Journal of Diabetes and Its Complications 34 (2020) 107674

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Diabetes-specific dementia risk score (DSDRS) predicts cognitive performance in patients with type 2 diabetes at high cardio-renal risk

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ARTICLE INFO

Article history:
Received 24 April 2020
Received in revised form 19 June 2020
Accepted 8 July 2020
Available online 16 July 2020

Keywords:
Dementia
Diabetes-specific dementia risk score
Cognitive impairment
Type 2 diabetes

ABSTRACT

Aim: To investigate the relationship between the diabetes-specific dementia risk score (DSDRS) and concurrent and future cognitive impairment (CI) in type 2 diabetes (T2D).
Methods: DSDRS were calculated for participants with T2D aged ≥60 years from the CARMELINA-cognition substudy (ClinicalTrials.gov Identifier: NCT01897532). Cognitive assessment included Mini-Mental State Examination (MMSE) and a composite attention and executive functioning score (A&E). The relation between baseline DSDRS and probability of CI (MMSE < 24) and variation in cognitive performance was assessed at baseline (n = 2241) and after 2.5 years follow-up in patients without baseline CI (n = 1312).
Results: Higher DSDRS was associated with a higher probability of CI at baseline (OR = 1.17 per point, 95% CI 1.12–1.22) and follow-up (OR = 1.24 per point, 95% CI 1.14–1.35). Moreover, in patients without baseline CI, higher DSDRS was also associated with lower baseline cognitive performance (MMSE: $F(1, 1930) = 47.07$, $p < .0001$, $R^2 = 0.02$); A&E z-score: ($F(1, 1871) = 33.44$ $p < .0001$, $R^2 = 0.02$) and faster cognitive decline at follow-up (MMSE: $F(3, 1279) = 38.41$, $p < .0001$; A&E z-score: $F(3, 1206) = 148.48$, $p < .0001$).
Conclusions: The DSDRS identifies patients with T2D at risk of concurrent as well as future CI. The DSDRS may thus be a supportive tool in screening strategies for cognitive dysfunction in patients with T2D.

1. Introduction

People with type 2 diabetes (T2D) are twice as likely to develop dementia compared to people without diabetes.[1] This is of concern, since cognitive impairment, also already in pre-dementia stages, can interfere with diabetes self-management and is associated with an increased risk of severe hypoglycemic events.[2,3] For this reason, recent diabetes management guidelines recommend clinicians to screen for cognitive impairment in patients with T2D.[2–6]

In 2013, the diabetes-specific dementia risk score (DSDRS) was introduced to help researchers and clinicians identify T2D individuals at risk of developing dementia.[7] The DSDRS predicts the 10-year dementia risk in patients with T2D and incorporates several readily available dementia-risk factors, such as diabetes-related complications, level of education, depression and cerebro- and cardiovascular disease. The DSDRS was developed based on a population-based registry, without availability of formal cognitive testing in all individuals. Hence, it is not clear yet if the DSDRS can also identify individuals with T2D with concurrent cognitive dysfunction cross-sectionally. Moreover, it is unknown if the DSDRS is able to predict future cognitive decline, even when it is less severe than frank dementia.

Therefore, we studied the relationship between DSDRS and concurrent cognitive performance at the moment of DSDRS assessment as well as change in cognition over 2.5 years in a large prospective cohort of people with T2D at high cardio-renal risk.

2. Methods

2.1. Population

We investigated data of 2694 T2D patients included in the CARMELINA-COG study.[8] The CARMELINA-COG study was an integral

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https://doi.org/10.1016/j.jdiacomp.2020.107674

part of a multicenter, international, randomized, double blind study in patients with type 2 diabetes at high cardio-renal risk (CARMELINA®: ClinicalTrials.gov Identifier: NCT01897532) that investigated if treatment with linagliptin vs placebo resulted in a lower incidence of accelerated cognitive decline.

CARMELINA included adults with type 2 diabetes, HbA1c 6.5–10.0%, at high cardiovascular risk (history of vascular disease and urine albumin-to-creatinine ratio (UACR) of 30 mg/g (or equivalent)) or high renal risk (estimated glomerular filtration rate (eGFR) of 45–75 mL/min/1.73 m2 and UACR of 200 mg/g (or equivalent) or eGFR of 15–45 mL/min/1.73 m2 regardless of UACR). Participants with end-stage kidney disease, defined as eGFR of <15 mL/min/1.73 m2 or requiring maintenance dialysis, were excluded (more details[9]). CARMELINA-COG only included participants from countries using the Latin alphabet with documented years of education and a valid baseline cognitive assessment. A cognitive assessment was considered invalid when documented test scores were considered implausible (i.e. unrealistic values). The CARMELINA-COG study found neutral results for the effect of linagliptin versus placebo on accelerated cognitive decline (more details[8]). Therefore we made no distinction between both treatment arms in the present study. The present study is restricted to participants with a minimum age of 60 at baseline, since the DSDRS model is only validated in a population of 60 years and older. A valid follow-up cognitive assessment was required for the longitudinal analyses (see below).

2.2. Measurements

2.2.1. Cognitive performance

Cognitive performance was assessed using three easy-to-administer neuropsychological tests:

- The Mini-Mental State Examination (MMSE), a widely known screening test, is used to assess global cognitive performance.[10] The MMSE has a maximum score of 30 and evaluates different cognitive functions including orientation in time and place, verbal registration, short term verbal memory, attention, language and visuoconstruction. A MMSE score below 24 indicates cognitive impairment (CI).[11,12] Participating centers used country-specific validated versions.
- The Trail Making Test (TMT) is a timed test, that assesses psychomotor speed, scanning, divided attention and mental flexibility.[13] Its timing aspect makes it sensitive for subtle changes in cognitive performance that are commonly seen in type 2 diabetes.[14] The TMT consists of two parts. In part A, participants are required to connect numbered circles in consecutive order as fast as possible (1 – 2 – 3 etc.). It measures psychomotor speed, scanning abilities and number sequencing. For part B, participants alternate between numbered and lettered circles, also in consecutive order (1 – A – 2 – B etc.). Part B measures divided attention, working memory and task shifting.[13,15] It is more time consuming and error-prone than part A. The TMT ratio score ((TMT-B – TMT-A)/TMT-A) reflects executive functioning and reflects the additional time needed to complete part B, corrected for the time needed to complete part A.
- The Verbal Fluency Test (VFT) is a timed test and measures someone's fluency of speech, which is dependent on vocabulary size, lexical access speed, strategy finding, updating and inhibition ability.[16] Participants are instructed to verbalize as many words from a certain category (i.e. animals) within 60 s. Participants were also asked to list words starting with the same letter (i.e. F – A – S). Word generation according to an initial letter gives the greatest scope for seeking strategies guiding the search for words. Category-driven search provides more structure in search strategy.[13] Both VFT measures are combined into one overall z-score. Since language-specific differences in word frequencies are known, all fluency scores were adjusted for each individual's native language, as described elsewhere.[8]

A composite score combining both the z-scores on the Trail Making Test (TMT) and the Verbal Fluency Test (VFT) is used to assess attention and executive functioning all together in one robust score (A&E score), sensitive for capturing the subtle changes that are seen in type 2 diabetes (for more details about the derivation[8]). A cognitive assessment at baseline is considered valid when it includes at least an available MMSE score. At follow-up at least a score on one of the cognitive tests (MMSE, TMT or/and VFT) should be available.

2.2.2. Diabetes-specific dementia risk scores

Individual dementia risk scores were calculated with help of the diabetes-specific dementia risk model (DSDRS).[7] This prognostic model was developed for calculating individual 10-year dementia risk in patients with T2D of 60 years and older, based on eight predictors that were most strongly predictive of clinical diagnosis of dementia in T2D; age, years of education, acute metabolic event, microvascular disease, clinical diagnosis of diabetic foot, depression, cerebro- and cardiovascular disease (Appendix Table A.1). Individual sum scores on the DSDRS, ranging from −1 (low risk) to 19 (high risk), were calculated by simply adding up each relative contribution of the predictors as defined in the original model (Appendix Fig. A.1).

For the main group analysis in the current study, we used a modified version of the model, since information about history of cardiovascular and cerebrovascular disease was only available in the CARMELINA dataset for participants with albuminuria. Hence, a maximum DSDRS of 16 rather than the original 19 could be obtained. All analyses were repeated separately in the albuminuria subgroup with available history of cardio-and cerebrovascular disease with the full 19-point model. For the predictor microvascular disease, the original DSDRS model used the definition of 'diabetic retinal disease and/or end-stage renal disease'. We used a definition of 'diabetic retinopathy and/or severe nephropathy with an eGFR < 30' instead, since the CARMELINA trial did not include patients with end-stage renal disease. For the predictor 'level of education', the original DSDRS model used the definition high school or less/college or more. We used years of formal education as an indicator of educational attainment, since multiple countries with different educational systems are included in CARMELINA. For the prediction model this was dichotomized in years of formal education at or below the median/above the median of the study population (Appendix Table A.1).

For both the main group and subgroup analyses, sum scores on the DSDRS above 10 were taken together in one category due to small sample sizes in the high risk groups. Because the treatment effect in the CARMELINA trial on cognition was neutral, treatment allocation was not considered in the analyses.[8]

2.3. Statistical analyses

2.3.1. Baseline

Logistic regression analysis was used to calculate the probability of CI (MMSE < 24) according to sum risk scores on the DSDRS. Next, for participants without CI (MMSE ≥ 24), the relationship between sum risk scores on the DSDRS and cognitive performance (MMSE and A&E z-score) was assessed using linear regression analysis. Demographic variables were not included as co-variates in the model, since these are already included in the DSDRS itself (i.e. age, years of education). We performed sensitivity analyses stratified by age bands in years (i.e. 60–64, 65–69, 70–74, 75–79, 80–84, 85+) to look at age independent effects.

2.3.2. Follow-up

In individuals that had no CI (MMSE ≥ 24) at baseline, we used logistic regression analysis for calculating the probability of developing CI

Table 1
Baseline characteristics.

	Total (n = 2241)
Sociodemographic characteristics	
Age [years]	70.6 ± 6.5
Female	835 (37.3%)
Education [years] (% > 12 years)	11.4 ± 4.0 (32.1%)
Mini-Mental State Examination score	27.1 ± 3.2
10-year diabetes-specific dementia risk [%]	26.9 ± 16.0
Race	
White	2038 (90.9%)
Black or African American	134 (6.0%)
Asian	52 (2.3%)
Other[1]	17 (0.8%)
Diabetes-specific characteristics	
Time since T2D diagnosis [years]	16.2 ± 9.6
Medical history	
Acute metabolic event[b,c]	66 (3.0%)
Microvascular disease[a]	850 (37.9%)
Diabetic retinopathy	618 (27.6%)
Diabetic severe nephropathy[d]	359 (16.0%)
Diabetic foot[a]	152 (6.8%)
Depression[b]	185 (8.3%)

Data shown in number and percentage (n (%)) or means and standard deviation (M ± SD).
For full list of definitions see Appendix Table A.1.
[1] American Indian or Alaska Native/Native Hawaiian or Other Pacific Islander.
[a] Medical history prior to baseline visit.
[b] In the two years prior to baseline visit.
[c] Defined as: hyper/hypoglycemia that required hospitalization.
[d] Defined as: renal impairment of eGFR < 30.

(MMSE < 24) at follow-up according to the sum scores on the DSDRS. Due to relatively small numbers of incident CI, no post-hoc age-stratified analyses were performed. Linear regression analysis was used to investigate if sum scores on the DSDRS predicted change from baseline in cognitive performance (MMSE and A&E z-score). Baseline cognitive performance and time from baseline till follow-up visit were used as covariates.

2.3.3. Subgroup analysis

The analysis steps above were repeated on a sub selection of the population with confirmed micro- or macro albuminuria (i.e. UACR ≥30 mg/g creatinine or ≥30 mg/L or ≥30 μg/min or ≥30 mg/24 h in two out of three unrelated spot urine or timed samples in the last 24 months prior to randomization) in whom data on history of previous cardio- and/or cerebrovascular disease was available, allowing us to use the complete 19-point DSDRS model (Appendix Table A.1). No age-related stratifications were performed on this sub-set due to small sample sizes.

All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

For a supportive overview of all analyses, outcomes and populations, please see Table 2.

3. Results

3.1. Baseline and follow-up analysis

Of the 2694 participants included in the CARMELINA-COG study, years of education and cognitive assessment were available in 2666, of whom 2253 were aged ≥60 years and therefore eligible for the baseline analysis in the current study. MMSE was available in 2241 and constituted baseline analysis. Of this group 37.3% was female. The mean age was 70.6 ± 6.5 and mean years of formal education 11.4 ± 4.0. The population was largely Caucasian (91%). The mean duration of diabetes was 16.2 ± 9.6 years (Table 1).

At baseline, 309 (13.8%) had CI (MMSE < 24). The DSDRS was related with baseline CI risk (Fig. 1a; OR for CI 1.17 per DSDRS point [95% CI 1.12–1.22]; $p < .0001$, $R^2 = 0.02$). The point estimate for prediction of CI by the DSDRS was similar in age-band stratified sensitivity analyses (Appendix Table A.2 and Fig. A.3), albeit with wider confidence intervals due to smaller sample sizes in subgroups.

Of those without CI at baseline (MMSE ≥ 24) ($n = 1932$), cognitive follow-up was obtained in 1312 (68%) after a median follow-up duration of 2.5 ± 0.8 years (Appendix Fig. A.2). A number of 620 (32%) participants dropped out before follow-up assessment because their last cognitive assessment was >7 days after end of treatment, there were missing or implausible values on the cognitive tests or participants died or discontinued trial medication (for more information[8,9]). Of those that did have a follow-up ($n = 1312$), 1283 had an available MMSE and 1228 an A&E z-score. Compared to those that did have a follow-up, those that dropped out were slightly older (70.9 ± 6.7 vs 70.1 ± 6.2), their duration of diabetes was longer (17.0 ± 10.0 vs 15.8 ± 9.3) and 10-year dementia risk was higher (28.0 ± 16.4 vs 25.0 ± 15.1).

Table 2
Overview of objectives, number of participants and outcomes.

Objective	Population	N[a]	Outcome	Figures	Post-hoc analysis	N[b]	Figures[c]
Predict baseline CI	All with baseline MMSE	2241	Baseline CI (n = 309) (MMSE < 24)	1a	Stratification by age[d]	309[f]	Fig. A.3 Table A.3
					Subset with known CVD[e]	124	Fig. A.4a Fig. A.5a
Predict baseline cognitive performance in those without CI	MMSE ≥ 24 at baseline	1932	Baseline cognitive performance (MMSE and A&E z-score)	2	Stratification by age[d]	1932[f]	Table A.4
					Subset with known CVD[e]	907	Fig. A.6
Predict incident CI	MMSE ≥ 24 at baseline and available follow-up	1312	Incident CI (n = 88) (MMSE < 24 at follow-up)	1b	Subset with known CVD[e]	645	Fig. A.4b Fig. A.5b
Predict cognitive decline in those without baseline CI			Change in cognitive performance (MMSE and A&E z-score)	3	Subset with known CVD[e]	645	Fig. A.7

CI: cognitive impairment, MMSE: Mini-Mental state examination, A&E: attention and executive, CVD: cardio-and/or cerebrovascular disease.
[a] Number of subjects in population.
[b] Numbers of subjects in post-hoc analyses.
[c] Figures in Appendix A.
[d] Stratification by the following age-bands in years: 60–64, 65–69, 70–74, 75–79, 80–84, 85 + .
[e] Outcomes repeated on sub selection of participants with confirmed micro- or macroalbuminuria and available history on previous cardio- and/or cerebrovascular disease.
[f] Numbers shown in Appendix Tables A.3 and A.4.

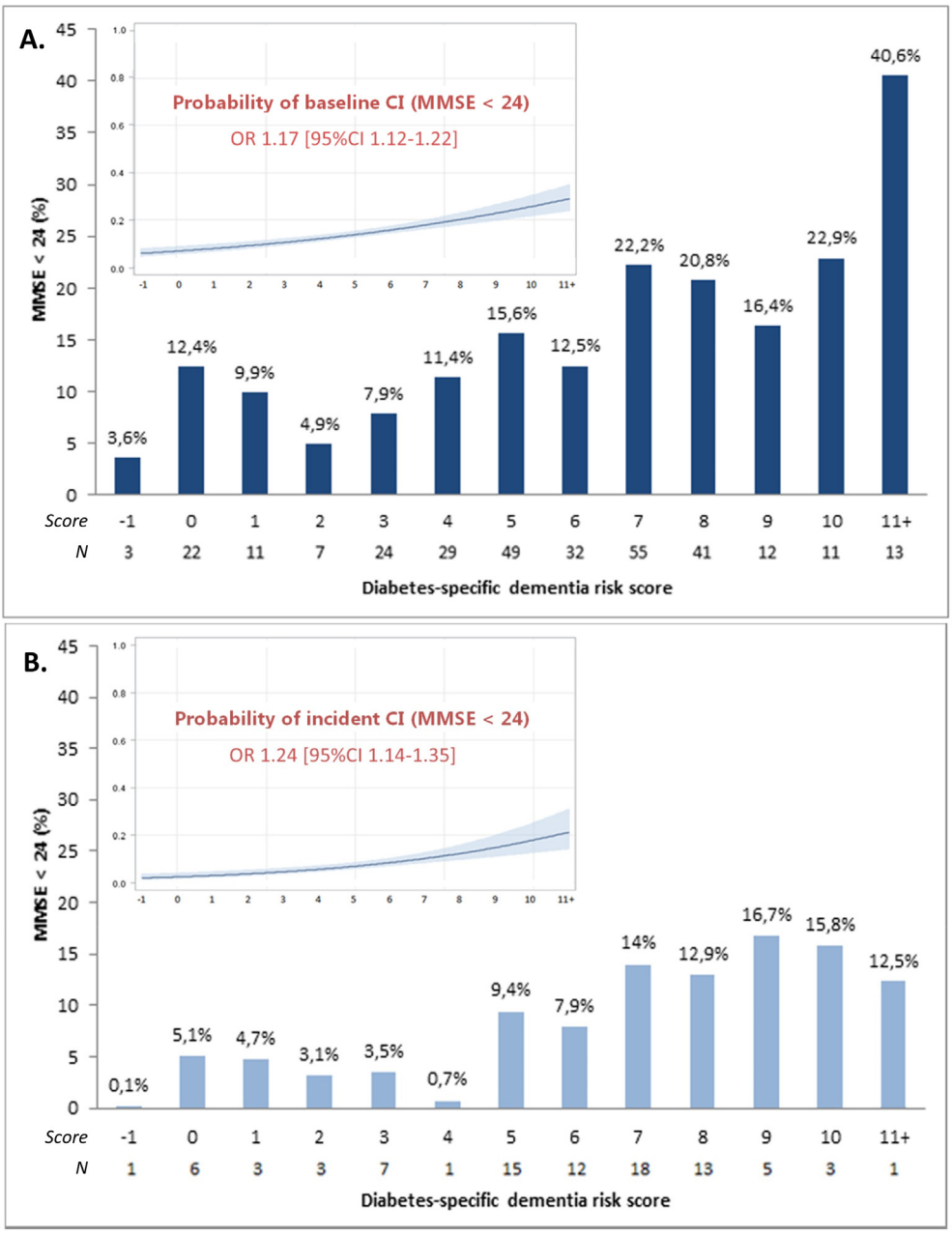

Fig. 1. Percentage and predicted probability of baseline CI (a) and incident CI at follow-up (b). Bar charts show: (a) percentage (%) of baseline CI (MMSE < 24) ($n = 309$) and (b) incident CI (MMSE < 24) at follow-up ($n = 88$). X-axis: sum risk scores for DSDRS, ranging from −1 to 11, and number of participants (N) with CI. Y-axis: Percentage of participants with CI (MMSE < 24). Probability models show: (a) predicted probability of baseline CI (MMSE < 24) from 0 to 1, including 95% confidence interval (OR 1.17 per DSDRS point [95% CI 1.12–1.22]; $p < .0001$, $R^2 = 0.02$) and (b) predicted probability of incident CI at follow-up (OR 1.24 per DSDRS point [95% CI 1.14–1.35]; $p < .0001$, $R^2 = 0.02$). X-axis: sum risk scores for DSDRS at baseline, ranging from −1 to 11. Y-axis: probability of CI (MMSE <24), ranging from 0 to 1 including 95% confidence interval. Results obtained using logistic regression analysis. DSDRS of 11 and higher are taken together due to small sample sizes. For overview of numbers per DSDRS sum risk score, see Appendix Table A.3. Median follow-up duration: 2.5 ± 0.8 years. CI: cognitive impairment, 95% CI: 95% confidence intervals, DSDRS: diabetes-specific dementia risk score, MMSE: Mini-Mental State Examination.

At follow-up, CI occurred in 88 participants (6.7%). The DSDRS significantly predicted incident CI (OR 1.24 per DSDRS point [95% CI 1.14–1.35]; $p < .0001$, $R^2 = 0.02$, Fig. 1b).

Mean baseline cognitive performance (i.e. MMSE and A&E z-score) for participants without baseline CI (MMSE ≥ 24) ($n = 1932$), was lower in those with higher sum risk scores on the DSDRS (Fig. 2). Linear regression analyses showed associations of DSDRS with both MMSE ($F(1, 1930) = 47.07$, $p < .0001$, $R^2 = 0.02$) and A&E z-score ($F(1, 1871) = 33.44$ $p < .0001$, $R^2 = 0.02$) at baseline. Age-stratified sensitivity analyses revealed significant associations for the age-bands 60–64, 70–74, 75–79 and 80–84 between the DSDRS and the MMSE. DSDRS was related with A&E z-score for the age-bands 60–64, 65–69, 75–79, 80–84 (Appendix Table A.4). In the 1312 participants included for follow-up assessment, after correction for follow-up duration and baseline cognitive performance, DSDRS was a significant predictor of decline in MMSE over time ($F(3, 1279) = 38.41$, $p < .0001$, $R^2 = 0.08$) and A&E z-score ($F(3, 1206) = 148.48$, $p < .0001$, $R^2 = 0.27$) (Fig. 3).

3.2. Subgroup analysis

A subset of 1035 participants with albuminuria (46% of total group), had available data on history of cardio- or cerebrovascular disease.

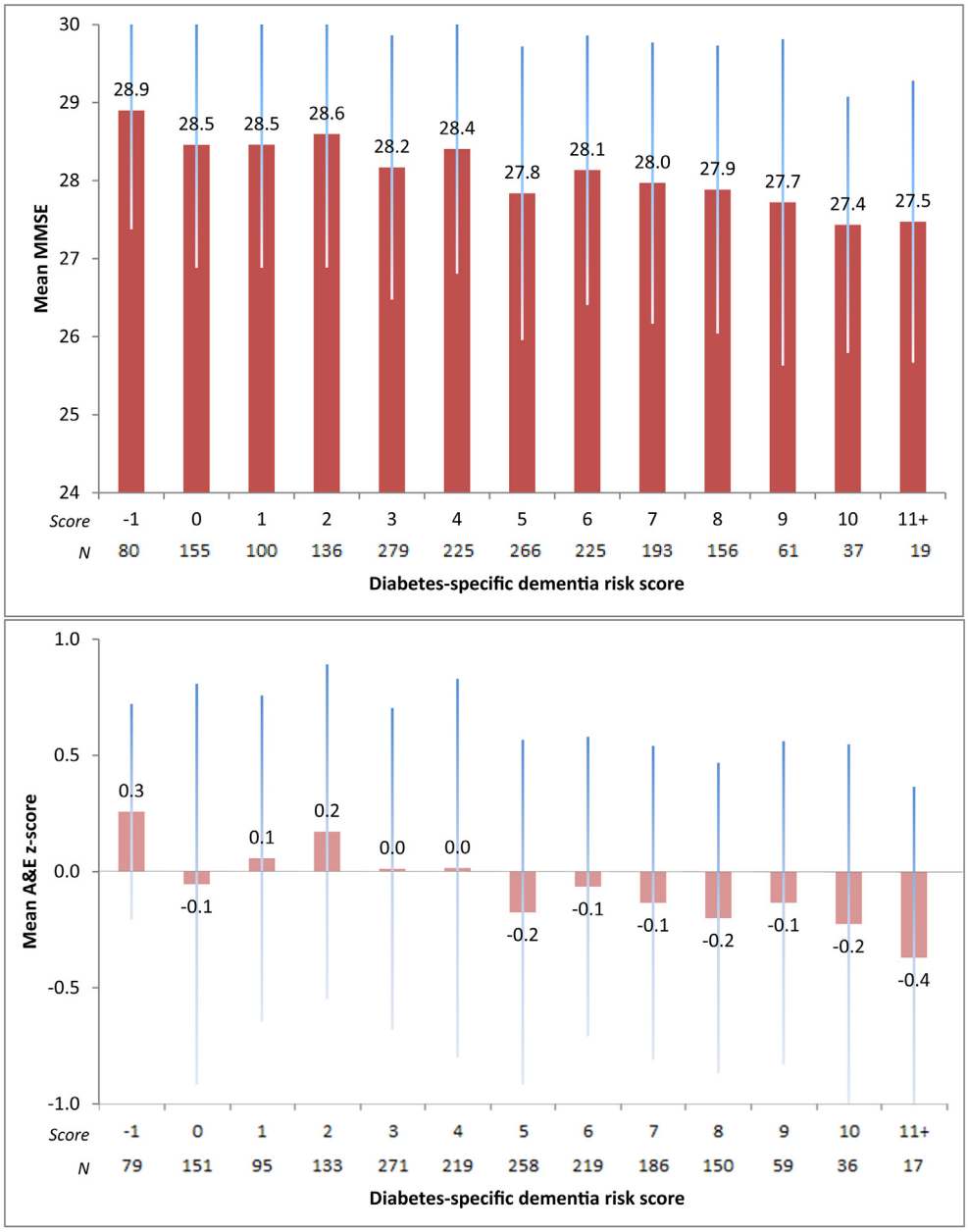

Fig. 2. Variation in cognitive performance (MMSE, A&E z-score) at baseline for participants without CI (MMSE ≥ 24). X-axis: Sum risk scores for DSDRS at baseline, ranging from −1 to 11. DSDRS of 11 and up are taken together due to small sample sizes. Y-axis: upper figure: MMSE ranging from 24 to 30 ($n = 1932$). Lower figure: A&E z-score, ranging from −1,0 to 1,0 ($n = 1873$). Linear regression analyses showed associations of DSDRS with both MMSE ($F(1, 1930) = 47.07$, $p < .0001$, $R^2 = 0.02$) and A&E z-score ($F(1, 1871) = 33.44$, $p < .0001$, $R^2 = 0.02$) for participants without baseline CI. Regression formula: MMSE = −0.097 * DSDRS + 28.589 + ε. A&E = −0.034 * DSDRS + 0.102 + ε. For age stratifications, please see Appendix Table A.4. CI: cognitive impairment (MMSE < 24), DSDRS: diabetes-specific dementia risk score, MMSE: Mini-Mental State Examination, A&E z-score: attention and executive composite z-score.

Analyses were performed with the complete DSDRS model on those with available MMSE ($n = 1031$; demographics in Appendix Table A.5). Results were essentially similar to the main analyses: CI at baseline was predicted by the sum risk scores on the DSDRS (OR 1.15 per DSDRS point [95% CI 1.07–1.23]; $p < .0001$, $R^2 = 0.02$). In the 644 participants (71% of those without baseline CI (MMSE ≥ 24)) with follow-up (Appendix Fig. A.2), CI occurred in 37 (5.3%) and was predicted by the DSDRS (OR 1.13 per DSDRS point [95% CI 1.01–1.28]; $p < .05$, $R^2 = 0.01$) (Appendix Figs. A.4 and A.5). Moreover, for participants without baseline CI (MMSE ≥ 24), DSDRS was significantly associated with both MMSE ($F(1, 905) = 22.16$, $p < .0001$, $R^2 = 0.02$) and A&E z-score ($F(1, 871) = 20.38$ $p < .0001$, $R^2 = 0.02$) and (Appendix Figs. A.4, A.5 and A.6). The DSDRS predicted decline in MMSE ($F(3, 631) = 17.66$, $p < .0001$, $R^2 = 0.08$) and A&E z-score ($F(3, 588) = 61.48$, $p < .0001$, $R^2 = 0.24$), after correction for baseline performance and follow-up duration (Appendix Fig. A.7).

4. Discussion

This study shows that higher scores on the DSDRS are also associated with concurrent CI and worse cognitive performance in a group of patients with T2D at high cardio-vascular renal risk, irrespective of age. Moreover, higher DSDRS predicted CI 2.5 years later, as well as more subtle cognitive decline over time.

Prognostic dementia models are – by definition – developed to predict future dementia. The question is if these models are also able to cross-sectionally identify people with a high probability of having CI, which could, for example, be supportive for screening. To our

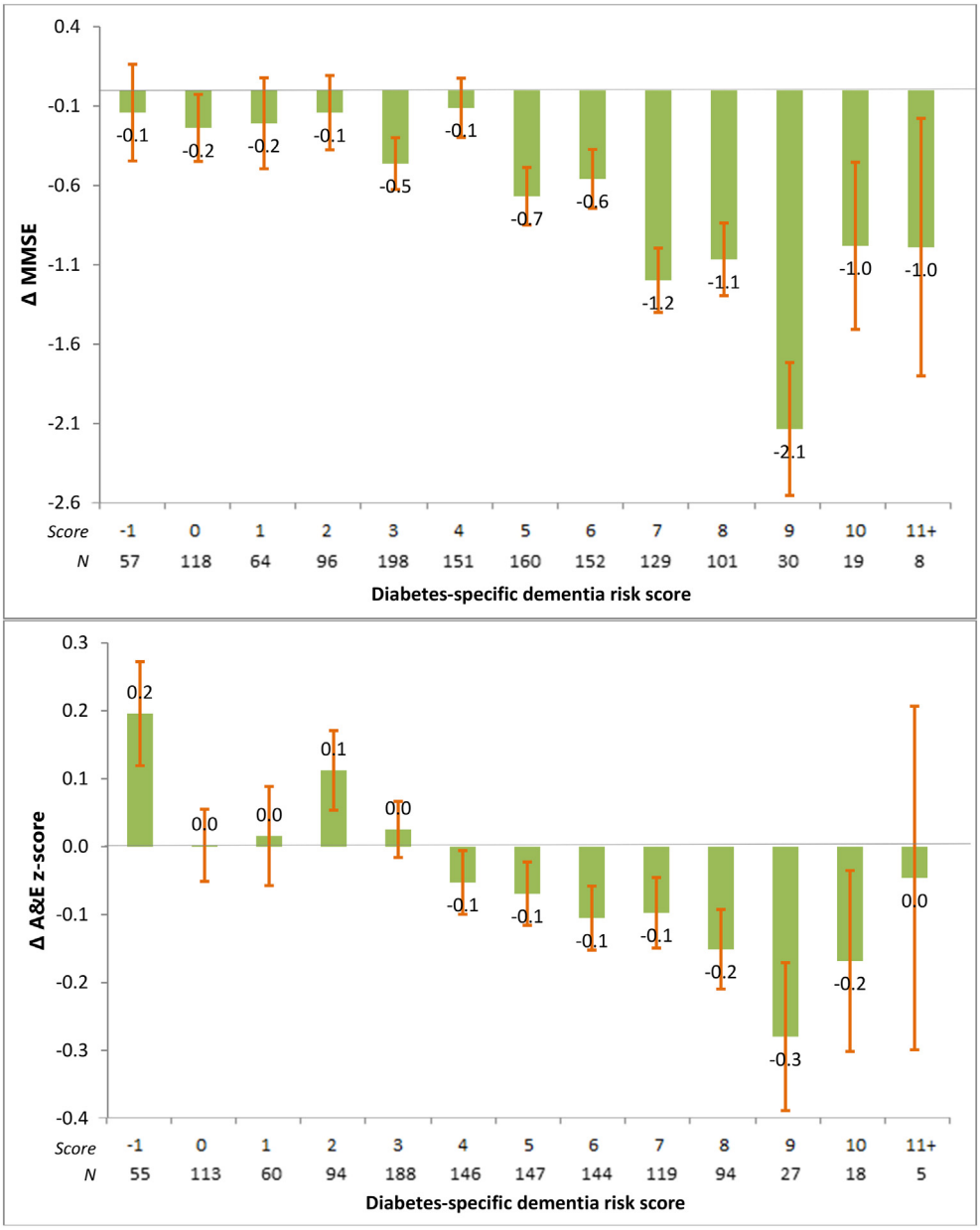

Fig. 3. Change from baseline in cognitive performance (MMSE and A&E z-score). X-axis: Sum risk scores for DSDRS at baseline, ranging from −1 to 11. DSDRS of 11 and up are taken together due to small sample sizes. Y-axis upper figure: change from baseline for MMSE ($n = 1283$). Y-axis lower figure: change from baseline for A&E z-score ($n = 1210$). Figures show least square means corrected for baseline performance and follow-up time, calculated using linear regression analyses. MMSE: $F(3, 1279) = 38.41$, $p < .0001$, $R^2 = 0.08$. A&E z-score: $F(3, 1206) = 148.48$, $p < .0001$, $R^2 = 0.27$. Analyses executed for participants that had no baseline CI (MMSE ≥ 24). Δ: change from baseline, CI: cognitive impairment, DSDRS: diabetes-specific dementia risk score, MMSE: Mini-Mental State Examination, A&E z-score: attention and executive composite z-score.

knowledge, no studies have tested this before. In our study population 13.8% of the participants has CI at baseline, defined as a MMSE <24, which is relatively high compared to previous studies, also considering the age of the populations involved.[17,18] This may reflect the fact that the CARMELINA population is at high cardiovascular risk and therefore also at higher risk of CI.[7] The DSDRS clearly separated people according to baseline CI risk: for example of those with a score of ≥8, over 20% has CI, compared to less than 10% CI in those with a score ≤ 3 (Fig. 1a, Table A.3). For those that do not have CI at baseline, higher DSDRS scores are also associated with worse cognitive performance on the MMSE and A&E z-score. However, effect sizes are small, and although the association was statistically significant, the variance explained by the DSDRS was only 2%. Another question is if prediction models for dementia are also able to predict more subtle cognitive decline. We identified no previous studies either in people with diabetes or in the general population that explored this. Our study shows that for participants without CI at baseline, 6.7% developed CI after 2.5 years. Of those with a score of ≥8, around 14% developed CI, compared to % CI in those with a score ≤ 3 (Fig. 1b, Table A.3). In those without CI at baseline, higher DSDRS are significantly associated with a greater cognitive decline over a period of 2.5 years, with small to moderate effect sizes. Our results show that the DSDRS predicts a wide range of cognitive decline, from accelerated cognitive decline, to cognitive impairment, to – as shown in former research – frank dementia.[7]

Several diabetes management guidelines recommend screening for cognitive problems in patients with T2D, but there is still uncertainty how this should be implemented.[2–6] Our findings on the cross-sectional analyses show that the DSDRS could support such

screening strategies. The strength of the DSDRS, or comparable risk scores that primarily rely on demographic and clinical data mostly already available in the patients records [19,20] is that it is very easy to implement in daily practice (e.g. as part of the electronic medical record system). Because of its low-cost and time-efficient characteristics, the DSDRS has an advantage over other dementia prediction models that also require additional biomarkers, such as MRI or other advanced laboratory variables,[21] making the DSDRS a suitable tool for primary care. An implementation study would be needed to evaluate the feasibility and practical applicability of this approach.

A few limitations of our study should be considered. The CARMELINA trial cohort consisted of a selected T2D group at high cardio-vascular risk.[8] Compared to the DSDRS distribution previously observed in a population based sample of patients with T2D,[7] fewer participants had low risk scores, likely reflecting the high cardiovascular burden in our cohort. Moreover, there were also fewer participants in the highest risk scores range, probably reflecting that the oldest old are less likely to participate in a drug trial. Importantly, despite this different risk distribution, the DSDRS remained nonetheless predictive. Possibly it may have even better discriminative ability in a less selected cohort. The optimal threshold for differentiating those with and without CI based on the DSDRS should also preferably be determined in a population-based setting. Another point to consider is that treatment could potentially play a role in our results, particularly because the data were derived from a randomized controlled trial. Yet, when the DSDRS was developed, diabetes treatment was considered as a dementia predictor, but not retained in the final model. Moreover, CARMELINA found neutral results for the effect of linagliptin versus placebo on the cognitive outcome.[8] Another limitation is that data on cardio- and/or cerebrovascular disease was not available for all subjects; it was only registered in those with albuminuria. However, subgroup analyses showed similar results compared to the total group, suggesting that the DSDRS is still predictive when predictors are missing, which would be a convenient feature when it comes to clinical implementation. Further, a limited test battery was used to measure cognitive performance. The inclusion of additional tests to cover other cognitive domains would have been informative when drawing up extensive cognitive profiles, but in the current research it would in essence not have changed the results. Nevertheless, the cognitive tests that were applied prove to be sufficient to answer our question.

Strengths of our study include the relatively large number of patients with T2D. Our results show that the relationship of the DSDRS with cognition is not solely driven by age. We used two complimentary cognitive tests; we included the more conservative, but widely-used and easily interpretable MMSE, and in addition we used a more sensitive cognitive composite score that covers relevant cognitive domains in T2D.[14]

5. Conclusion

The DSDRS effectively identifies patients with T2D at risk of concurrent and future cognitive impairment, also in those without dementia. In addition to informing clinicians on future dementia risk, the DSDRS can thus, in an individualized, time- and cost efficient way, advice clinicians on which T2D patients to screen or monitor for cognitive problems.

Author statement

Chloë Verhagen: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Visualization, **Jolien Janssen:** Conceptualization, Methodology, Writing - Review & Editing, **Lieza G Exalto:** Conceptualization, Methodology, Writing - Review & Editing, **Esther van den Berg:** Writing - Review & Editing, **Odd Erik Johansen:** Resources, Writing - Review & Editing, Funding acquisition, **Geert Jan Biessels:** Conceptualization, Methodology, Writing - Review & Editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

G.J.B.'s institution receives study grants from Boehringer Ingelheim. O.E.J. is an employee of Boehringer Ingelheim.

No other potential conflicts of interest relevant to this article were reported.

Acknowledgements

This study was sponsored by Boehringer Ingelheim.

Appendix A

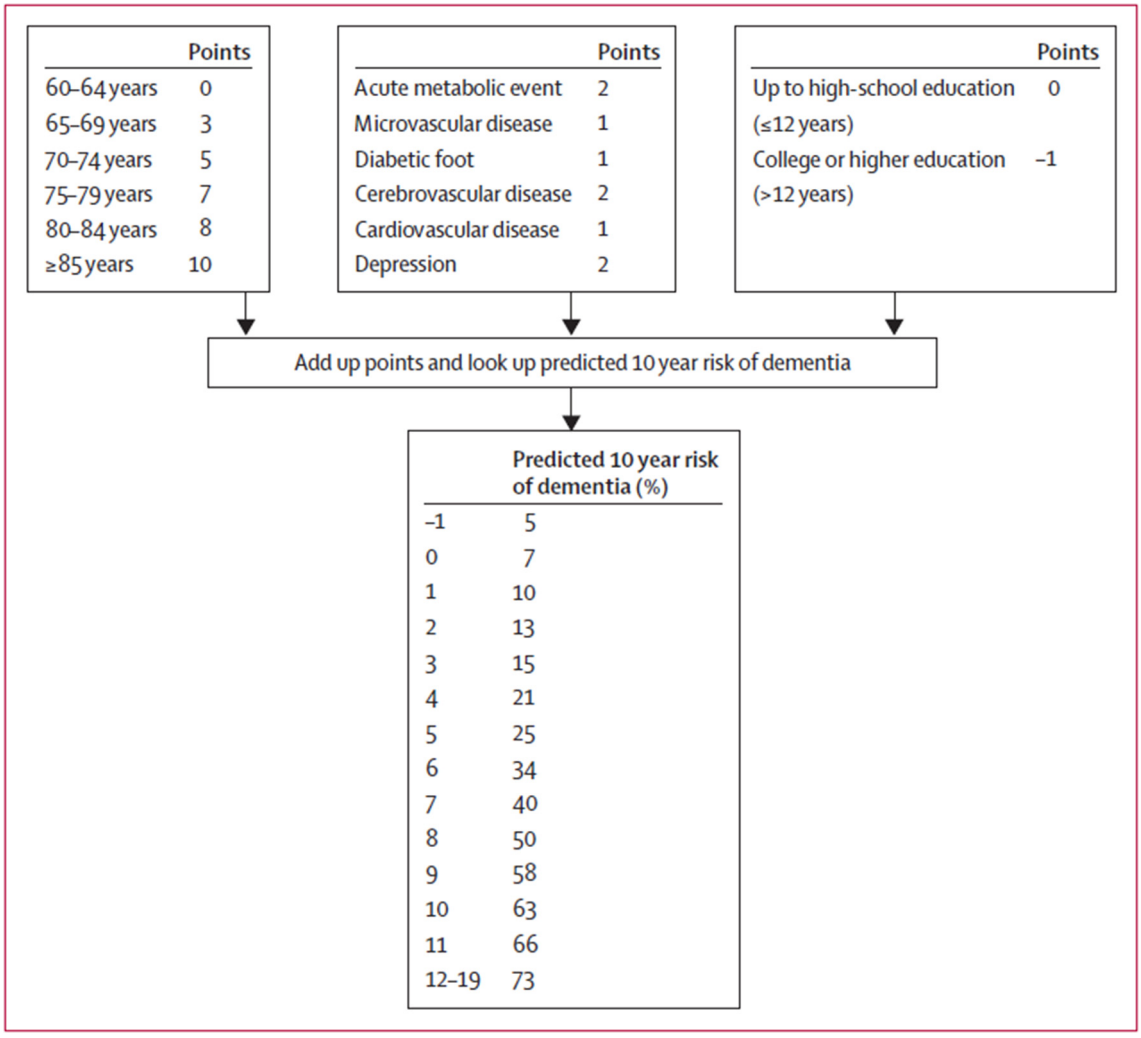

Fig. A.1. Summary of the type 2 diabetes-specific dementia risk score (DSDRS). Figure adapted from.[7] In the current study predictors on cerebro- and cardiovascular disease are not available for the complete population, but only for a subgroup (see Methods). As a result the maximum points for predicted 10-year risk of dementia that can be assigned to each person in the complete population is 16.

Table A.1
Used definitions for dementia predictors in the DSDRS.

Predictor	Definitions current study	Definitions[7]
Age	Age in years	Age in years
Years of education	Years of formal education at or below median/above median	High school or less/college or more.
Acute metabolic event	Hyper- or hypoglycemia that required hospitalization in the 2 years prior to baseline assessment.	Hyper- and/or hypoglycemia event severe enough to be hospitalized based on medical history in the 2 years prior to baseline.
Microvascular disease	eGFR (MDRD) [mL/min/1.73 m2] <30 at baseline.	End-stage renal disease (including dialysis and kidney transplantation) in the two years prior to baseline.
	And/or prior clinical diagnosis of diabetic retinopathy requiring retinal laser coagulation therapy or intravitreal injection(s) of an antivascular endothelial growth factor therapy.	*And/or* diabetic retinal disease in the 2 years prior to baseline.
Diabetic foot	Clinical diagnosis of diabetic foot defined as gangrene, amputation or lower limb ulcer that required hospitalization.	- Gangrene or lower limb ulcer that required hospitalization in the two years prior to baseline. - Lower extremity amputation in the 2 years prior to baseline.
Cerebrovascular disease[d]	- History of ischemic or hemorrhagic stroke - Carotid artery disease[a] - High-risk single-vessel coronary artery disease[b]	History of: - Cerebrovascular attacks - Precerebral arterial disease - Carotid endarterectomy
Cardiovascular disease[d]	- History of myocardial infarction, - PAOD: peripheral arterial occlusive disease[c] - Clinical diagnosis of congestive heart failure	- Myocardial infarction - Peripheral arterial disease - Congestive heart failure - Coronary artery bypass graft - Percutaneous transluminal coronary angioplasty

Table A.1 (*continued*)

Predictor	Definitions current study	Definitions[7]
Depression	Clinical diagnosis of depression in the two years prior to baseline assessment.	History of depression based on medical history in the 2 years prior to baseline.

Definitions in[7] are according to ICD-9 CM codes.

[a] Documented by at least one lesion estimated to be ≥50% narrowing of the luminal diameter with imaging techniques or prior percutaneous or surgical carotid revascularization.

[b] 50% narrowing of the luminal diameter of one major coronary artery by coronary angiography, MRI angiography in patients not revascularized and at least: a positive non-invasive stress test or patient discharged from hospital with a documented diagnosis of unstable angina pectoris between 2 and 12 months prior to screening visit.

[c] Documented by previous limb angioplasty by stenting or by-pass surgery, previous limb or foot amputation due to macrocirculatory insufficiency, angiographic evidence of peripheral artery stenosis 50% narrowing of the luminal diameter in at least one limb (definition of peripheral artery: common iliac artery, internal iliac artery, external iliac artery, femoral artery, popliteal artery).

[d] History on previous cerebro- and cardiovascular disease is only available in a subgroup of the current study and investigated with subgroup analyses.

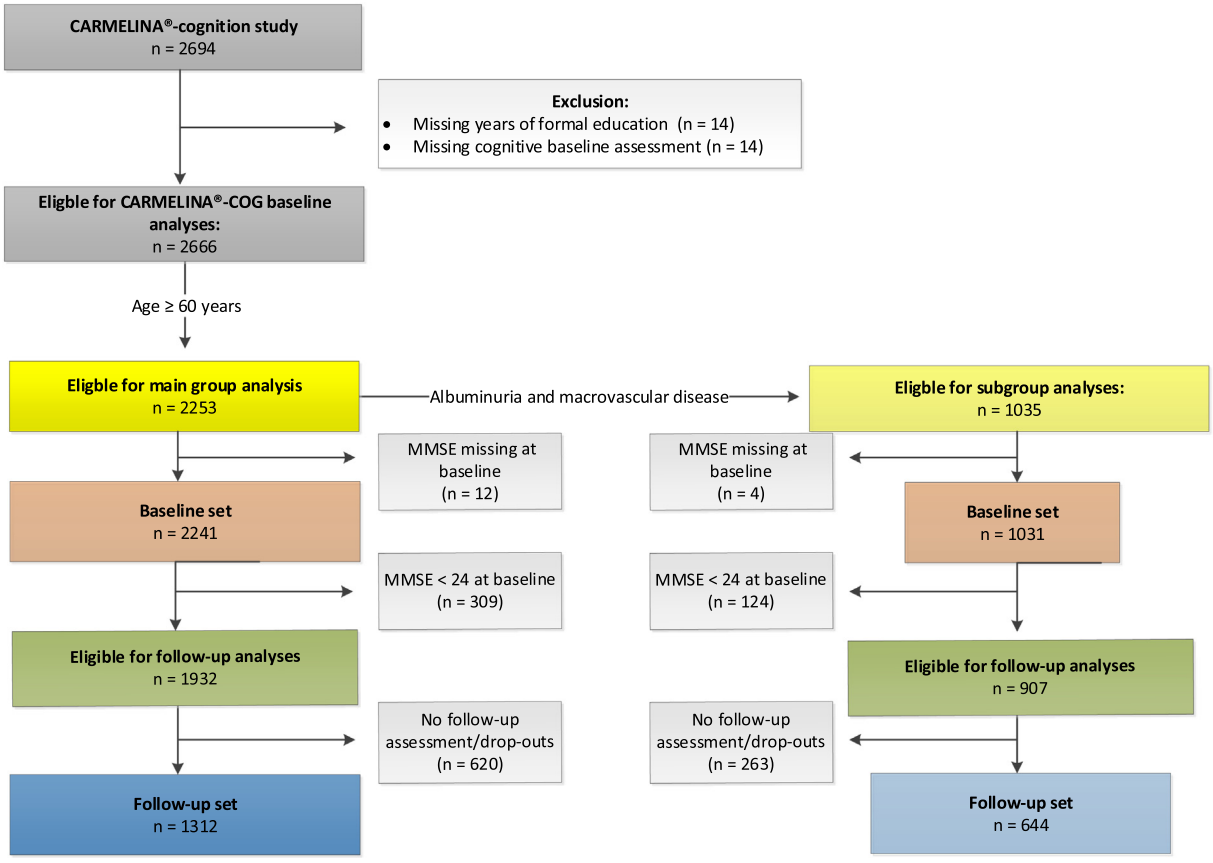

Fig. A.2. Flowchart. *Note*: Reasons for drop-out were because the last cognitive assessment was >7 days after end of treatment, there were only missing or implausible values on the cognitive tests, participants died or discontinued trial medication due to adverse events, non-compliance to protocol, refusal to continue taking medication, other or missing (for more information[8,9]). MMSE: Mini-Mental State examination.

Table A.2
Number and predicted probability of baseline CI (MMSE < 24), stratified by age.

	n (affected)	OR per DSDRS point (95% CI)
Total	2241 (309)	1.17 (1.12–1.22)
60–64	427 (42)	1.18 (0.89–1.55)
65–69	621 (65)	1.70 (1.37–2.12)
70–74	579 (76)	1.12 (0.88–1.43)
75–79	386 (79)	1.30 (1.04–1.62)
80–84	176 (34)	1.46 (1.01–2.10)
85+	52 (13)	2.41 (0.88–6.61)

Total number (n) and number with CI (affected). Odds ratio for CI and 95% confidence intervals, stratified by age-bands: 60–64, 65–69, 70–74, 75–79, 80–84 and 85. CI: cognitive impairment, 95% CI: 95% confidence intervals, MMSE: Mini-Mental State Examination, DSDRS: diabetes-specific dementia risk score, OR: Odds ratio.

Table A.3
Number of participants with CI (MMSE < 24) at baseline and at follow-up.

DSDRS	Total baseline	60–64	65–69	70–74	75–79	80–84	85+	Total follow-up
−1	83 (3)	83 (3)						57 (1)
0	177 (22)	177 (22)						118 (6)
1	111 (11)	111 (11)						64 (3)
2	143 (7)	36 (5)	107 (2)					96 (3)
3	303 (24)	16 (0)	287 (24)					198 (7)
4	254 (29)	3 (0)	158 (25)	93 (4)				152 (1)
5	315 (49)	1 (1)	44 (6)	271 (43)				160 (15)
6	257 (32)		20 (5)	167 (22)	69 (4)			152 (12)
7	248 (55)		2 (2)	36 (7)	178 (43)	32 (3)		129 (18)
8	197 (41)		2 (1)	9 (0)	98 (23)	88 (17)		101 (13)
9	73 (12)		1(0)		23 (3)	39 (8)	10 (1)	30 (5)
10	48 (11)			1 (0)	11 (2)	9 (3)	27 (6)	19 (3)
11+	32 (13)			2 (0)	7 (4)	8 (3)	15 (6)	8 (1)
Total	2241 (309)	427 (42)	621 (65)	579 (76)	386 (79)	176 (34)	52 (13)	1283 (88)

Number of participants for each sum risk score on the DSDRS (n total (n with CI)).
CI: cognitive impairment (MMSE <24), DSDRS: diabetes-specific dementia risk score.

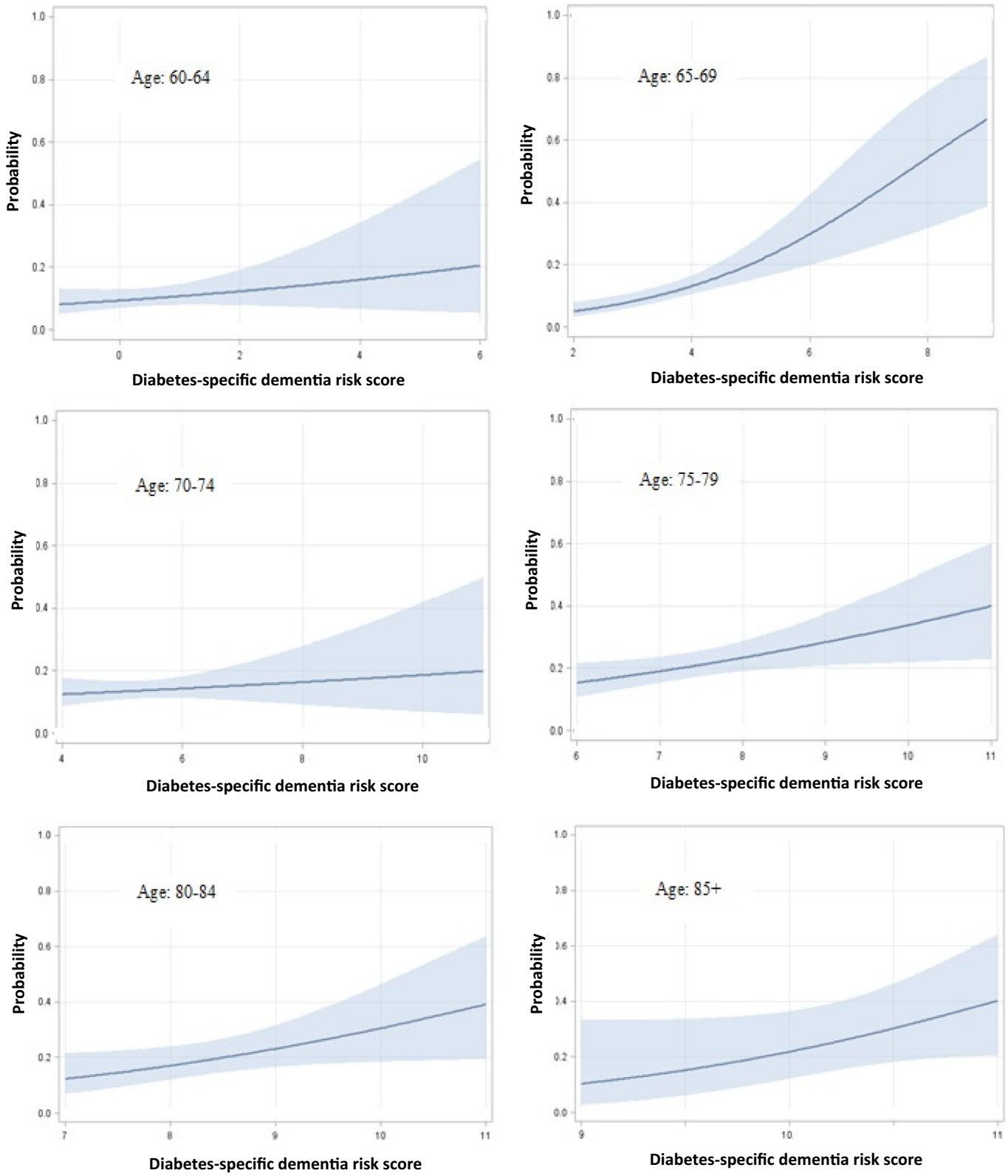

Fig. A.3. Predicted probability of baseline CI (MMSE < 24) according to DSDRS, stratified by age-bands. Predicted probability of CI (MMSE < 24) stratified by age-bands: 60–64, 65–69, 70–74, 75–79, 80–84 and 85+. X-axis: DSDRS at baseline, ranging from −1 to 11. DSDRS of 11 and up are taken together due to small sample sizes. Y-axis: predicted probability of CI (MMSE < 24), ranging from 0 to 1. CI: cognitive impairment, DSDRS: diabetes-specific dementia risk score.

Table A.4
Linear regression analyses for DSDRS and cognitive performance (MMSE, A&E z-score) for participants without baseline CI (MMSE ≥ 24).

	n	MMSE				A&E		
		β [95% CI]	R^2	*p*	*n*	β [95% CI]	R^2	*p*
Total	1932	−0.10 [−0.12, −0.07]	0.02	<.0001	1873	−0.03 [−0.05, −0.02]	0.02	<.0001
60–64	385	−0.20 [−0.35, −0.05]	0.02	.008	373	−0.08 [−0.15, −0.01]	0.01	.035
65–69	556	−0.09 [−0.23, 0.05]	0.003	.219	542	−0.08 [−0.14, −0.02]	0.01	.012
70–74	503	−0.17 [−0.33, −0.003]	0.01	.046	487	−0.03 [−0.10, 0.04]	0.002	.369
75–79	307	−0.22 [−0.41, −0.03]	0.02	.021	297	−0.11 [−0.18, −0.03]	0.03	.005
80–84	176	−0.70 [−1.28, −0.13]	0.03	.017	145	−0.15 [−0.26, −0.03]	0.04	.011
85+	39	−0.61 [−1.57, 0.35]	0.04	.204	36	−0.19 [−0.54, 0.16]	0.03	.283

Beta's and 95% confidence intervals calculated with linear regression analysis, stratified by age-bands. CI: cognitive impairment. 95% CI: 95% confidence interval. MMSE: Mini-Mental State Examination, A&E: attention and executive functioning. DSDRS: diabetes-specific dementia risk score.

Table A.5
Baseline characteristics for total T2D population and subgroup with albuminuria and data on macrovascular disease.

	Total	Subgroup[1]
	(*n* = 2241)	(n = 1031)
Sociodemographic characteristics		
Age [years]	70.6 ± 6.5	69.8 ± 6.3
Female	835 (37.3%)	266 (25.8%)
Education [years] (% > 12 years)	11.4 ± 4.0 (32.1%)	11.7 ± 4.0 (34.0%)
Mini-Mental State Examination score	27.1 ± 3.2	27.3 ± 3.0
10-year diabetes-specific dementia risk [%]	26.9 ± 16.0	32.1 ± 18.0
Race		
White	2038 (90.9%)	953 (92.4%)
Black or African American	134 (6.0%)	41 (4.0%)
Asian	52 (2.3%)	28 (2.7%)
Other[2]	17 (0.8%)	9 (0.9%)
Diabetes-specific characteristics		
Time since T2D diagnosis [years]	16.2 ± 9.6	16.0 ± 9.7
Medical history		
Acute metabolic event[b,c]	66 (3.0%)	34 (3.3%)
Microvascular disease[a,d]	850 (37.9%)	332 (32.2%)
Diabetic retinopathy	618 (27.6%)	277 (26.9%)
Diabetic severe nephropathy[e]	359 (16.0%)	86 (8.3%)
Cerebrovascular disease	n.a.	335 (32.5%)
History of stroke		229 (22.2%)
Carotid artery disease		126 (12.2%)
Cardiovascular disease	n.a.	656 (63.6%)
Myocardial infarction		474 (46.0%)
PAOD		141 (13.7%)
Congestive heart failure[a]		233 (22.6%)
Diabetic foot[a]	152 (6.8%)	87 (8.4%)
Depression[b]	185 (8.3%)	95 (9.2%)

Data shown in number and percentage (n (%)) or means and standard deviation (M ± SD).
For full list of definitions see Appendix Table A.1. PAOD: (peripheral arterial occlusive disease).
[1] Sub selection of T2D patients with albuminuria and data on macrovascular disease (for details, see Methods).
[2] American Indian or Alaska Native/Native Hawaiian or Other Pacific Islander.
[a] Medical history prior to visit 1.
[b] In the two years prior to visit 1.
[c] Defined as: hyper/hypoglycemia that required hospitalization.
[d] Defined as: diabetic retinopathy and/or diabetic severe nephropathy.
[e] Defined as: renal impairment of eGFR < 30.

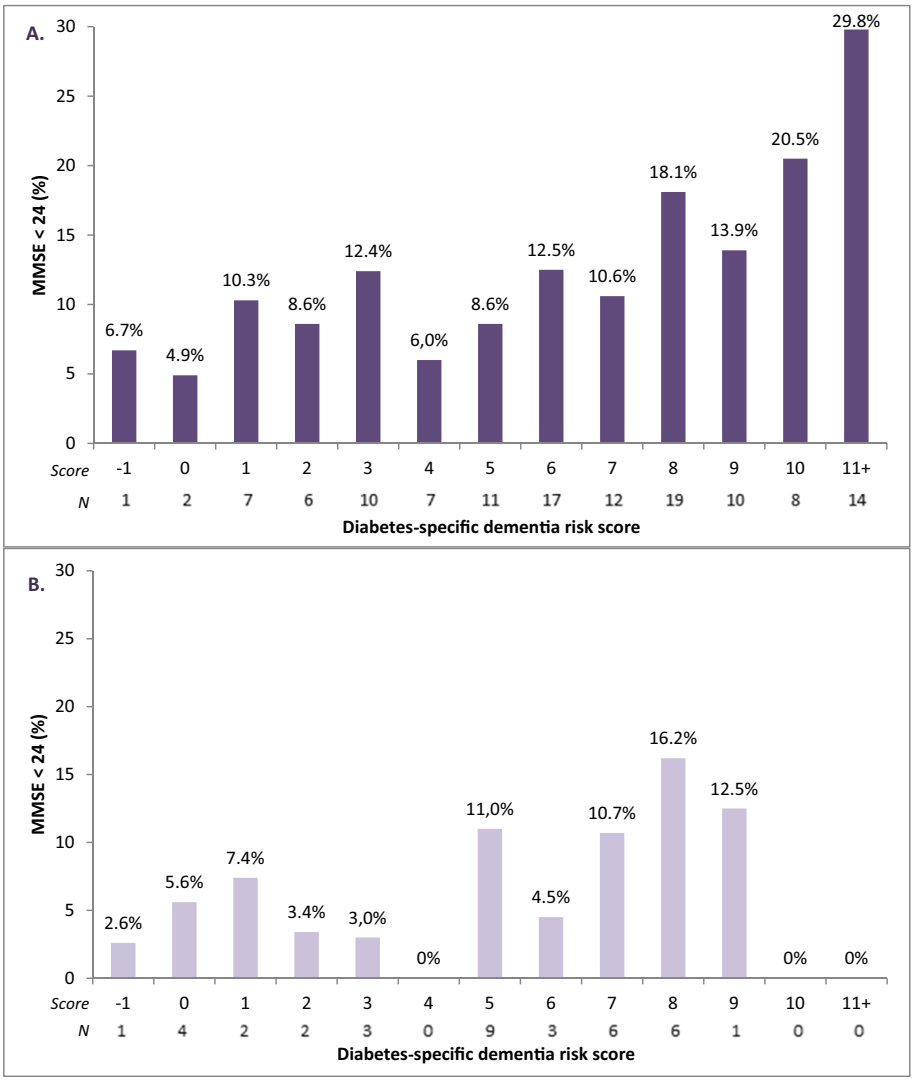

Fig. A.4. Percentage of baseline CI (MMSE < 24) (a) and incident CI at follow-up (b) – subgroup analysis.[1] (a) Percentage (%) of baseline CI (MMSE < 24) ($n = 124$) and (b) incident CI (MMSE < 24) at follow-up ($n = 37$) for subgroup of T2D patients with albuminuria and data on macrovascular disease (for details, see Methods). X-axis: sum risk scores for DSDRS, ranging from −1 to 11, and number of participants with CI. Y-axis: Percentage of participants with CI (MMSE < 24). DSDRS of 11 and higher are taken together due to small sample sizes. Median follow-up duration: 2.4 ± 0.8 years. CI: cognitive impairment, 95% CI: 95% confidence intervals, DSDRS: diabetes-specific dementia risk score, MMSE: Mini-Mental State Examination.

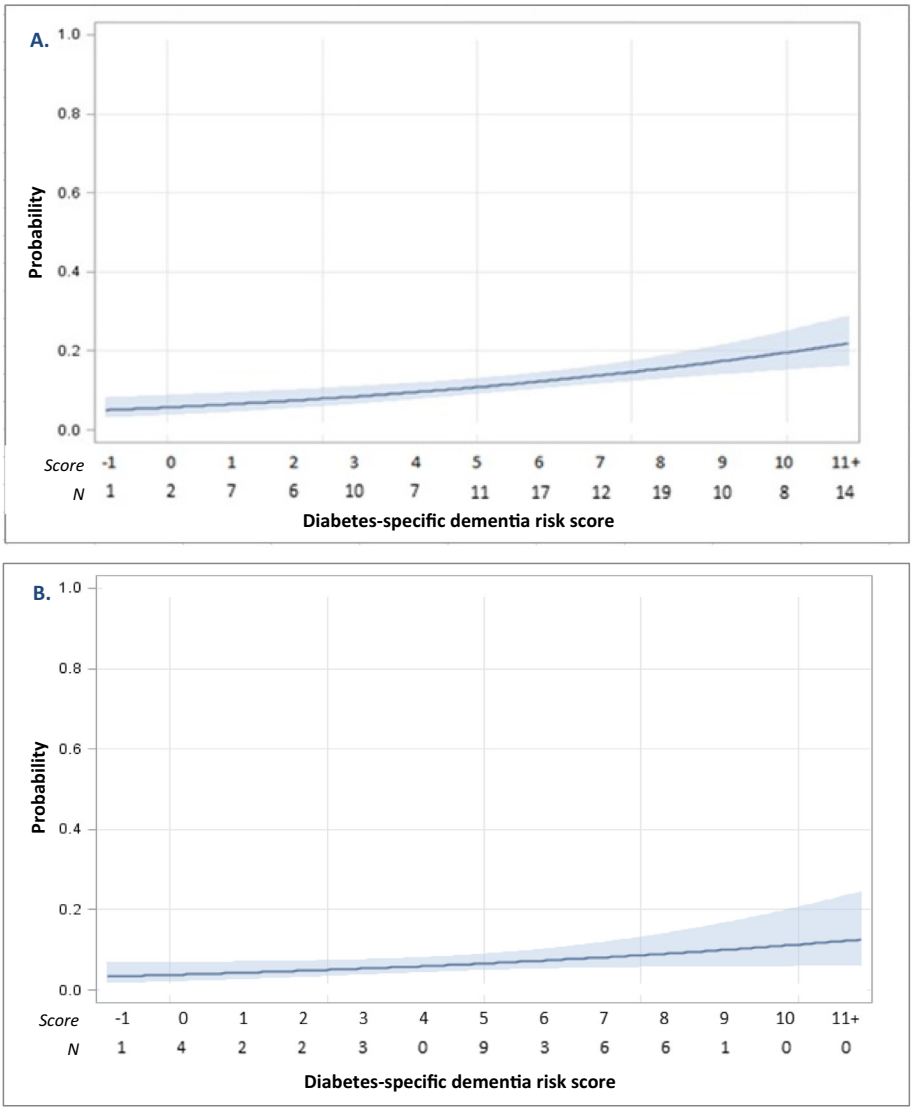

Fig. A.5. Predicted probability of baseline CI (MMSE < 24) and incident CI at follow-up (b) – subgroup analysis.[1] Predicted probability of baseline CI (MMSE < 24) from 0 to 1, including 95% confidence interval (n with CI = 124) (a) (OR 1.15 per DSDRS point [95% CI 1.07–1.23]; $p < .0001$, $R^2 = 0.02$) and predicted probability of incident CI at follow-up (n with CI = 37) (b) (OR 1.13 per DSDRS point [95% CI 1.01–1.28]; $p = .04$, $R^2 = 0.01$). X-axis: sum risk scores for DSDRS at baseline, ranging from −1 to 11. Y-axis: probability of CI (MMSE < 24), ranging from 0 to 1 including 95% confidence interval. Results obtained using logistic regression analysis. DSDRS of 11 and higher are taken together due to small sample sizes. [1]Sub selection of T2D patients with albuminuria and data on macrovascular disease (for details, see Methods). CI: cognitive impairment, DSDRS: diabetes-specific dementia risk score, MMSE: Mini-Mental State examination.

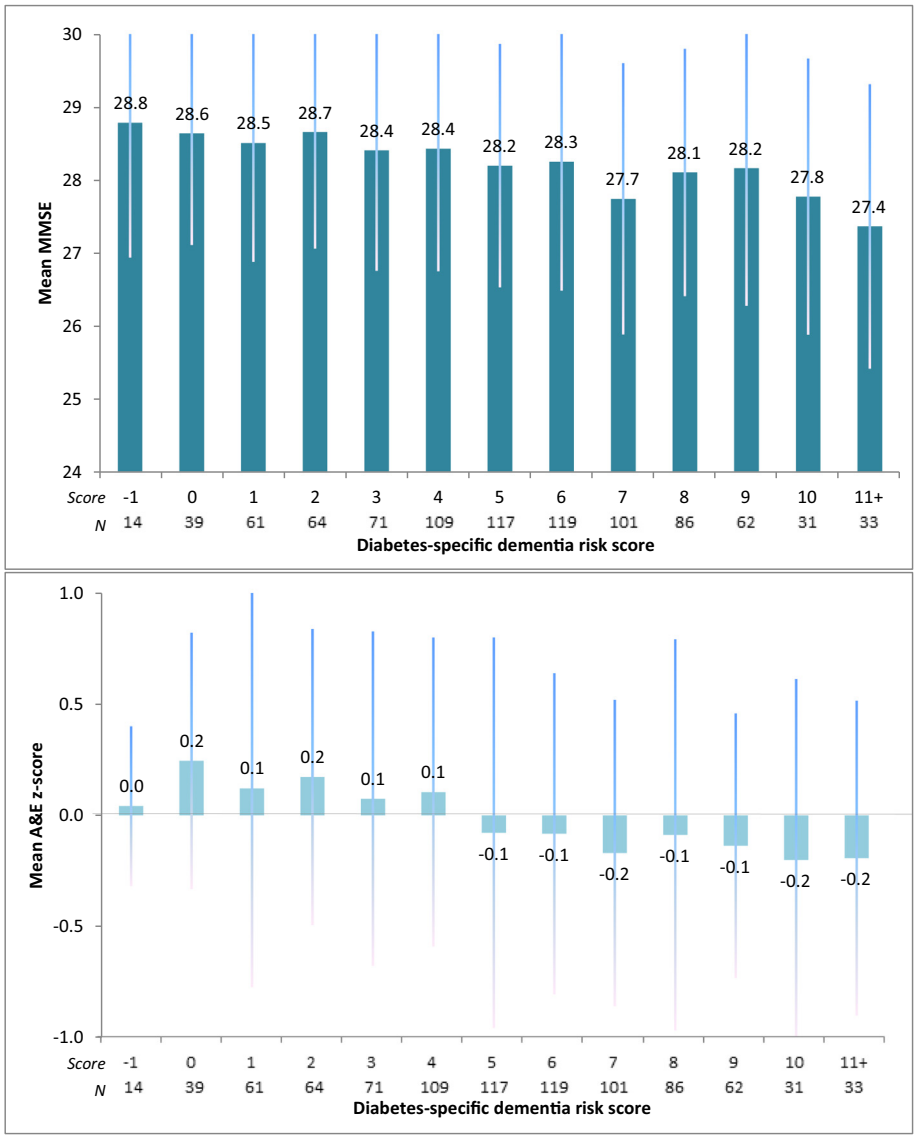

Fig. A.6. Variation in cognitive performance (MMSE, A&E z-score) and DSDRS for participants without baseline CI (MMSE ≥ 24) – subgroup analysis.[1] X-axis: Sum risk scores for DSDRS at baseline, ranging from −1 to 11. DSDRS of 11 and up are taken together due to small sample sizes. Y-axis: upper figure: MMSE ranging from 24 to 30 ($n = 907$). Lower figure: A&E z-score, ranging from −1,0 to 1,0 ($n = 873$). Linear regression analyses showed associations of DSDRS with both MMSE ($F(1, 905) = 22.16$, $p = .0001$, $R^2 = 0.02$) and A&E z-score ($F(1, 871) = 20.38$ $p < .0001$, $R^2 = 0.02$) for participants without baseline CI. Regression formula: MMSE: $-0.09 * \text{DSDRS} + 28.71 + \varepsilon$. A&E z-score $= -0.04 * \text{DSDRS} + 0.18 + \varepsilon$. [1]Sub selection of T2D patients with albuminuria and data on macrovascular disease (for details, see Methods). CI: cognitive impairment (MMSE < 24), DSDRS: diabetes-specific dementia risk score, MMSE: Mini-Mental State Examination, A&E z-score: attention and executive composite z-score.

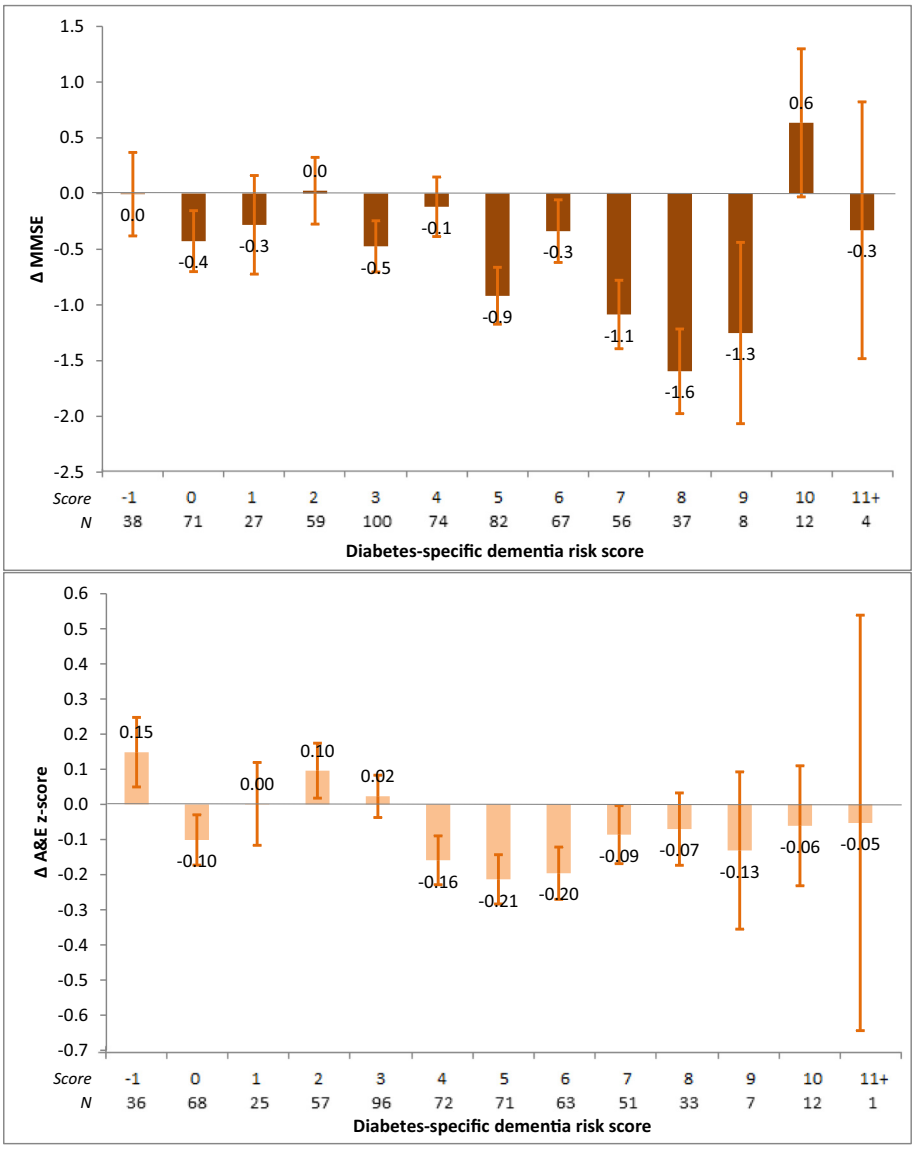

Fig. A.7. Change from baseline in cognitive performance (MMSE and A&E z-score) – subgroup analysis.[1] X-axis: Sum risk scores for DSDRS at baseline, ranging from −1 to 11. DSDRS of 11 and up are taken together due to small sample sizes. Y-axis upper figure: change from baseline for MMSE ($n = 635$). Y-axis lower figure: change from baseline for A&E z-score ($n = 592$). Figures show least square means corrected for baseline performance and follow-up time, calculated using linear regression analyses. MMSE: $F(3, 631) = 17.66$, $p < .0001$, $R^2 = 0.08$. A&E z-score: $F(3, 588) = 61.48$, $p < .0001$, $R^2 = 0.24$. Analyses executed for participants that had no baseline CI (MMSE ≥ 24). [1]Sub selection of T2D patients with albuminuria and data on macrovascular disease (for details, see Methods). Δ: change from baseline, CI: cognitive impairment, DSDRS: diabetes-specific dementia risk score, MMSE: Mini-Mental State Examination, A&E z-score: attention and executive composite z-score.

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