Can Type 2 Diabetes Therapies Slow Cognitive Decline?
The Evidence

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Outline

- Type 2 diabetes & cognitive decline
- Glucose lowering & cognitive decline in Type 2 DM
- Type 2 diabetes drugs & cognitive decline in RCTs
- Effect of GLP-1 RAs on cognitive decline in RCTs
- The future

Diabetes & Cognitive Decline – Definitions

Biessels and Despa. Nat Rev Endocrin 2018; 14:591

- *MCI - Mild Cognitive Impairment*
  - Performance on cognitive tests that is 1.5 SD or more below "normal"
  - Affects at least 1 domain of cognitive function
  - Preserved activities of daily life
  - At high risk of transition to dementia
- *Dementia*
  - Objective cognitive impairment in multiple cognitive domains
  - Affects activities of daily life

Diabetes & Cognitive Decline – Epidemiology

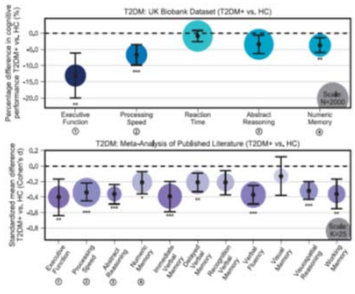
Biessels and Despa. Nat Rev Endocrin 2018; 14:591

- *Risk of MCI (Mild Cognitive Impairment) with Type 2 Diabetes*
  - 50% higher risk *vs.* no diabetes (HR ~1.5)
  - 70% higher risk of conversion MCI to dementia *vs.* MCI & no DM (RR ~1.7)
- *Risk of Dementia with Type 2 Diabetes*
  - 70% higher risk of all types of dementia *vs.* no DM (RR ~ 1.7)
    - Alzheimer's disease: 50% higher risk (RR ~ 1.5)
    - Vascular dementia: More than double the risk (RR ~2.3)

Diabetes & Cognitive Function - Epidemiology

Antal et al. Elife 2022 Online

- UK Biobank & meta-analysis
- N= 1012 Type 2 DM & 19,302 healthy controls (HC)
- Cognitive tests & imaging
- Compared to HC, type 2 DM
  - More cognitive deficits
  - More gray matter atrophy



New Diabetes & Dementia – Epidemiology

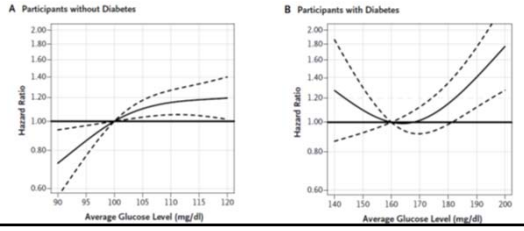
Haroon et al. Diabetes Care 2015; 38:1868

- Population-based matched cohort study of seniors in Ontario, Canada
- N= 225,045 with new DM & 668,070 no DM
  - Median age = 73
  - ID between 1995-2007 & followed → 2012 in the database for dementia
- HRs (adj for income, kidney disease, hypertension, vascular diseases)
  - Overall: 1.16 (95%CI 1.15 - 1.18)
  - Prior CVD: 2.03 (95%CI 1.18 - 2.19)
  - Prior PVD: 1.47 (95%CI 1.19 - 1.82)
  - Hypo hosp: 1.73 (95%CI 1.62 - 1.84)

Glucose Levels & Dementia

Crane et al. NEJM 2013;369:540

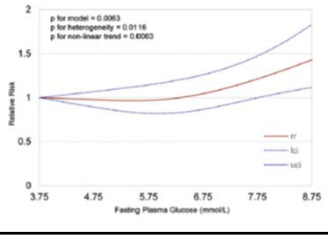
- N = 2067 without dementia (median age 76) followed for median 6.8 y
  - Each person's daily average glucose was estimated using G & GHb levels
- Risk of dementia by average glucose over the prior 5 y



Glucose Levels & Dementia

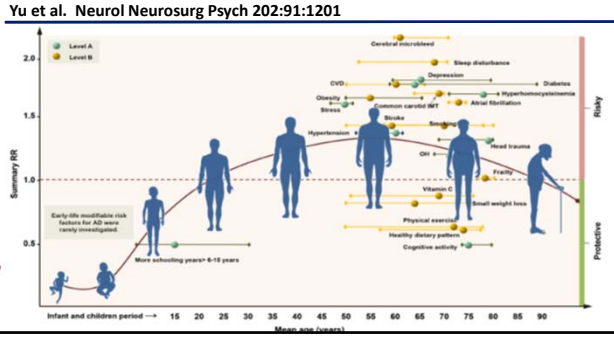
Xue et al. Aging Res Rev 2019;55:100944

- Meta-regression analysis of 4 prospective studies with available data
- FPG & risk of cognitive disorders (MCI or dementia)



Modifiable Risk Factors for Dementia

Yu et al. Neurol Neurosurg Psych 202:91:1201



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Glucose-Lowering & Cognitive Decline

Fink et al. Ann Intern Med 2018;168:39

Pharmacologic Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia
A Systematic Review

Outcome	Conclusion for Normal Cognition	Strength of Evidence (Justification)	Conclusion for MCI	Strength of Evidence (Justification)
Intensive vs. standard diabetes medication treatment (*k* = 2; *n* = 15 514)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Incident cognitive impairment (incident dementia or MMSE score <24)	No benefit (HR, 0.93 [95% CI, 0.86–1.00]) (*k* = 1; *n* = 11 685; 6.2 y)	Low (SLH, UC)	No data	Insufficient
Brief cognitive test	No benefit (*k* = 2; *n* = 14 479; 3.3–6.2 y)	Low (SLM, ND, NP)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	No benefit (*k* = 2; *n* = 14 479; 3.3–6.2 y)	Low (SLM, ND, NP)	No data	Insufficient
Memory	No benefit (*k* = 1; *n* = 2794; 3.3 y)	Low (SLM, ND, NP)	No data	Insufficient

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Diabetes Drugs & Cognitive Decline

- Metformin
  - Six observational studies (Campbell et al. J Alz Dis 2018;1255)
  - Meta-analyzed HR = 0.76 (95%CI 0.60 - 0.97)
- RCTs of Diabetes Drugs
  - Cochrane meta-analysis (Sastre et al. Cochrane Database Syst Rev 2017;6:6)

Authors' conclusions

We found no good evidence that any specific treatment or treatment strategy for Type 2 diabetes can prevent or delay cognitive impairment. The best available evidence related to the comparison of intensive with standard glycaemic control strategies. Here there was moderate-quality evidence that the strategies do not differ in their effect on global cognitive functioning over 40 to 60 months.

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GLP-1 RA CVOT Meta-analysis

Sattar et al. Lancet Diabetes & Endocrinology 2021; Online

Cardiovascular Event	GLP-1 RA (*n* = 30,694)	Placebo (*n* = 29,386)	HR (95% CI)	Number Needed to Treat (95% CI)	*P*
MI, stroke, CV death	3,137	3,429	0.86 (0.80–0.93)	65 (45–130)	<0.001
Cardiovascular death	1,288	1,421	0.87 (0.80–0.94)	163 (103–353)	0.001
Fatal or nonfatal MI	1,631	1,724	0.90 (0.83–0.98)	175 (103-878)	0.020
→ Fatal or nonfatal stroke	769	884	→ 0.83 (0.76–0.92)	198 (140–421)	<0.001

Assessment of Neuroprotection in REWIND

Gerstein et al. Lancet D&E 2020;8:106 & Cukierman-Yaffe et al. Lancet Neur 2021; 19:582

REWIND (Researching CV Events with a Weekly INcretin in Diabetes)
Dulaglutide CV Outcomes Trial

In men & women with established or newly detected type 2 diabetes & additional CV risk factors…

… wkly sc. injection of the GLP-1 analog dulaglutide* (1.5 mg) vs. placebo

• **9901 Pts:**	Age 66; 46% Women
• **Prior CVD:**	31%
• **Median F/U:**	5.4 y (IQR 5.1, 5.9)
• **Pt - years F/U:**	51820
• **Retention:**	97%
• **Vital Status:**	99.7%
• **Adherence:**	82%
• **Stopped for AE:**	11% dulaglutide; 7.5% placebo

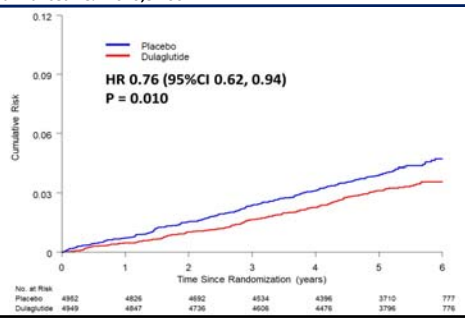
GLP-1 RA Neuroprotection in REWIND

Using Dulaglutide 1.5 mg/wk

- Dulaglutide reduced the MACE composite (nonfatal stroke, nonfatal MI or CV death) with consistent effects across all 3 components
- The REWIND data suggests a greater effect on stroke *vs.* other components of the composite

Effect on All Stroke

Gerstein et al. Lancet D&E 2020;8:106



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- The meta-analysis of all 8 GLP-1 RA trials supports the hypothesis of a greater effect on stroke with a meta-analysed
  - HR for stroke: 0.83 (95%CI 0.76, 0.92)
  - HR for stroke (without ELIXA): 0.81 (95%CI 0.74, 0.90)

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  - HR for stroke: 0.83 (95%CI 0.76, 0.92)
  - HR for stroke (without ELIXA): 0.81 (95%CI 0.74, 0.90)
- Animal studies suggest neuroprotective effects of GLP-1 RAs
- Dulaglutide's effects on cognitive impairment were therefore explored

Cognitive Tests in REWIND

Cukierman-Yaffe et al. Lancet Neur 2021; 19:582

The Montreal Cognitive Assessment (MoCA) & Digit Symbol Substitution Test (DSST) were administered at t = 0, 2 y, 5 y & study end

MoCA: 1 page, 30 items, tests 7 cognitive domains; takes ~ 10 min
Completed forms all validated at PHRI (before study end)
Mean normal score = 27.4 (2.2)

DSST: 1 page, tests cognitive function, takes 2 min
Scores were sent centrally by the site & recorded
Mean scores in RCTs = 36-52 (max = 135)

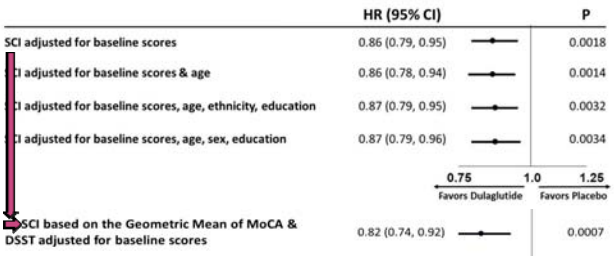
The Primary Cognitive Outcome

Country-standardized Substantive Cognitive Impairment (SCI)

- A follow-up country-standardized, baseline-adjusted MoCA or DSST value ≤ -1.5 (i.e. 1.5 SDs or more below baseline)
- All analyses were restricted to the 8828 people who had:
  - a baseline & at least 1 follow-up MoCA
  - a baseline & at least 1 follow-up DSST
- Cox models assessed the HR of SCI for dulaglutide *vs.* placebo (i.e. the time to the 1st follow-up score ≤ -1.5)

Effect on Country-Standardized SCI

Adjusted for Each Person's Baseline MoCA & DSST Score

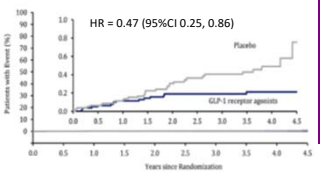


Cukierman-Yaffe, Gerstein et al. Lancet Neur 2021; 19:582 & JCEM 2022 Online

Other GLP-1 RAs & Dementia

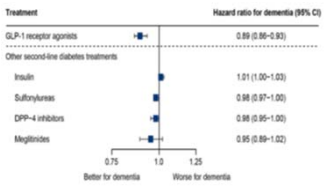
Norgaard et al. Trans Res Clin Int 2022; Online

- N=15,820; median follow-up 3.6 y
- LEADER, SUSTAIN 6, & PIONEER 6
- Pooled analysis: dementia-related AEs
- 15 on GLP-1 RA; 32 on placebo → Dx



Database Analysis

- N=120, 054 in the Danish Rx registry
- All 2nd line Rx from Jan 1995 – Dec 2017
- Linked to dementia Dx: 2009 onwards



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Oral Semaglutide for Early Alzheimer's - Trial

EVOKE Trial (Clinicaltrials.gov NCT04777396)

- Design: Double Blind RCT
- Pts: Age 55-85 with MCI & MMSE ≥ 22
  Amyloid in PET or CSF
  CDR (Clinical Dementia Rating) Score ≥ 0.5 in ADL, or global score ≥ 1
  RBANS (Repeatable Battery for Assessment of Neuropsych Status) ≤ 85
  Exclude small vessel disease
- Size: N = 1840
- Rx: Oral semaglutide 14 mg or placebo
- Duration: 173 wks
- Outcome: CDR Score Change Baseline → 104 Mo

Oral Semaglutide for Early Alzheimer's - Trial

EVOKE Plus Trial (Clinicaltrials.gov NCT04777409)

- Design: Double Blind RCT
- Pts: Age 55-85 with MCI & MMSE ≥ 22
  Amyloid in PET or CSF
  CDR (Clinical Dementia Rating) Score ≥ 0.5 in ADL, or global score ≥ 1
  RBANS (Repeatable Battery for Assessment of Neuropsych Status) ≤ 85
  No exclusion of small vessel disease
- Size: N = 1840
- Rx: Oral semaglutide 14 mg or placebo
- Duration: 173 wks
- Outcome: CDR Score Change Baseline → 104 Mo

Summary & Conclusions

- Diabetes independently increases cognitive decline
- Except for GLP-1 RAs, no RCT evidence that Rx reduces cognitive decline
- Large outcomes trials in people with type 2 DM consistently show that
  - GLP-1 RAs reduce CV outcomes, & have the largest benefit on stroke
  - The REWIND trial shows
    - Stroke benefit was for ischemic stroke
    - Dulaglutide reduced cognitive impairment *vs.* placebo
  - A pooled analysis of LEADER, SUSTAIN6 & PIONEER 6
    - suggests reduced dementia AEs with liraglutide or semaglutide
- Ongoing trials are prospectively assessing GLP-1 RA cognitive effects
- GLP-1 RAs hold significant promise for mitigating cognitive decline