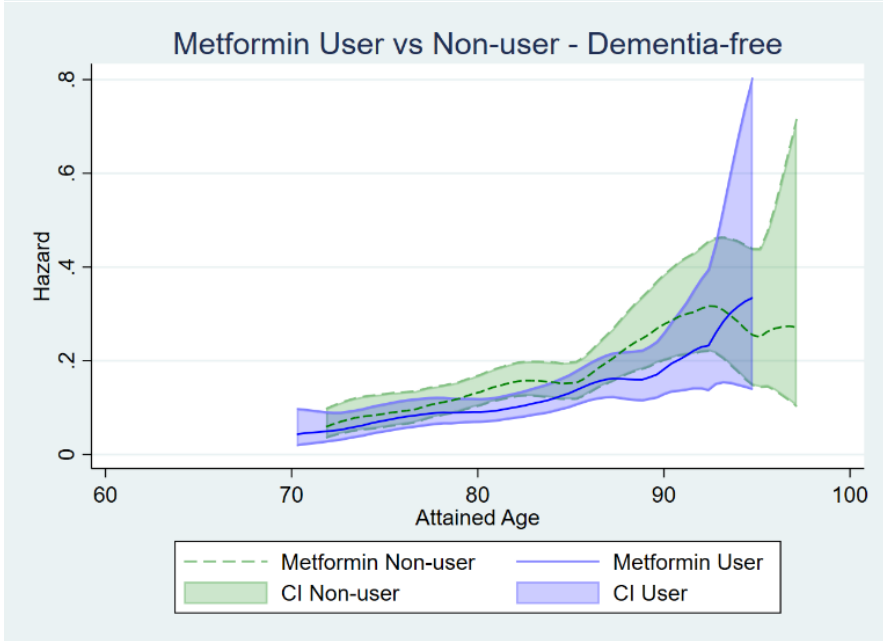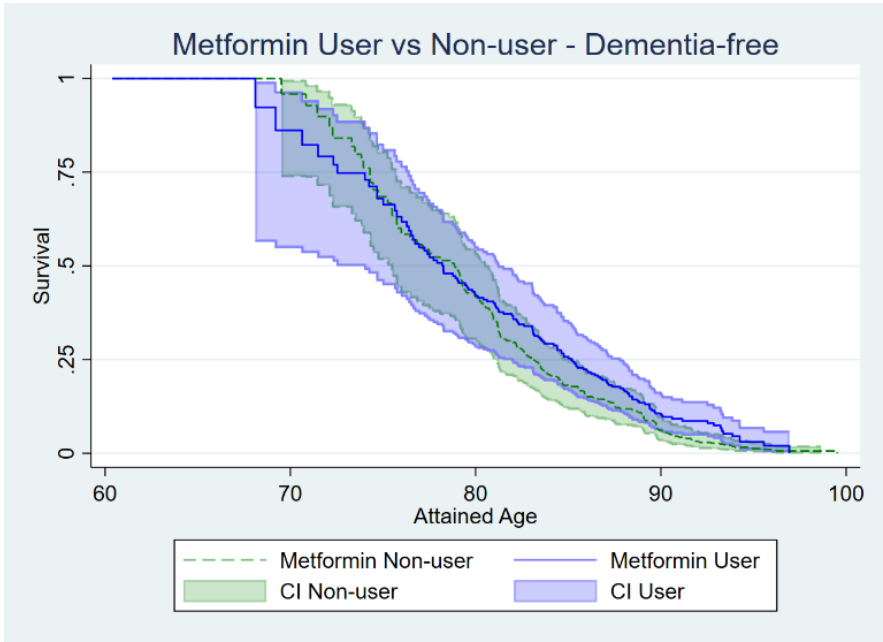IPTCW, inverse-probability of treatment and censoring weights; SU, sulfonylurea derivates; DPP-4i, dipeptidyl-peptidase-4 inhibitors; GLP-1a, glucagon-like peptide-1 analogues; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SD, standard deviation. Stabilized weights were created using baseline and time-updated covariates.

Supplementary Figure 3. Summarized three analytical approaches – sulfonylureas as example.
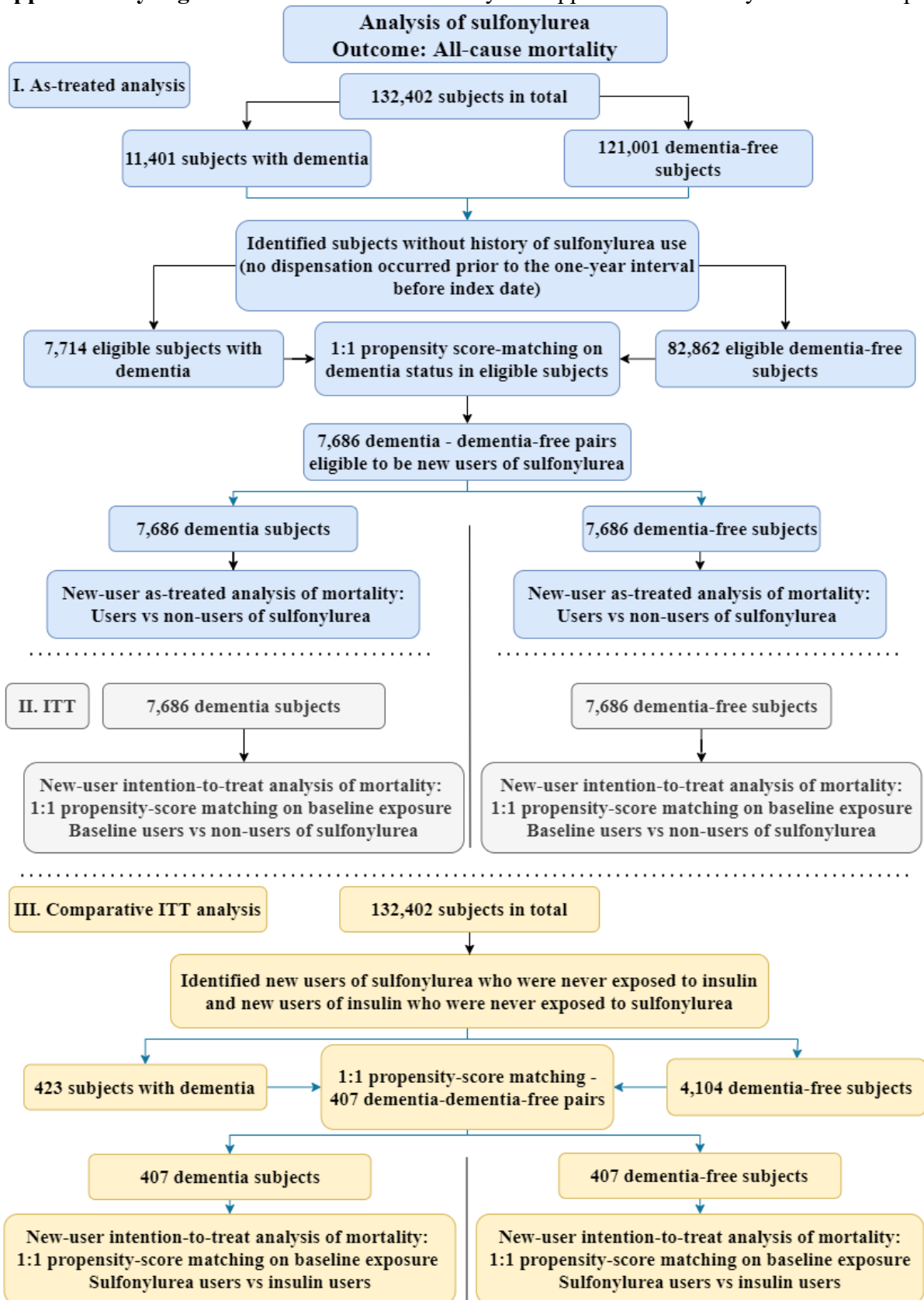
Supplementary Figure 4. Kaplan-Meier hazard and survival curves based on intention-to-treat analyses

Metformin User vs Non-user - Dementia-free

Metformin User vs Non-user - Dementia-free

Insulin User vs Non-user - Dementia

Insulin User vs Non-user - Dementia

14

Insulin User vs Non-user - Dementia-free

Insulin User vs Non-user - Dementia-free
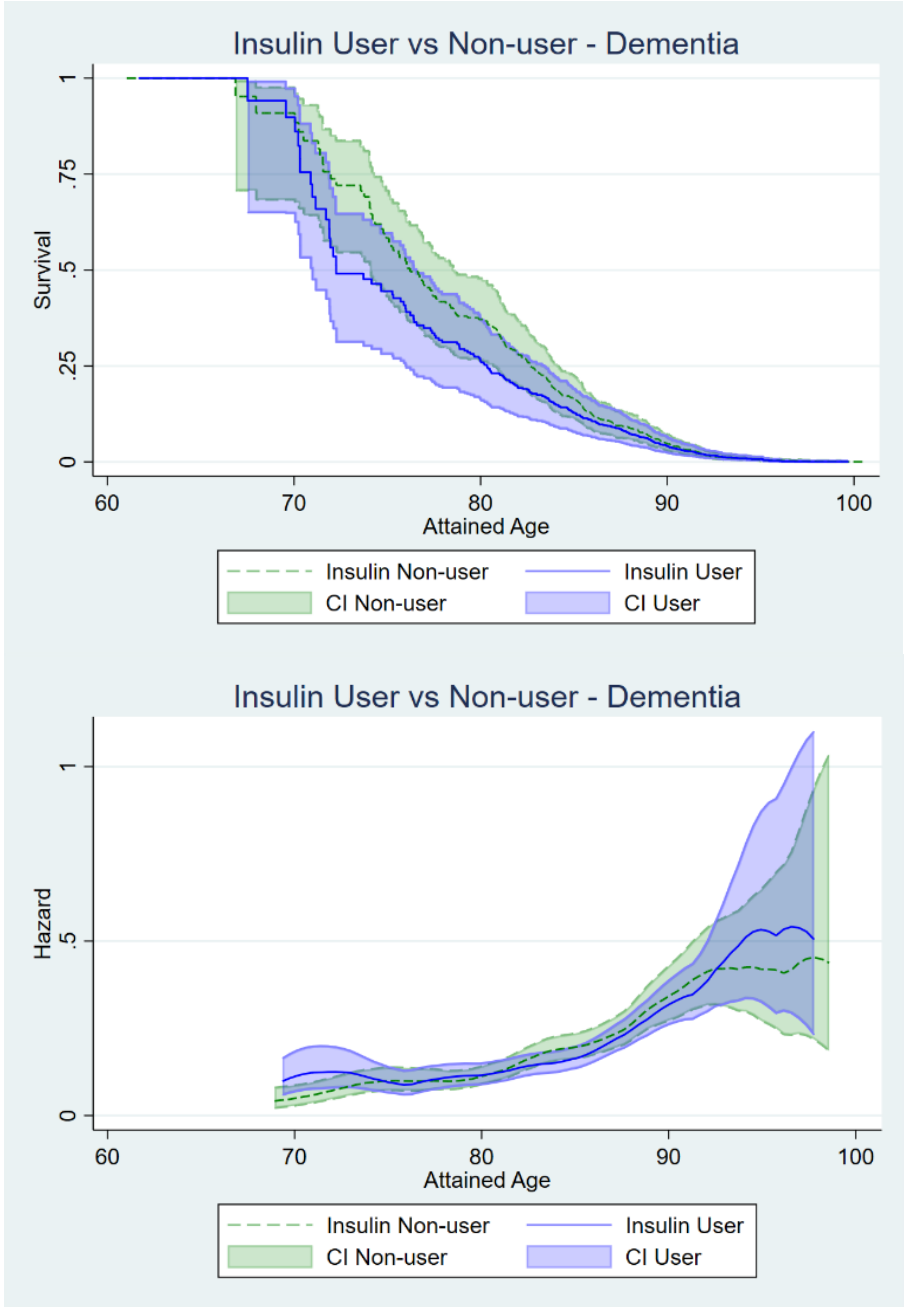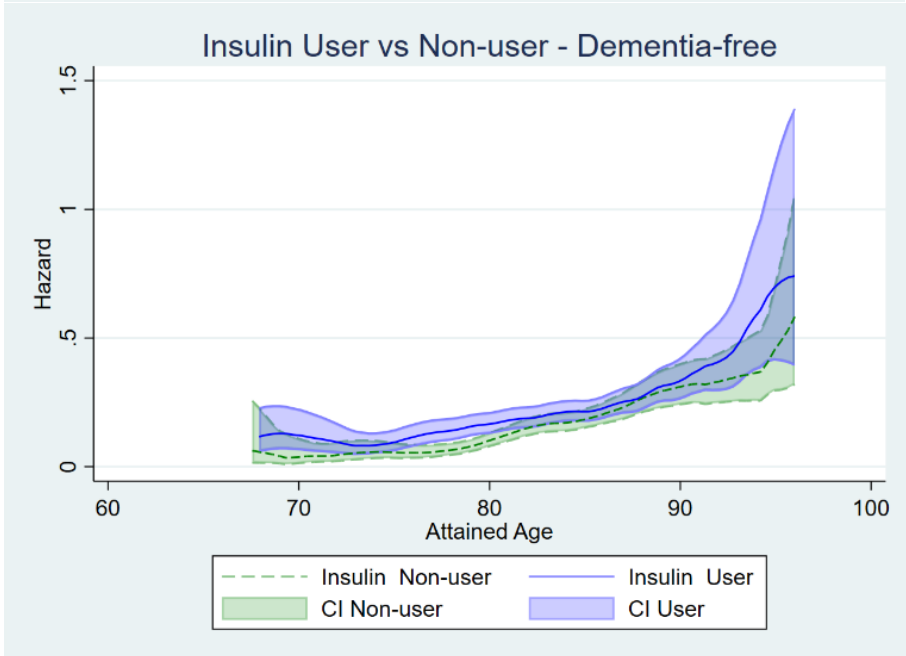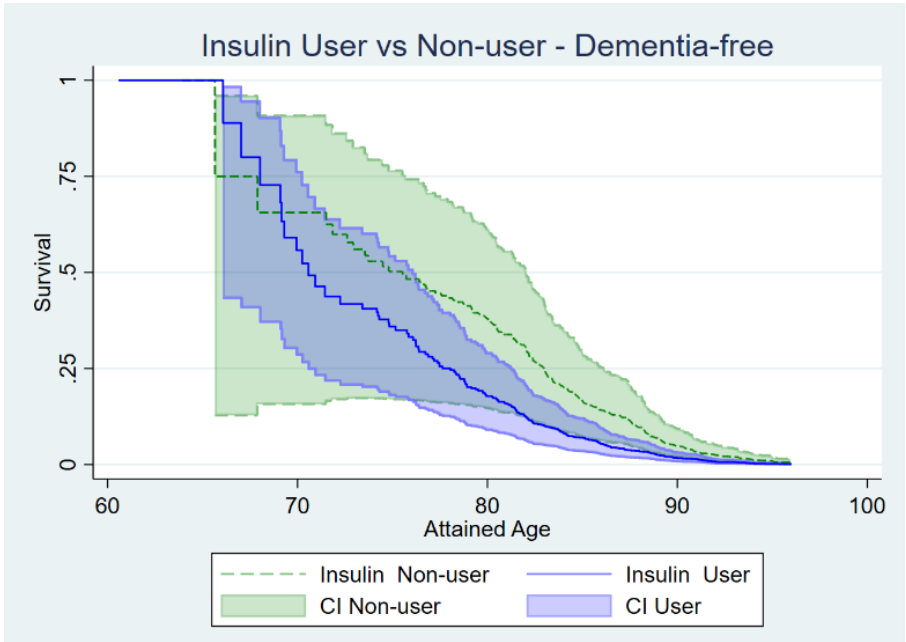
Supplementary Table 5. Distribution of dementia diagnoses among baseline exposure groups of the as-treated dementia cohorts

	Dementia cohort – baseline exposure as-treated user non-user cohorts								
	Metformin Yes (n=573)	Metformin No (3,389)	p	Insulin Yes (504)	Insulin No (6,985)	p	SU Yes (190)	SU No (7,496)	p
Alzheimer's disease	129 (22.5%)	774 (22.8%)		93 (18.5%)	1,734 (24.8%)		57 (30.0%)	1,729 (23.1%)	
Mixed dementia	113 (19.7%)	801 (23.6%)		107 (21.2%)	1,531 (21.9%)		35 (18.4%)	1,555 (20.7%)	
Vascular dementia	172 (30.0%)	935 (27.6%)		141 (28.0%)	1,769 (25.3%)		53 (27.9%)	2,098 (28.0%)	
Lewy body dementia	11 (1.9%)	71 (2.1%)	0.31	6 (1.2%)	180 (2.6%)	0.001	3 (1.6%)	184 (2.5%)	0.28
Frontotemporal dementia	9 (1.6%)	30 (0.9%)		5 (1.0%)	98 (1.4%)		4 (2.1%)	95 (1.3%)	
Unspecified dementia	126 (22.0%)	704 (20.8%)		134 (26.6%)	1,521 (21.8%)		34 (17.9%)	1,657 (22.1%)	
Other	13 (2.3%)	74 (2.2%)		18 (3.6%)	152 (2.2%)		4 (2.1%)	178 (2.4%)	
	DPP-4i Yes (230)	DPP-4i No (10,526)	p	GLP-1a Yes (40)	GLP-1a No (11,203)	p	SGLT-2i Yes (51)	SGLT-2i No (11,282)	p
Alzheimer's disease	57 (24.8%)	2,424 (23.0%)		9 (22.5%)	2,574 (23.0%)		14 (27.5%)	2,579 (22.9%)	
Mixed dementia	46 (20.0%)	2,300 (21.9%)		5 (12.5%)	2,456 (21.9%)		7 (13.7%)	2,472 (21.9%)	
Vascular dementia	69 (30.0%)	2,896 (27.5%)		17 (42.5%)	3,080 (27.5%)		16 (31.4%)	3,118 (27.6%)	
Lewy-body dementia	4 (1.7%)	249 (2.4%)	0.92	0 (0.0%)	268 (2.4%)	0.24	2 (3.9%)	267 (2.4%)	0.78
Frontotemporal dementia	3 (1.3%)	126 (1.2%)		0 (0.0%)	131 (1.2%)		1 (2.0%)	129 (1.1%)	
Unspecified dementia	47 (20.4%)	2,295 (21.8%)		7 (17.5%)	2,440 (21.8%)		10 (19.6%)	2,460 (21.8%)	
Other	4 (1.7%)	237 (2.3%)		2 (5.0%)	254 (2.3%)		1 (2.0%)	257 (2.3%)	
	Dementia cohort – baseline exposure intention-to-treat user non-user cohorts								
	Metformin Yes (n=478)	Metformin No (478)	p	Insulin Yes (496)	Insulin No (496)	p	SU Yes (190)	SU No (190)	p
Alzheimer's disease	102 (21.3%)	122 (25.5%)		92 (18.5%)	100 (20.2%)		57 (30.0%)	52 (27.4%)	
Mixed dementia	101 (21.1%)	91 (19.0%)	0.05	107 (21.6%)	85 (17.1%)	0.18	35 (18.4%)	39 (20.5%)	0.52
Vascular dementia	151 (31.6%)	117 (24.5%)		137 (27.6%)	154 (31.0%)		53 (27.9%)	51 (26.8%)	

	DPP-4i Yes (230)	DPP-4i No (230)	p	GLP-1a Yes (39)	GLP-1a No (155)	p	SGLT-2i Yes (51)	SGLT-2i No (201)	p
Lewy body dementia	7 (1.5%)	10 (2.1%)		6 (1.2%)	12 (2.4%)		3 (1.6%)	10 (5.3%)	
Frontotemporal dementia	5 (1.0%)	6 (1.3%)		5 (1.0%)	8 (1.6%)		4 (2.1%)	3 (1.6%)	
Unspecified dementia	105 (22.0%)	114 (23.8%)		131 (26.4%)	127 (25.6%)		34 (17.9%)	29 (15.3%)	
Other	7 (1.5%)	18 (3.8%)		18 (3.6%)	10 (2.0%)		4 (2.1%)	6 (3.2%)	
Alzheimer's disease	57 (24.8%)	58 (25.2%)		9 (23.1%)	27 (17.4%)		14 (27.5%)	42 (20.9%)	
Mixed dementia	46 (20.0%)	50 (21.7%)		5 (12.8%)	39 (25.2%)		7 (13.7%)	40 (19.9%)	
Vascular dementia	69 (30.0%)	68 (29.6%)		16 (41.0%)	48 (31.0%)		16 (31.4%)	63 (31.3%)	
Lewy-body dementia	4 (1.7%)	8 (3.5%)	0.86	0 (0.0%)	6 (3.9%)	0.37	2 (3.9%)	4 (2.0%)	0.84
Frontotemporal dementia	3 (1.3%)	3 (1.3%)		0 (0.0%)	0 (0.0%)		1 (2.0%)	5 (2.5%)	
Unspecified dementia	47 (20.4%)	41 (17.8%)		7 (17.9%)	30 (19.4%)		10 (19.6%)	39 (19.4%)	
Other	4 (1.7%)	2 (0.9%)		2 (5.1%)	5 (3.2%)		1 (2.0%)	8 (4.0%)	

Dementia cohort – baseline exposure intention-to-treat comparative cohorts

	Insulin (135)	SU (135)	p	DPP-4i (81)	SU (81)	p	DPP-4i (123)	Insulin (123)	p
Alzheimer's disease	32 (23.7%)	28 (20.7%)		25 (30.9%)	20 (24.7%)		28 (22.8%)	25 (20.3%)	
Mixed dementia	29 (21.5%)	29 (21.5%)		9 (11.1%)	14 (17.3%)		26 (21.1%)	32 (26.0%)	
Vascular dementia	37 (27.4%)	41 (30.4%)		23 (28.4%)	23 (28.4%)		39 (31.7%)	34 (27.6%)	
Lewy-body dementia	1 (0.7%)	3 (2.2%)	0.84	2 (2.5%)	2 (2.5%)	0.92	1 (0.8%)	1 (0.8%)	0.93
Frontotemporal dementia	1 (0.7%)	3 (2.2%)		1 (1.2%)	1 (1.2%)		2 (1.6%)	1 (0.8%)	
Unspecified dementia	32 (23.7%)	28 (20.7%)		20 (24.7%)	19 (23.5%)		26 (21.1%)	28 (22.8%)	
Other	3 (2.2%)	3 (2.2%)		1 (1.2%)	2 (2.5%)		1 (0.8%)	2 (1.6%)	

SU, sulfonylurea derivates; DPP-4i, dipeptidyl-peptidase-4 inhibitors; GLP-1a, glucagon-like peptide-1 analogues; SGLT-2i, sodium-glucose cotransporter-2 inhibitors. Dementia with Lewy bodies and Parkinson's disease dementia were merged into one group "Lewy body dementia".

Supplementary Table 6. Variables used in the individual exposure PS-matchings for intention-to-treat analyses

Patients with dementia

PS-matching exposure	Age	Sex	MMSE	Cohabitation	Dementia type	Diabetes duration	CCI	RF	Anti-hypertensives	Diuretics	Statins	Anti-thrombotics	Anti-psychotics	Anti-depressants	ChEI	Income	MET	Other GLD
Metformin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Insulin	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sulfonylurea	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DPP-4i	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GLP-1a	X					X									X			X
SGLT-2i	X			X		X					X					X		
INS versus SU	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
DPP-4i versus SU	X		X	X	X	X	X	X			X				X	X	X	X
DPP-4i versus INS	X		X	X	X	X	X	X			X				X	X	X	X

Dementia-free patients

PS-matching exposure	Age	Sex	MMSE	Cohabitation	Dementia type	Diabetes duration	CCI	RF	Anti-hypertensives	Diuretics	Statins	Anti-thrombotics	Anti-psychotics	Anti-depressants	ChEI	Income	MET	Other GLD
Metformin	X	X	n/a	n/a	n/a	X	X	X	X	X	X	X	X	X	n/a	X		X
Insulin	X	X	n/a	n/a	n/a	X	X	X	X	X	X	X	X	X	n/a	X	X	X
Sulfonylurea	X	X	n/a	n/a	n/a	X	X	X	X	X	X	X	X	X	n/a	X	X	X
DPP-4i	X	X	n/a	n/a	n/a	X	X	X	X	X	X	X	X	X	n/a	X	X	X
GLP-1a	X		n/a	n/a	n/a	X									n/a	X		
SGLT-2i	X		n/a	n/a	n/a	X					X				n/a	X		
INS versus SU	X	X	n/a	n/a	n/a	X	X	X	X	X	X	X	X	X	n/a	X	X	X
DPP-4i versus SU	X		n/a	n/a	n/a	X	X	X	X		X	X	X	X	n/a	X	X	X
DPP-4i versus INS	X	X	n/a	n/a	n/a	X	X	X	X	X	X	X	X	X	n/a	X	X	X

DPP-4i, dipeptidyl-peptidase-4 inhibitors; GLP-1a, glucagon-like peptide-1 analogues; INS, insulin; MET, metformin; SU, sulfonylureas; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; MMSE, Mini-Mental State Examination; CCI, Charlson comorbidity index; RF, renal disease; ChEI, cholinesterase inhibitors; GLD, glucose-lowering drugs. X means the variable was included in the PS matching. The matching was limited by the number of available subjects in the least frequent category – 10 subjects per predictor.

Supplementary Table 7. Concurrent use of glucose-lowering drugs in the new-user as-treated and intention-to-treat analyses

	AT: Total exposed / out of total	Metformin	Insulin	Sulfonylurea	TZD	DPP-4i	GLP-1a	SGLT-2i
Dementia	Metformin (960 out of 3,962)	X	676 (70.4%)	493 (51.4%)	9 (0.94%)	59 (6.2%)	8 (0.8%)	12 (1.3%)
	Insulin (1,876 / 7,489)	1,330 (70.9%)	X	810 (43.2%)	56 (3.0%)	344 (18.3%)	32 (1.7%)	30 (1.6%)
	Sulfonylurea (449 / 7,686)	344 (76.6%)	95 (21.2%)	X	9 (2.0%)	58 (12.9%)	5 (1.1%)	9 (2.0%)
	DPP-4i (1,003 / 10,756)	734 (73.2%)	482 (48.1%)	298 (29.7%)	20 (2.0%)	X	17 (1.7%)	31 (3.1%)
	GLP-1a (165 / 11,243)	105 (63.6%)	137 (83.0%)	37 (22.4%)	3 (1.8%)	55 (33.3%)	X	20 (12.1%)
	SGLT-2i (194 / 11,333)	152 (78.4%)	102 (52.6%)	62 (32.0%)	5 (2.6%)	69 (35.6%)	28 (14.4%)	X
Dementia-free	Metformin (824 out of 3,962)	X	428 (51.9%)	395 (47.9%)	11 (1.3%)	68 (8.3%)	13 (1.6%)	10 (1.2%)
	Insulin (1,577 / 7,489)	1,095 (69.4%)	X	702 (44.5%)	44 (2.8%)	352 (22.3%)	72 (4.6%)	52 (3.3%)
	Sulfonylurea (442 / 7,686)	361 (81.7%)	89 (20.1%)	X	7 (1.6%)	76 (17.2%)	16 (3.6%)	16 (3.6%)
	DPP-4i (1,100 / 10,756)	813 (73.9%)	473 (43.0%)	369 (33.6%)	23 (2.1%)	X	32 (2.9%)	55 (5.0%)
	GLP-1a (271 / 11,243)	192 (70.9%)	188 (69.4%)	75 (27.7%)	8 (3.0%)	89 (32.8%)	X	39 (14.4%)
	SGLT-2i (342 / 11,333)	276 (80.7%)	169 (49.4%)	105 (30.7%)	6 (1.8%)	90 (26.3%)	52 (15.2%)	X
	ITT: PS-matched baseline exposed	**Metformin**	**Insulin**	**Sulfonylurea**	**TZD**	**DPP-4i**	**GLP-1a**	**SGLT-2i**
Dementia	Metformin (478)	X	90 (18.8%)	70 (14.6%)	2 (0.4%)	14 (2.9%)	1 (0.2%)	4 (0.8%)
	Insulin (496)	281 (56.7%)	X	184 (37.1%)	7 (1.4%)	58 (11.7%)	5 (1.0%)	5 (1.0%)
	Sulfonylurea (190)	113 (59.5%)	23 (12.1%)	X	2 (1.1%)	12 (6.3%)	1 (0.5%)	2 (1.1%)
	DPP-4i (230)	142 (61.7%)	97 (42.2%)	69 (30.0%)	3 (1.3%)	X	6 (2.6%)	3 (1.3%)
	GLP-1a (39)	20 (51.3%)	31 (79.5%)	6 (15.4%)	0 (0.0%)	12 (30.8%)	X	4 (10.3%)
	SGLT-2i (51)	36 (70.6%)	25 (49.0%)	12 (23.5%)	0 (0.0%)	11 (21.6%)	8 (15.7%)	X
Dementia-free	Metformin (326)	X	54 (16.6%)	44 (13.5%)	0 (0.4%)	8 (2.5%)	0 (0.0%)	0 (0.0%)
	Insulin (481)	249 (51.8%)	X	159 (33.1%)	7 (1.5%)	42 (8.7%)	4 (0.8%)	5 (1.0%)

Sulfonylurea (169)	103 (60.9%)	28 (16.6%)	X	0 (0.0%)	12 (7.1%)	3 (1.8%)	2 (1.2%)
DPP-4i (233)	151 (64.8%)	78 (33.5%)	62 (26.6%)	6 (2.6%)	X	4 (1.7%)	6 (2.6%)
GLP-1a (35)	25 (71.3%)	24 (68.6%)	10 (28.6%)	0 (0.0%)	13 (37.1%)	X	2 (5.7%)
SGLT-2i (45)	30 (66.7%)	21 (46.7%)	13 (28.9%)	1 (2.2%)	8 (17.8%)	5 (11.1%)	X

Concurrent use was determined, either if the combination of drugs was observed at least once during the follow-up (as-treated analyses) or at baseline (intention-to-treat); DPP-4i, dipeptidyl-peptidase-4 inhibitors; GLP-1a, glucagon-like peptide-1 analogues; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; AT, as-treated; ITT, intention-to-treat;