Supplementary Material

Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers

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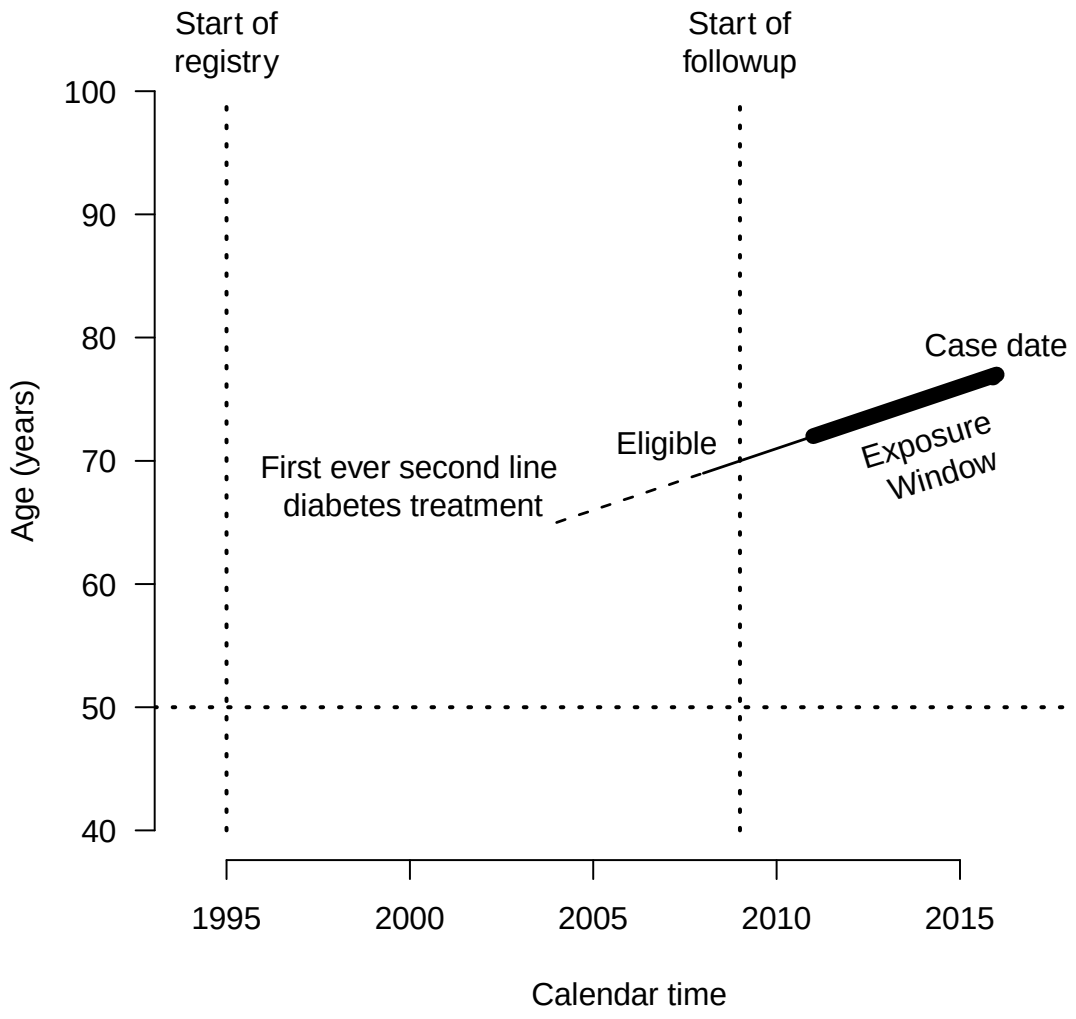
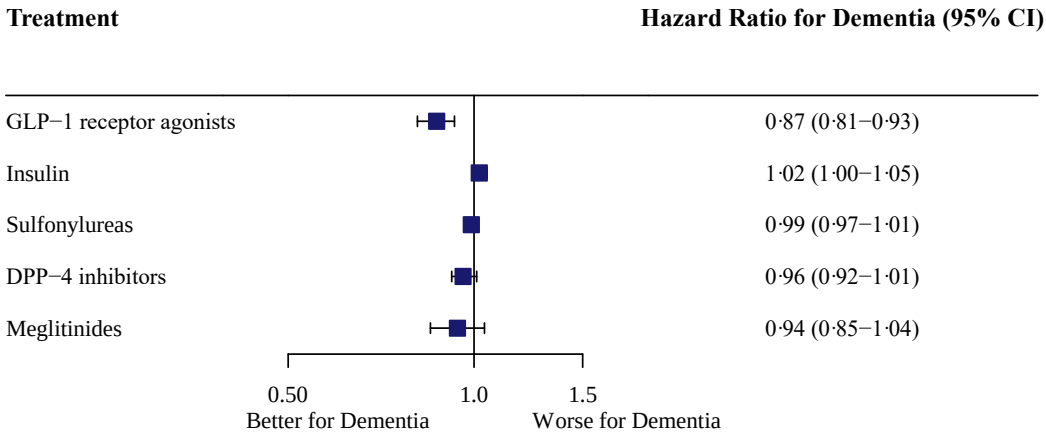
Figure S1. Study design used in the nationwide cohort



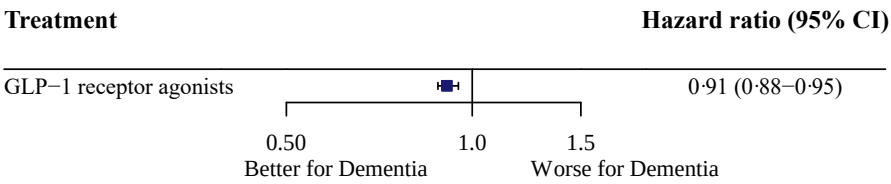
*First ever second-line diabetes treatment = first treatment with diabetes treatment not including metformin; eligible = eligible for cohort of diabetes patients; case date = date of dementia diagnosis with matching of each case to ten controls without dementia; exposure window 5-year window prior to case date, where duration of cumulative diabetes treatment is assessed.

Figure S2. HRs for dementia with increase in exposure duration to GLP-1RAs and other second-line diabetes treatments in the nationwide cohort excluding the last 2 years prior to case date



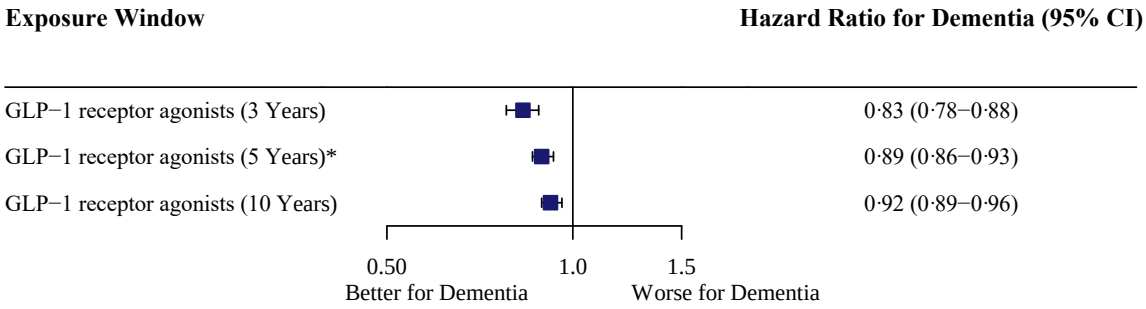
Cox proportional hazards regression models conducted for exposure to each treatment. Estimates denote the HR for a 1-year increase in duration of exposure. The models were adjusted for history of stroke, myocardial infarction, hypertension, educational attainment, and diabetes duration. Sex, age, and calendar date were included via matching. SGLT-2 inhibitors (HR: 0.98 (95% CI: 0.66–1.45) were not available throughout the entire study period. CI, confidence interval; DPP–4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; SGLT-2, sodium-glucose co-transporter-2.

Figure S3. HRs for dementia with yearly increase in exposure duration to GLP-1RAs and other second-line diabetes treatments in the nationwide cohort, where diabetes duration was defined as “time since first treatment with metformin or second-line diabetes treatment"



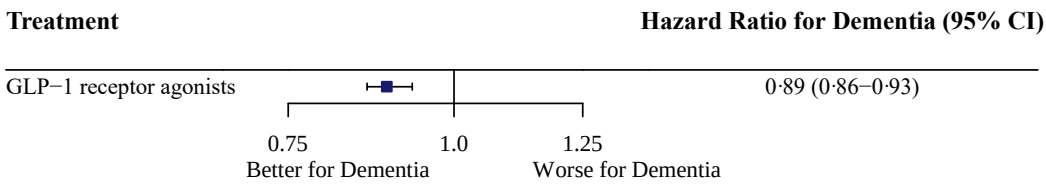
Cox proportional hazards regression models conducted for exposure to each treatment. Estimates denote the hazard ratio for a 1-year increase in duration of exposure. The models were adjusted for history of stroke, myocardial infarction, hypertension, educational attainment, and diabetes duration. Sex, age, and calendar date were included via matching. CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Figure S4. HRs for dementia with yearly increase in exposure duration to GLP-1RAs assessed 3, 5, and 10 years before diagnosis of dementia in the nationwide cohort



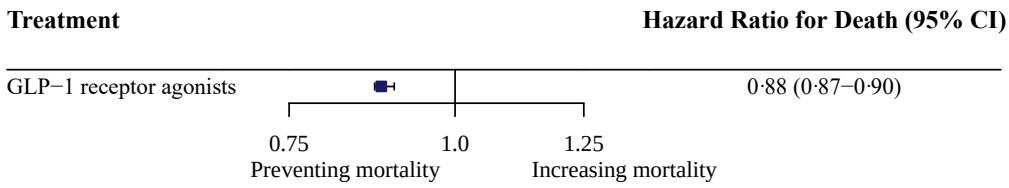
*Primary analysis. Cox proportional hazards regression models conducted for GLP-1RA exposure and assessed during a 3, 5, and 10-year exposure window prior to dementia. Estimates denote the hazard ratio for a 1-year increase in duration of exposure. The models were adjusted for history of stroke, myocardial infarction, hypertension, educational attainment, and diabetes duration. Sex, age, and calendar date were included via matching. CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Figure S5. HR for dementia with yearly increase in exposure duration to GLP-1RA exposure in the nationwide cohort adjusted for age, sex, and calendar date via matching



Cox proportional hazards regression model conducted for exposure to GLP-1 receptor agonists. The estimate denotes the hazard ratio for a 1-year increase in duration of exposure. The model was adjusted sex, age, and calendar date via matching. CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist.

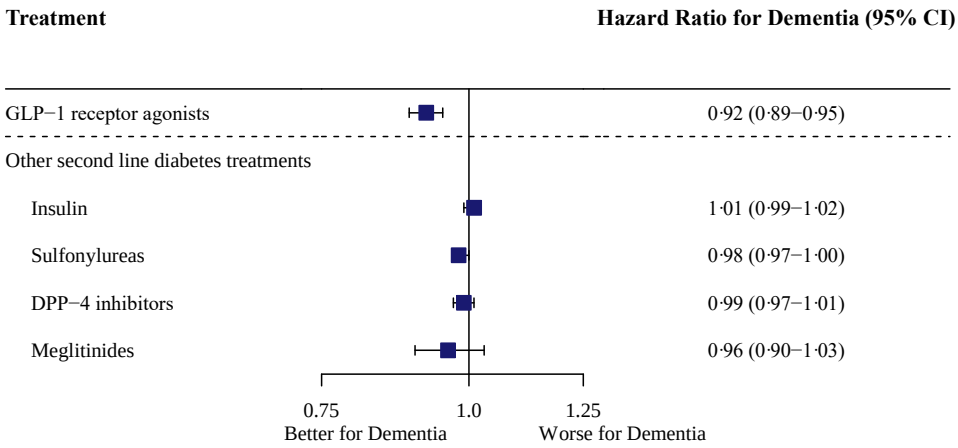
Figure S6. HR for competing risk of death with yearly increase in exposure duration to GLP-1RA in the nationwide cohort



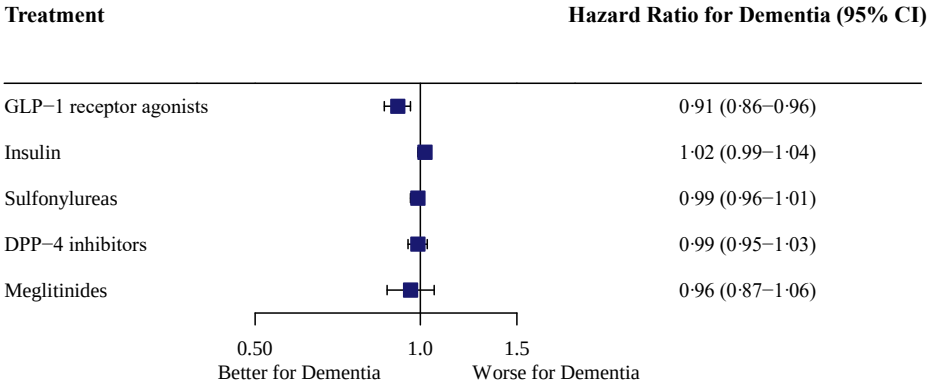
Cox proportional hazards regression model conducted for exposure to GLP-1 receptor agonists. The estimate denotes the hazard ratio for a 1-year increase in duration of exposure. The model was adjusted for history of stroke, myocardial infarction, hypertension, educational attainment, and diabetes duration. Sex, age, and calendar date were included via matching. CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist.

Figure S7. HRs for dementia with yearly increase in exposure duration to GLP-1RAs and other second-line diabetes treatments in the nationwide cohort (updated with 2018 register data)

A) Main analysis



B) Excluding the last 2 years prior to case date



Cox proportional hazards regression models conducted for exposure to each treatment. Estimates denote the hazard ratio for a 1-year increase in duration of exposure. As the nationwide cohort draws from living database it became possible during the reporting phase to update the cohort with 2018 data. Results based on re-running the primary statistical model on these updated data was aligned with primary pre-specified results. The models were adjusted for history of stroke, myocardial infarction, hypertension, educational attainment, diabetes duration, and income level. Sex, age, and calendar date were included via matching. SGLT-2 inhibitors (A) main analysis: HR: 0.87; 95% CI:

0.78–0.96, B) Excluding the last 2 years prior to case date: HR: 0.83; 95% CI: 0.67–1.03) were not available throughout the entire study period. CI, confidence interval; DPP–4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; SGLT-2, sodium-glucose co-transporter-2.

Table S1. Data sources

Data source	Registers/databases/ Clinical trial information	Variables
Pooled RCTs		
LEADER	ClinicalTrials.gov number, NCT01179048. Multicenter, double-blind, placebo-controlled trial conducted at 410 sites in 32 countries	Liraglutide vs. placebo
SUSTAIN-6	ClinicalTrials.gov number, NCT01720446. Multicenter, double-blind, placebo-controlled trial conducted at 230 sites in 20 countries	Subcutaneous semaglutide vs. placebo
PIONEER 6	ClinicalTrials.gov number, NCT02692716 Multicenter, double-blind, placebo-controlled trial conducted at 214 sites in 21 countries	Oral semaglutide vs. placebo
Nationwide cohort	The Danish National Patient Register	Diagnosis of: Dementia, hypertension, myocardial infarction, stroke, and chronic renal disease
	The Danish register of Medicinal Product Statistics	Treatment for: Dementia, diabetes, and hypertension
	Danish Register of Causes of Death	Vital status, causes of death
	Population Education Register	Educational attainment

RCTs, randomized controlled trials.

Table S2. Overview of definitions of diabetes treatments, dementia, and comorbidities for the nationwide cohort

Condition/treatment	ATC codes and ICD codes
Diabetes treatments (ATC codes)	
Metformin	A10BA02
Second-line diabetes treatments	
GLP-1RAs	A10BJ
Other second-line diabetes treatments	
Insulin	A10A
Acarbose	A10BF
DPP–4 inhibitors	A10BH
Sulfonylureas	A10BB
Meglitinides	A10BX
TZD*	A10BG
SGLT-2 inhibitors	A10BK
Dementia	
(ATC codes)	
Donepezil	N06DA02
Rivastigmine	N06DA03
Galantamine	N06DA04
Memantine	N06DX01
(ICD codes)	DF00, DG30, DF01, DF023, DF028, DF03
Comorbidities	
(ICD codes)	
Hypertension	ICD-10: DI10-DI13, DI15
	ATC: C02-C03, C07, C09
Myocardial infarction	ICD-8: 410
	ICD-10: DI21, DI22
Stroke	ICD-8: 433-438
	ICD-10: DI63, DI64, DG458, DG459
Chronic renal disease	ICD-8: 25002, 40039, 59009, 59320, 75310-75311, 75319
	ICD-10: DN158-DN159, DQ612-DQ613, DQ615, DG619, DE102,DE112

	DE132, DE142, DI120, DN160, DN162-DN164, DN168, DM300, DM313, DM319, DM321B

*These products were not available at the same calendar period as GLP-1 receptor agonists and thus were not considered alternative treatment options to GLP-1 receptor agonists.

ATC, Anatomical Therapeutic Chemical; ICD, International Classification of Diseases; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP–4, dipeptidyl peptidase-4; SGLT-2, sodium-glucose co-transporter-2; TZD, thiazolidinedione.

Table S3. Median follow-up and rates of dementia in each of the included RCTs

	N	Treatment groups	Median follow-up duration	Dementia SMQ GLP-1RAs		Dementia SMQ Placebo	
				No. of events	Rate	No. of events	Rate
LEADER* EX2211-3748	9340	Liraglutide vs. placebo	3.8 years	12	0.67	25	1.41
SUSTAIN-6† NN9535-3744	3297	Semaglutide (s.c) vs. placebo	2.1 years	3	0.88	5	1.47
PIONEER 6‡ NN9924-4221	3183	Semaglutide (oral) vs. placebo	1.3 years	0		2	0.96

*In LEADER, the minimum planned follow-up was 42 months, with a maximum of 60 months of receiving the assigned regimen and subsequently 30 days of follow-up.

†In SUSTAIN-6, the planned observation period was 109 weeks, consisting of 104 weeks of the assigned regimen and subsequently 5 weeks of follow-up.

‡In PIONEER 6, no predefined minimum treatment duration was required, but follow-up was required to continue until 122 events of the primary outcome had occurred.

*†‡In all three trials, the treatment for diabetes (excluding GLP-1 receptor agonists, dipeptidyl peptidase-4 inhibitors (DPP–4 inhibitors), and pramlintide) was adjusted or added in both arms, at the investigator's discretion.

GLP-1RA, glucagon-like peptide-1 receptor agonist; RCTs, randomized controlled trials; SMQ, Short-Memory Questionnaire.

Table S4. Dementia (Narrow Scope) SMQs search terms* applied in the post hoc analysis of the pooled RCTs

Name	Scope
Clinical dementia rating scale score abnormal	Narrow
Corticobasal degeneration	Narrow
Creutzfeldt-Jakob disease	Narrow
Dementia	Narrow
Dementia Alzheimer's type	Narrow
Dementia of the Alzheimer's type, uncomplicated	Narrow
Dementia of the Alzheimer's type, with delirium	Narrow
Dementia of the Alzheimer's type, with delusions	Narrow
Dementia of the Alzheimer's type, with depressed mood	Narrow
Dementia with Lewy bodies	Narrow
Early onset familial Alzheimer's disease	Narrow
Frontotemporal dementia	Narrow
Hippocampal sclerosis	Narrow
Korsakoff's syndrome	Narrow
Mini mental status examination abnormal	Narrow
Mixed dementia	Narrow
Presenile dementia	Narrow
Prion disease	Narrow
Progressive supranuclear palsy	Narrow
Scatolia	Narrow
Senile dementia	Narrow
Variant Creutzfeldt-Jakob disease	Narrow
Vascular dementia	Narrow

*Version 21.1.

RCTs, randomized controlled trials; SMQs, Standardized MedDRA Queries.

Table S5. Prespecified sensitivity analyses in the nationwide cohort

Sensitivity analyses
1) Exposure two years before the case date was ignored
2) Diabetes duration defined as “time since first treatment with metformin or second-line diabetes treatment
3) Shortening and lengthening the exposure windows (3- and 10-year, respectively)
4) Adjustment only via matching on age, sex, and calendar date
5) Competing risk of death

Table S6. HR for dementia in the pooled RCTs with specified dementia subtypes

Diagnoses	**GLP-1RA** No. of patients	**Placebo** No. of patients	**HR for dementia (95% CI)**
Dementia	6	15	
Dementia Alzheimer's type	5	7	
Dementia with Lewy bodies	0	2	
Mixed dementia	2	2	
Senile dementia	1	3	
Vascular dementia	1	3	
Total	15 (0.19%)	32 (0.40%)	0.47 (0.25–0.86)

CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; RCTs, randomized controlled trials.