SUPPLEMENTARY INFORMATION for

Type 2 diabetes in dementia and Alzheimer's disease: Intertwined global health issues brewing on the horizon

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Table S1. Summary of select studies of diabetes on cognitive impairment/decline or Alzheimer's disease/dementia risk.

Entries arranged alphabetically by the first author's name.

*Incomplete years of study enrollment and duration rounded to the indicated year.

**Limitations and strengths as cited by papers.

Study	Country & region	Time*	Study participants	Study design	Study tools	Study findings	Study limitations/strengths**
Barbiellini Amidei et al.[1]	United Kingdom	1985-2019	10,095 participants	Population-based, prospective, longitudinal	Whitehall II study. T2D by FBG ≥126 mg/dL, physician diagnosis, diabetes medication use, hospital record of diabetes from 1985 to 2019; incident dementia by EHR; clinical variables, lifestyle factors.	1,710 T2D and 639 dementia cases recorded at median 31.7-y follow-up. Vs. without T2D at age 70 y, T2D onset >10 y earlier had HR 2.12 (95%CI 1.50, 3.00), T2D onset 6 to 10 y earlier had HR 1.49 (95%CI 0.95, 2.32), and T2D onset <5 y earlier had HR 1.11 (95%CI 0.70,1.76) for dementia, adjusted for age, sex, race, BMI, hypertension, cardiovascular disease (coronary heart disease, heart failure, stroke), antidepressant use, cardiovascular disease drug use, education, smoking, alcohol, physical activity, diet, and birth cohort; linear trend ($p<0.001$) indicates graded link of T2D onset age to dementia. At age 70 y, every 5-y younger T2D onset age significantly linked to dementia (HR 1.24, 95%CI 1.06, 1.46), adjusted as above. Analysis by *APOE4* did not alter results of the main analysis.	*Limitations*: Lacked data on dementia subtypes; diabetes (16.5%), dementia (6.3%) prevalence lower than general UK population, participants healthier; lacked HbA1c data earlier in the study, so not used for diabetes diagnosis; dementia based on EHR not in-person, may have missed mild cases; participant age at follow-up 69-89 y, did not all reach the age when dementia is more prevalent. *Strengths*: None stated.
Chatterjee et al.[2]	Worldwide	Included studies with baseline years ranging from 1974 to 2008	2,310,330 participants and 102,174 dementia cases from 14 studies	Meta-analysis	Included prospective studies measuring the T2D (measured or by self-report) association to dementia (assessed by clinical exam/tests/criteria, ICD codes); excluded randomized controlled trials as nongeneralizable to the population. Methodological quality of studies assessed by the Newcastle-Ottawa Scale; heterogeneity assessed by I^2.	T2D linked to 60% higher dementia risk in both sexes (females: RR 1.62 [95%CI 1.45–1.80]; males: RR 1.58 [95%CI 1.38–1.81]), multiply adjusted for age and various other covariates. T2D linked to VaD (females: RR 2.34 [95%CI 1.86–2.94); males: RR 1.73 [95%CI 1.61–1.85]) non-VaD (females: RR 1.53 [95%CI 1.35–1.73]; males: RR 1.49 [95%CI 1.31–1.69]), adjusted as above. T2D females had 19% higher VaD risk vs. T2D males (multiple-adjusted female-to-male ratio of RR 1.19 [95%CI 1.08–1.30; $p<0.001$]).	*Limitations*: Variation in study design, duration, diabetes ascertainment of included studies; impact of differing dementia diagnosis methods on conclusions unquantifiable; VaD overlap with AD may have overestimated diabetes link to dementia; lacked diabetes duration and control data; did not include data from 14 eligible cohorts (2,300 incident dementia cases; most dementia cases from 2 large studies. *Strengths*: None stated.
Jancev et al.[3]	Sweden	1996-2019	43,440 T1D participants; 217,109 age-, sex-, and county-matched controls	Nationwide, register-based, prospective, longitudinal	Swedish National Diabetes Register for T1D participants; Swedish Total Population Register for controls. T1D defined by treatment with insulin only and diabetes onset age ≤30 y; all-cause dementia from Swedish National Patient Register by ICD-10 codes for all-cause dementia, AD, VaD, non-AD-non-VaD dementia; clinical variables.	14.3-y median follow-up, 530 (1.2%) and 1,867 (0.9%) incident dementia cases in T1D and matched controls participants, respectively. Vs. control, T1D linked to higher all-cause dementia risk (HR 2.02 [95%CI 1.83–2.23]), AD (HR 1.38 [95%CI 1.13–1.69]), VaD (HR 3.73 [95%CI 3.07–4.52]), and non-AD–non-VaD (HR 1.87 [95%CI 1.63–2.15]), adjusted for age, sex, education, marital status. Dementia risk factors in T1D beyond age were longer T1D duration, higher HbA1c, higher systolic blood pressure, history of stroke or transient ischemic attack, history of cardiovascular disease, lower education level, single marital status.	*Limitations*: Lacked data on potential confounding factors; used ICD-10 codes, lacked cognitive tests, mixed dementia subtypes, biomarker data, may have underestimated diabetes-dementia relation due to missed early cases; 53% missingness for LDL-c; baseline analyses, lacked cumulative effect of risk exposure, may have underestimated diabetes-dementia relation; lacked trajectories information; population mostly born in Sweden, generalizability uncertain. *Strengths*: Large, prospective, nationwide cohort; prospective dementia ascertainment; available covariate data.

Study	Country & region	Time*	Study participants	Study design	Study tools	Study findings	Study limitations/strengths**
Rawlings et al.[4]	USA	1990-1992 baseline; 2011-2013 follow-up	13,351 participants	Community-based, prospective, longitudinal	Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Diabetes by self-reported physician diagnosis, diabetes medication use, or HbA1c ≥ 6.5%; cognition by DWRT (verbal learning, recent memory), DSST (executive function and processing speed), WFT (executive function and language); clinical variables, lifestyle factors.	20-y follow-up; midlife diabetes linked to 19% more cognitive decline (adjusted global Z-score difference −0.15, 95%CI −0.22, −0.08) vs. without diabetes, adjusted for age, age squared, sex, race/center, BMI, hypertension, history of coronary heart disease, history of stroke, *APOE4*, education, smoking, alcohol, and interactions between all covariates and time. Cognitive decline significantly higher in persons with prediabetes (HbA1c 5.7-6.4%; vs. those without diabetes and HbA1c<5.7%), with poorly controlled diabetes (HbA1c≥7.0%; vs. those whose diabetes was controlled), and longer diabetes duration. No significant differences by race.	*Limitations*: Observational, precludes causal inference, and possible residual confounding; only one test per cognitive domain at each visit; single HbA1c baseline measurement; attrition, possible bias; Black participants from just 2 study sites. *Strengths*: Large, community-based population of Black and White participants; long follow-up; assessed cognition over time; rigorously assessed variables that might impact link of diabetes to cognitive function; methods reduced effects of attrition.
Schneider et al.[5]	USA	2011-2013	1,713 participants	Community-based, prospective; cross-sectional analysis	Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Diabetes by self-reported physician diagnosis, diabetes medication use, or HbA1c ≥ 6.5%; brain imaging by MRI for total and regional brain volumes, microhemorrhages, cortical and lacunar infarcts, WMH volumes; clinical variables, lifestyle factors.	Diabetes with HbA1c ≥7.0% linked to smaller total brain volume (β −0.20 SD, 95%CI −0.31, −0.09), smaller regional brain volumes (including frontal, temporal, occipital, parietal lobes; deep GM; Alzheimer disease signature region; hippocampus), and higher WMH burden (p=0.016) vs. without diabetes, adjusted for age, sex, race/center, hypertension, cardiovascular disease, *APOE4*, education, smoking, and total intracranial volume (when outcome is volume). No significantly different brain volumes or vascular pathology in prediabetes and diabetes with HbA1c <7.0%. Diabetes with HbA1c ≥7.0% (vs. diabetes with HbA1c <7.0%) had smaller total and regional brain volumes and higher WMH burden. Diabetes with longer ≥10-y duration (vs. diabetes duration <10 y) had smaller brain volumes and higher lacune burden. No evidence for mediation by WMH in diabetes associations to smaller brain volumes.	*Limitations*: Lacked within-person MRI assessments; cross-sectional, reverse causation possible (participants with impaired cognition become less compliant with medication). *Strengths*: Detailed diabetes, diabetes severity, MRI, covariate, assessments.
Shang et al.[6]	United Kingdom	2006-2021	1,376 diabetes participants, 2,752 randomly selected controls for brain volume analysis; 25,141 diabetes participants and 50,282 randomly selected controls for dementia analysis	Community-based, prospective, longitudinal	UK Biobank study. Diabetes by self-report along with age of diagnosis; dementia by hospital inpatient records and mortality register for all-cause, AD, VaD; brain imaging by MRI for total brain, GM, WM volumes; clinical variables, lifestyle factors.	Median 11.9-y follow-up; only T2D diagnosed <50 y and T1D diagnosed <30 y linked to smaller total brain, GM, and WM volumes, adjusted for age, sex, ethnicity, HbA1c, BMI, HDL-c, LDL-c, TGs, hypertension, heart disease, stroke, depression, *APOE4*, education, smoking, alcohol, physical activity, sleep duration, and income. At median 11.9-y follow-up, 2,035 incident dementia cases; younger T2D diagnosis age linked to higher risk of dementia, adjusted as above; T2D diagnosed <50 y linked to highest HR 2.03 (95%CI 1.53, 2.69) for all-cause dementia, HR 1.72 (95%CI 1.08, 2.75) for AD, HR 2.37 (95%CI 1.45, 3.85) for VaD, adjusted as above; T1D diagnosed <30 y linked to all-cause dementia (HR 2.08, 95%CI 1.40, 3.09) and VaD (HR 2.87, 95%CI 1.34, 6.12), adjusted as above.	*Limitations*: For dementia, participants mostly of European descent, generalizability uncertain; for MRI, higher proportion of male and high-income participants, generalizability uncertain; may not have captured all dementia cases; individuals with dementia may have dropped out, possible selection bias; some controls may have developed diabetes at follow-up; effect sizes of diabetes on brain volume small; small sample size of participants <40 y of age; single HbA1c measurement. *Strengths*: Large population.

Study	Country & region	Time*	Study participants	Study design	Study tools	Study findings	Study limitations/strengths**
Wang et al.[7]	China	2011-2018	6,125 participants	Longitudinal	China Health and Retirement Longitudinal Study. Prediabetes by FBG 100-125 mg/dL or HbA1c 5.7-6.4%; diabetes by FBG ≥126 mg/dL or HbA1c ≥ 6:5%; cognition by TICS-10 (orientation and attention), word recall (episodic memory), figure drawing (visual-spatial abilities); clinical variables, lifestyle factors.	At baseline, mean age (SD) 58.93 (9.76) y, 3,987 (45.7%) male, 1,802 (20.7%) with newly diagnosed prediabetes, 935 (10.7%) with diabetes. 8-y follow-up; diabetes significantly linked to cognitive decline (unstandardized β estimate −0.50, 95%CI −0.98, −0.02), adjusted for age, sex, BMI, dyslipidemia, hypertension, HbA1c, HDL-c, LDL-c, TGs, baseline cognitive function, baseline depressive symptoms, blood urea nitrogen, creatinine, high-sensitivity C-reactive protein, hemoglobin, cystatin C, education, ever smoking, ever drinking, marital status, and self-reported health status. By sex, diabetes significantly linked to cognitive decline in females (β −0.75, 95%CI −1.43, −0.07) but not males. In prediabetes, TG levels negatively linked to cognitive decline; in diabetes, high-sensitivity C-reactive protein linked to cognitive decline.	*Limitations*: Participants aged >45 y, generalizability uncertain; follow-up possibly not long enough to capture cognitive decline; undiagnosed diabetes prevalence considerable in China, uncontrolled long-term diabetes possible in the "newly diagnosed" group; lacked data on antidiabetic medication use. *Strengths*: Large sample, longitudinal, long follow-up; assessed prediabetes and diabetes as exposures; collected comprehensive data on covariates.
Zhang et al.[8]	Worldwide	Included studies from 1997 to 2014	Participants (n=1,746,777) from 17 studies	Meta-analysis	Included longitudinal, observational studies measuring the diabetes (clinically measured) association to dementia (diagnostic criteria). Excluded low-quality studies; quality assessed via STROBE criteria; heterogeneity assessed by I^2.	Vs. control, diabetes significantly linked to higher AD risk (RR 1.53, 95%CI 1.42, 1.63). Stratified by race, 5 cohorts were Eastern (Asian), 12 were Western (European descent). Diabetes linked to higher AD risk in Western populations (RR 1.36, 95%CI 1.18, 1.53) and Eastern populations (RR 1.62, 95%CI 1.49, 1.75).	*Limitations*: Fewer diabetic participants of Eastern descent (n=63,253), so results should be interpreted cautiously. *Strengths*: None stated.
Zhou et al.[9]	United Kingdom	2006-2021	Female (n=243,659) and male (n=204,256) participants	Community-based, prospective, longitudinal	UK Biobank study. Diabetes by EHR ICD codes; dementia by EHR ICD codes for all-cause, AD, VaD; clinical variables, lifestyle factors.	Median 11.9-y follow-up; Vs. non-T2D, T2D significantly linked to higher all-cause dementia (HR 2.85, 95%CI 2.56, 3.17), AD (HR 2.38, 95%CI 2.07, 2.73), VaD (HR 3.93, 95%CI 3.36, 4.59) risk, adjusted for age at last follow-up, race/ethnicity, BMI, hypertension, *APOE4*, smoking, education, income, physical activity, leisure activities. Vs. non-T2D, T2D males and females at significantly higher all-cause dementia, AD, VaD risk, adjusted as above. Vs. T2D males, T2D females at significantly higher AD risk (ratio HR 1.56, 95%CI 1.20, 2.02), adjusted as above. Insulin use linked to higher VaD risk. Comorbidities linked to higher dementia, AD, VaD risk.	*Limitations*: Mostly White population, generalizability uncertain; lacked data on T2D duration, dose of insulin use, other antidiabetic medication use, other comorbidity covariates. *Strengths*: Large sample; T2D, dementia ascertained by EHR, avoid bias from self-report; examined dementia subtypes.

95%CI, 95% confidence interval; *APOE4*, apolipoprotein E4; BMI, body mass index; DSST, Digit Symbol Substitution Test; DWRT, Delayed Word Recall Test; EHR, electronic health record; GM, grey matter; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; HR, hazard ratio; ICD, International Classification of Diseases; LDL-c, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; RR, relative risk; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; T1D, type 1 diabetes; T2D, type 2 diabetes; TGs, triglycerides; TICS-10, Telephone Interview of Cognitive Status; WFT, Word Fluency Test; VaD, vascular dementia; WM, white matter; WMH, white matter hyperintensities; y, year.

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