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Females with type 2 diabetes are at higher risk for accelerated cognitive decline than males: CAROLINA-COGNITION study

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Abstract *Background and aim:* Cognitive dysfunction is increasingly recognized as an important comorbidity of type 2 diabetes (T2D). We aimed to establish if the risk of accelerated cognitive decline (ACD) is higher in females with T2D than males.
Methods and results: 3163 participants (38% female) with T2D from the cognition substudy of CAROLINA® (NCT01243424) were included (mean age 64.4 ± 9.2 years; T2D duration 7.6 ± 6.1 years). The cognitive outcome was occurrence of ACD at end of follow-up, defined as a regression based index score ≤16th percentile on either the Mini-Mental State Examination (MMSE) or a composite measure of attention and executive functioning (Trail Making and Verbal Fluency Test). Potential confounders, were taken into account at an individual patient level. Logistic regression analysis was used to investigate ACD risk by sex. We assessed potential mediators for sex differences in ACD using Causal Mediation Analysis (CMA). After a median follow-up duration of 6.1 ± 0.7 years, 361 (30.0%) females compared to 494 (25.2%) males exhibited ACD (OR 1.27 [95%CI 1.08–1.49], $p = .003$). Depressive symptoms, which were more common in females (24.3% vs 12.5%), mediated between sex and ACD (mediation effect 20.3%, $p = 0.03$). There were no other significant mediators.
Conclusion: Females with T2D had a higher risk of ACD compared to males. This was partly explained by depressive symptoms. After evaluation of vascular and diabetes-related risk factors, complications and treatment, a major share of the higher risk of ACD in females remained unexplained. Our results highlight the need for further research on causes of sex-specific ACD in T2D.

Abbreviations: A&E, Attention and Executive functioning score; ACD, Accelerated cognitive decline; CABG, Coronary artery bypass grafting; CAROLINA-COGNITION, cognition substudy of the CAROLINA® trial (NCT01243424); CES-D, Centre for Epidemiologic Studies Depression Scale; Cholesterol ratio, HDL + LDL/HDL; CMA, Causal Mediation Analysis; CV, Cardiovascular; M, Mediator; MDRD, Modification of Diet in Renal Disease study equation; MMSE, Mini-Mental State Examination; PAOD, Peripheral arterial occlusive disease; PCI, Percutaneous coronary intervention; RBI, Regression-based index score; TMT, Trail Making Test; TMT A, Trail Making Test part A; TMT B, Trail Making Test part B; TMT ratio, (TMT B - TMT A)/TMT A; UACR, Urine albumin-to-creatinine ratio in mg/g; VFT, Verbal Fluency Test.

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Introduction

Cognitive dysfunction is increasingly recognized as an important comorbidity of type 2 diabetes (T2D) [1,2]. A meta-analysis including fourteen studies with all together more than two million participants, estimated an almost twofold higher risk for dementia in people with T2D, compared to those without [3]. Sex differences in both diabetes and dementia receive growing attention, since the underlying mechanisms and risks might differ by sex. Sex differences in cognitive (or other) outcomes in people with diabetes can be explored in two ways. First, occurrence of the outcome can be directly compared between females and males with diabetes. Second, the occurrence of the outcome can be compared between females with and without diabetes and between males with and without diabetes, subsequently these diabetes-associated risks can be compared between the sexes. Previous studies mostly used the second approach and have shown that the presence of diabetes confers a higher risk of cognitive impairment in females compared to males. Sex-stratified analyses showed that T2D-associated dementia risk appears to be relatively greater for females than males, especially for vascular dementia (relative risk females 2.34 (95% confidence interval (CI) 1.86–2.94); males 1.73 (95% CI 1.61–1.85)). Exploring these diabetes-associated sex differences can help to discern the differential impact of diabetes in the general population between males and females. Whereas, a direct comparison between female T2D patients and male T2D patients can point towards sex-specific mechanisms in diabetes. And thus help to unravel the pathophysiology of T2D-associated cognitive dysfunction.

Data on a direct comparison between female T2D patients and male T2D patients and the risk of cognitive decline is scarce and contradicting. The spectrum of T2D-associated cognitive changes ranges from dementia to subtle decrements. For dementia, previous studies have not observed sex differences among patients with T2D [4,5]. Only few small studies have compared the occurrence of cognitive decline, also considering cognitive changes other than dementia, over time between female and males with T2D [6,7]. Of note, cognitive decline in older individuals with T2D is not a unitary construct [8]. On average – at group level – cognition declines only very slowly over time [9–12]. Yet, there is a subset of individuals with accelerated decline. Exploring sex differences in accelerated cognitive decline (ACD) among patients with T2D is important as it can point towards sex-specific mechanisms and thus help to unravel the pathophysiology of T2D-associated cognitive dysfunction. This could eventually lead to improved personalized care and sex-specific recommendations for preventing ACD in T2D.

In the current study, we assess sex differences in the occurrence of ACD in subjects with T2D and without cognitive impairment at baseline. Additionally, we explored if differences in ACD can be explained by diabetes-related and vascular risk factors, complications or treatment.

Methods

Study population

Participants were from the CAROLINA-COGNITION study (39% women), an integral part of the CAROLINA® trial (CARdiovascular Outcome Study of LINAgliptin versus Glimepiride in T2D (NCT01243424)) that studied patients with relatively early T2D (HbA1c 48–69 mmol/mol (6.5–8.5%)) and exclusion of those with insulin treatment) with risk factors for, or established, cardiovascular (CV) disease (detailed inclusion- and exclusion criteria for CAROLINA are described elsewhere [13]). The CAROLINA-COGNITION study found no relative benefits of linagliptin, a selective, once-daily, DPP-4 inhibitor, versus glimepiride, a second generation sulfonylureas, when given in addition to the usual standard of care, for the risk of ACD, overall, or by sex [14]. Both treatment arms are therefore combined in the current analyses.

The derivation of our current study population is the same as in the CAROLINA-COGNITION study (n = 3163, Figure A1) [14]. Participants from countries using the Latin alphabet were eligible for CAROLINA-COGNITION (n = 4529). They were included in the baseline population (n = 4297) when participants were literate, their language and years of education were recorded and they had a valid cognitive assessment at baseline (i.e. no missing or implausible cognitive values at baseline). Participants with scores below 24 on the Mini-Mental State Examination (MMSE) at baseline (i.e. indicating already existing cognitive impairment) were not included for follow-up cognitive analyses (n = 279). This resulted in 4018 participants eligible for follow-up. In 855 (21%) of these 4018 participants, there was no valid follow-up cognitive assessment, for the following reasons: 161 (4.0%) participants died during follow-up before cognitive re-assessment, in 405 (10.1%) no valid cognitive re-assessment was available, and in 289 (7.2%) participants the cognitive re-assessment was not within 7 days after the last study drug intake, a pre-specified criterion for eligibility of the follow-up assessment for the primary analysis in the CAROLINA-COGNITION study [12]. Supplementary table A4 provides an overview of participating countries in the CAROLINA-COGNITION study.

Demographics

Demographics were collected at baseline. Information on sex and race was captured, based on self-classification by trial participants as reported in the electronic case record form (fixed categories) by investigators. Age was determined based on the information on the medical chart whereas educational level (documented in years of formal

education) was based on self-report by trial-participants. Data are expressed in means (M) ± standard deviation (SD) or number (n) (percentage (%)).

Potential mediators

Potential mediators for the relationship between sex and ACD were recorded at baseline. The diabetes-related and CV risk factors were based on measurements, except for smoking which was self-reported. Weight (measured after urine sampling), height, waist-circumference, systolic and diastolic blood pressure were measured on-site. BMI (in kg/m^2) was calculated. Parameters that were determined from clinical chemistry were: HbA1c, total-, HDL- and LDL-cholesterol, triglycerides and eGFR (MDRD, ml/min/1.73m2). Urinalysis included albumin and creatinine using morning spot urine measurements. All blood and urine sampling were done in fasted state. All laboratory calculations were executed by one central lab. Cholesterol ratio was calculated as HDL cholesterol + LDL cholesterol/HDL cholesterol. A cholesterol ratio above 4 is considered abnormal. eGFR was subdivided in the following categories: $\geq$ 60 ml/min/1.73 m^2 normal kidney function to mild decrease, $<$ 60 ml/min/1.73 m^2 moderate to severe decrease. Medical history on micro- and macro complications, depression and treatment were collected from medical records. Participants with diagnosis of depression had an ongoing diagnosis at enrolment. In addition, a 20-item questionnaire on depressive symptoms experienced over the last week, the Centre for Epidemiologic Studies Depression Scale (CES-D), was performed. A score $\geq$16 indicates presence of depressive symptoms [15]. For full definitions of all potential mediators for the relationship between sex and ACD see Table A2.

Cognitive assessment

A comprehensive description of the cognitive assessment and corresponding procedures have previously been published [16]. Cognitive assessment was done at baseline, planned after 160 weeks and at end of follow-up. At least one follow-up cognitive assessment was needed for analysis. In short, cognitive assessment consisted of three cognitive test; the MMSE, Trail Making Test (TMT) and Verbal Fluency Test (VFT). The MMSE is a widely used and validated screening test for global cognition in older adults [17]. It briefly evaluates different cognitive functions including orientation in time and place, verbal registration, attention and calculation, short term verbal memory, language and visuoconstruction. A score below 24 is generally accepted to indicate cognitive impairment. The TMT is a timed test of scanning, visuomotor tracking, divided attention and cognitive flexibility [18]. The VFT requires a subject to generate as many words as possible in 60 seconds and is dependent on vocabulary size, lexical access speed and executive control ability [19]. Both the TMT and VFT are sensitive measures for subtle cognitive decline and cognitive decrements that are known for T2D [20,21]. Performance on the TMT and VFT are used to generate one composite score for attention and executive functioning expressed as z-score (A&E z-score) [19]. Details on the A&E z-score derivation are described previously [16] and can be found in the supplementary methods.

Outcome

The primary cognitive outcome was defined as the incidence of ACD at end of follow-up (median of 6.12 years), using a regression-based index (RBI), consistent with the primary cognitive outcome measure of the CAROLINA trial. The RBI score reflects the difference between the observed and predicted cognitive score for each individual, and takes potential confounders (i.e. baseline test performance, age, years of formal education, race and test-retest interval) into account at subject level, as opposed to raw change in test scores. The derivation and calculation of the RBI is previously described [16], and additional information on the calculation can be found in the supplementary methods. Here the only difference from the primary cognitive analyses in CAROLINA is that sex was not included as confounder in the RBI.

Participants were classified as having ACD when their cognitive decline score was at or below the 16th percentile of the RBI score of the total study population: this cut-off was chosen as it corresponds approximately to one SD below the mean. Participants were also classified as having ACD at follow up if: *1)* the reason for a missing cognitive score was the inability of the participant to understand the instructions at follow-up, while a valid baseline assessment had been performed. *2)* No second follow-up assessment was performed, but the participant had ACD at the first follow-up assessment [16]. The ACD classification thus identifies individuals that decline faster than would be expected compared with other participants, while considering the confounders listed above at an individual level.

Statistical analysis

We considered both treatment arms for the current study, since the effect of linagliptin versus glimepiride on the cognitive outcome in CAROLINA-COGNITION study was neutral, overall, and by sex [14]. Female-to-male differences adjusted for age and race were calculated at baseline for demographics, diabetes-related and CV risk factors, vascular and non-vascular complications and vascular risk factor treatment with general linear models. Logistic regression analysis was used to investigate if females are at higher risk for ACD compared to males.

Based on all observed female-to-male differences and the literature, potential mediators for the relationship between sex and ACD were selected. Next, relationships (Fig. 1) between sex and mediator (pathway a), and mediator and ACD (pathway b), were studied separately using regression analysis, corrected for multiple testing using the Benjamini-Hochberg Procedure to decrease the false discovery rate [22]. When both relationships (pathways a and b) were found to be significant ($p < .05$) or

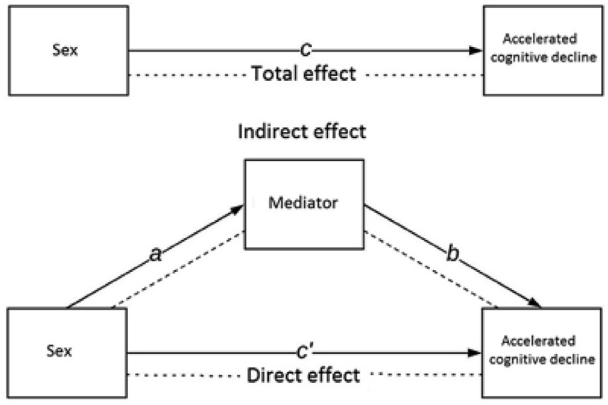

Figure 1 Conceptual diagram of Causal Mediation Analysis. *Note.* A conceptual diagram depicting how total effect of sex on accelerated cognitive decline (c) is decomposed in a direct effect (c') and an indirect effect through the mediator (a*b). The total effect can therefore be parameterized as: c = a*b + c'.

borderline significant ($p < .10$), Causal Mediation Analysis (CMA) [23–25], was used to decompose total relative risk and explained variance in *1)* a direct effect (c') of sex on ACD, and *2)* an indirect effect (ab) explained by the potential mediator (Fig. 1). All required assumptions were met prior to CMA [26]. No additional mediator-outcome confounders (such as age) were included in the mediation analyses, since these are already incorporated in the ACD outcome itself (i.e. RBI-score calculation). Males denoted the reference group in all analyses.

All statistical analyses were performed with SAS software, version 9.4M6 (SAS Institute, Cary, NC, USA).

Results

The analysis population consisted of 1203 (38.0%) females and 1960 (62.0%) males. Female-to-male differences (with 95% CI) for sociodemographic characteristics, risk factors, complications and treatment are shown in Table 1. The average age was 64.4 ± 9.2 and average T2D duration was 7.6 ± 6.1 years; comparable for both sexes. The distribution of race differed significantly by sex (White: 80.9% female vs 86.8% male, Black/African American: 8.8% female vs 4.1% male). The proportion of females with ≥12 years of formal education was lower than in males (19.9% vs 26.2%). Diabetes duration and glycaemic control were comparable for both sexes. Females had a higher BMI (31.4 ± 5.4 vs 30.4 ± 4.6 kg/m^2) and a smaller waist-circumference (102.2 ± 12.5 vs 106.9 ± 12.0 cm). Systolic blood pressure was similar between sexes and diastolic blood pressure was lower in females (78.0 ± 9.4 vs 79.2 ± 9.4 mmHg). LDL-cholesterol and HDL-cholesterol were higher in females (LDL-cholesterol: 2.5 ± 0.9 vs 2.3 ± 0.8 mmol/L, HDL-cholesterol: 1.4 ± 0.3 vs 1.2 ± 0.3 mmol/L). Cholesterol ratio was lower in females (3.7 ± 1.2 vs 3.9 ± 1.3), with less individuals exceeding a ratio of 4 (29.6% vs 36.7%). More males were currently smoking (15.6% vs 19.4%). Males had significantly more macrovascular complications overall (21.6% vs 37.4%). A higher proportion had a history of coronary artery disease (8.9% vs 20.2%). However, female-to-male differences for stroke (5.5% vs 6.3%) and peripheral arterial occlusive disease (4.8% vs 6.0%) were comparable. Microvascular complications were similar between females and males except that females more commonly had an eGFR <60 mL/min/1.73 m^3 (20.7% vs 16.6%). Females were also more often diagnosed with depression (15.1% vs 6.7%) and showed a significant higher indication for current depressive symptoms on the CES-D (24.3% vs 12.5%). Males were prescribed anti-coagulants more often (10.8% vs 18.0%). The use of lipid-lowering and anti-hypertensive drugs was similar between sexes.

The baseline characteristics of the 855 participants without valid follow-up cognitive assessment, were comparable to the participants with follow-up, but those without follow-up had slightly more prevalent CV disease and a slightly higher proportion reporting depressive symptoms (Table A3) [12]. Cognitive follow up was obtained in a similar proportion of eligible females (78.5%) and males (78.8%). In the participants without follow-up cognitive assessment female-to-male differences in baseline characteristics were similar to that for the participants with follow-up (Table A3).

After a median follow-up duration of 6.12 (min 0.02 – max 7.42) years, which was similar between sexes, 361 (30.0%) females compared to 494 (25.2%) males developed ACD (OR 1.27 [95% CI 1.08–1.49], $p = .003$). The average test results and absolute changes from baseline for the cognitive tests that were used to calculate the ACD-outcome (i.e. MMSE, TMT and VFT), are shown for those with and without ACD, for females and males separately in Table 2. On average, females showed larger declines over time compared to males on MMSE (−0.5 ± 2.6 points vs −0.3 ± 2.5), and TMT A (4.8 ± 29.4 s vs 3.3 ± 25.6), also after adjusting for age, level of education, language, test-retest interval and baseline performance. There were no statistical differences between females and males in decline for TMT B, TMT ratio and both the fluency tests.

From the fifteen evaluated potential mediators for the relationship between sex and ACD (Table A1), only CES-D (≥16) and macrovascular disease met the criteria for analysis with CMA; i.e. they both had a relationship with sex (pathway a) and with ACD (pathway b). Female sex significantly predicted CES-D ≥ 16 (OR: 2.24, 95% CI [1.86–2.71], $p < .0001$) and CES-D ≥ 16 significantly predicted ACD (OR: 1.44, 95% CI [1.18–1.76], $p < .001$). CMA revealed that the relationship between sex and ACD was partly (20.3% ($p = .03$)) explained by CES-D score ≥16 (OR: 1.04 [95% CI 1.01–1.08], $p = .008$) (Fig. 2A). Male sex significantly predicted macrovascular disease (OR: 2.17, 95% CI [1.84–2.56], $p < .0001$) and macrovascular disease significantly predicted ACD (OR: 1.21, 95% CI [1.02–1.43], $p = .03$). Consequently, CMA revealed that female sex attenuated the risk of ACD through macrovascular complications (OR: 0.96 [95% CI: 0.93–0.99], $p < .01$) (Fig. 2B), indicating that the effect of sex on ACD is even larger if the imbalance of macrovascular disease between the sexes is taken into account. Explained variance could not be

Table 1 Baseline characteristics.

	Female (n = 1203)	Male (n = 1960)	Female-to-male differences (95% CI)
Age [years]	64.5 ± 9.3	64.4 ± 9.1	0.3 (−0.4, 0.9)
Race			
White	973 (80.9%)	1701 (86.8%)	−6% (−9, −3)*
Black/African American	106 (8.8%)	80 (4.1%)	5% (3, 6)*
Asian	70 (5.8%)	111 (5.7%)	−0.2% (−1, 2)
Other	54 (4.5%)	68 (3.5%)	1% (−0.3, 2.4)
Educational level [years]	10.3 ± 3.5 (239 (19.9%))	11.1 ± 3.4 (514 (26.2%))	−0.8 (−10.0, −0.5)*
n (%) > 12 years education			(-7% (−10, −3))*
Diabetes-related and CV risk factors			
Duration of diabetes [years]	7.5 ± 6.2	7.6 ± 5.9	−0.1 (−0.5, 0.3)
HbA1c [mmol/mol]	54.3 ± 6.0	54.5 ± 0.6	−0.2 (−0.6, 0.3)
HbA1 [%]	7.1 ± 0.5	7.1 ± 0.6	−0.01 (−0.05, 0.03)
Triglycerides [mmol/L]	1.9 ± 2.1	1.9 ± 1.8	−0.03 (−0,17, 0.11)
BMI [kg/m^2]	31.4 ± 5.4	30.4 ± 4.6	1.0 (0.6,1.3)*
Waist circumference [cm]	102.2 ± 12.5	106.9 ± 12.0	−4.6 (−5.4, −3.7)*
Systolic blood pressure [mmHg]	135.3 ± 16.5	136.5 ± 15.9	−1.1 (−2.2, 0.1)
Diastolic blood pressure [mmHg]	78.0 ± 9.4	79.2 ± 9.4	−1.2 (−1.9. −0.5)*
LDL-cholesterol [mmol/L]	2.5 ± 0.9	2.3 ± 0.8	0.2 (0.1, 0.2)*
HDL-cholesterol [mmol/L]	1.4 ± 0.3	1.2 ± 0.3	0.2 (0.2, 0.2)*
Cholesterol ratio	3.7 ± 1.2	3.9 ± 1.3	−0.2 (−0.3, −0.2)*
> 4	356 (29.6%)	720 (36.7%)	−7% (−10, −4)*
Currently smoking	188 (15.6%)	381 (19.4%)	−3% (−6, −1)*
Microvascular complications	312 (25.9%)	480 (24.5%)	1% (−2, 5)
Diabetic neuropathy	197 (16.4%)	293 (15.0%)	1% (−2, 3)
Diabetic retinopathy	51 (4.2%)	97 (5.0%)	−1% (−2, 1)
Diabetic foot	18 (1.5%)	29 (1.5%)	0.1% (−1, 1)
Diabetic nephropathy	123 (10.2%)	195 (10.0%)	−0.3% (−2, 2)
eGFR, [ml/min/1.73m^2]	75.2 ± 19.7	77.0 ± 18.4	−2.2 (−3.4, −0.9)*
< 60	249 (20.7%)	325 (16.6%)	4% (2, 7)*
Macrovascular complications	260 (21.6%)	733 (37.4%)	−16% (−19, −13)*
Myocardial infarction	86 (7.2%)	327 (16.7%)	−10% (−12, −7)*
Stroke	66 (5.5%)	124 (6.3%)	−1% (−3, 1)
Coronary artery disease	107 (8.9%)	396 (20.2%)	−11% (−14, −9)*
PCI or CABG	89 (7.4%)	372 (19.0%)	−12% (−14, −9)*
Peripheral arterial occlusive disease	58 (4.8%)	118 (6.0%)	−1% (−3, 0)
Non-vascular complications			
Current diagnosis of depression	181 (15.1%)	132 (6.7%)	9% (6, 11)*
CES-D	10.09 ± 8.9	7.9 ± 7.4	3.0 (2.4, 3.6)*
≥ 16	286 (24.3%)	242 (12.5%)	12% (9, 15)*
Cardiovascular therapies			
Lipid-lowering drugs	889 (73.9%)	1488 (75.9%)	−2% (−5, 2)
Anti-hypertensive	1082 (89.9%)	1733 (88.4%)	1% (−1, 3)
Anti-coagulants	130 (10.8%)	352 (18.0%)	−7% (−10, −5)*

Note. Data are shown for mean ± standard deviation or number (%).*$p < .05$.

calculated for the effect of macrovascular disease, since the direct effect (positive) and indirect effect (negative) are opposite in direction.

Discussion

Our results show that in patients with T2D at elevated CV risk, females were at higher risk for ACD compared to males. Analysis of differences in diabetes-related factors, CV profile, and treatment between females and males, revealed that the higher risk for ACD in females was partly explained by a higher presence of depressive symptoms among females.

It has been shown previously that the T2D-associated dementia risk is greater for females than males [3]. However, few studies have directly compared occurrence of cognitive decline between males and females with T2D. In the Fremantle Diabetes Study risk for dementia did not differ between males and females with T2D [4], even after a median follow-up of 12.7 years [27]. A limitation of that study, however, is that the final sample size was limited (n = 180). In a much larger American cohort study (n = 29 961) of T2D subjects aged ≥60 year, there also was no sex difference in the occurrence of dementia during 10-year follow-up (hazard ratio of 0.97 (95% CI 0.91–1.02)) [5]. Apart from dementia, T2D is also known to be associated with more subtle decline in cognitive performance. Most longitudinal studies on cognitive performance in T2D adjusted for sex, rather than investigating sex differences. A recently published paper using data from the ADVANCE trial [28] reported that during five year follow-up, males

Table 2 Absolute changes from baseline for cognitive scores for females and males with and without ACD.

	Females with ACD (n = 361)			Males with ACD (n = 494)			Female-to-male differences in Δ[a] (95% CI)
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	
MMSE	27.8 ± 1.8	25.2 ± 3.4	−2.6 ± 3.1	28.4 ± 1.7	26.1 ± 3.7	−2.3 ± 3.6	−0.2 (−0.7, 0.3)
TMT A	62.3 ± 39.9	70.3 ± 50.0	9.7 ± 41.1	54.9 ± 29.2	60.8 ± 41.7	5.0 ± 36.0	4.4 (−1.2, 10.0)
TMT B	130.0 ± 70.7	175.8 ± 83.8	47.6 ± 74.6	123.2 ± 63.0	168.6 ± 80.1	49.6 ± 79.4	3.5 (−14.7, 7.7)
TMT ratio	1.4 ± 1.0	2.3 ± 1.3	0.9 ± 1.3	1.4 ± 1.0	2.5 ± 1.6	1.2 ± 1.0	−0.2 (−0.5, 0.01)
VFT category	14.0 ± 6.0	12.1 ± 5.7	−2.1 ± 5.7	15.2 ± 6.3	12.5 ± 6.2	−2.8 ± 6.6	0.6 (−0.2, 1.3)
VFT letter	8.0 ± 3.9	7.0 ± 3.8	−1.0 ± 2.9	8.7 ± 4.1	7.2 ± 3.6	−1.4 ± 3.2	0.2 (−0.2, 0.6)
A&E z-score	−0.18 ± 0.72	−0.72 ± 0.76	−0.57 ± 0.82	−0.07 ± 0.79	−0.77 ± 0.85	−0.73 ± 0.97	0.1 (−0.001, 0.2)
	Females without ACD (n = 842)			Males without ACD (n = 1466)			Female-to-male differences in Δ[a] (95% CI)
	Baseline	Follow-up	Δ	Baseline	Follow-up	Δ	
MMSE	28.5 ± 1.7	28.9 ± 1.3	0.4 ± 1.6	28.7 ± 1.6	29.0 ± 1.2	0.3 ± 1.5	−0.03 (−0.12, 0.07)
TMT A	50.9 ± 25.3	54.8 ± 29.0	2.9 ± 23.3	46.6 ± 23.1	49.8 ± 23.6	2.7 ± 21.1	1.9 (0.1, 3.7)*
TMT B	113.0 ± 58.2	115.1 ± 57.5	5.1 ± 50.2	104.4 ± 54.7	106.0 ± 50.0	4.3 ± 47.6	3.8 (0.01, 7.69)*
TMT ratio	1.4 ± 1.1	1.2 ± 0.7	−0.04 ± 0.8	1.4 ± 1.0	1.2 ± 0.7	−0.03 ± 0.8	−0.01 (−0.1, 0.1)
VFT category	15.8 ± 6.7	16.1 ± 7.1	0.1 ± 6.9	17.0 ± 6.2	17.0 ± 7.1	−0.1 ± 6.8	0.1 (−0.5, 0.7)
VFT letter	9.4 ± 3.8	9.5 ± 4.0	0.1 ± 2.7	9.7 ± 4.3	9.9 ± 4.4	0.2 ± 3.1	−0.03 (−0.3, 0.2)
A&E z-score	0.01 ± 0.71	0.11 ± 0.62	0.10 ± 0.67	0.07 ± 0.69	0.16 ± 0.57	0.10 ± 0.63	0.002 (−0.04, 0.05)

Note. For TMT A, TMT B and TMT ratio higher scores indicate worse performance. Δ: difference score: follow-up score − baseline score. [a]Adjusted for age, level of education, language, test-retest interval and baseline performance. *$p < .05$.

were at higher risk for cognitive decline compared to females with T2D. An essential difference with our study is the definition of cognitive decline; a 3-point decline in MMSE. In contrast to our study, this does not take potential confounders, such as age, education, race, baseline cognitive performance and test-retest interval, into account. The few other small studies that directly compared the occurrence of cognitive decline between female and males with T2D, did not show a consistent sex difference [6,7]. Our current study, in a large cohort with repeated cognitive assessments, indicated that females with T2D were at higher risk for ACD compared to males with T2D. This is in apparent contradiction to the aforementioned studies comparing risk for dementia between males and females with T2D, which may be due to differences in outcome measures. By contrast, a clinical diagnosis of dementia, which was the outcome of the previous studies, is a construct. In large cohorts [10], this construct is

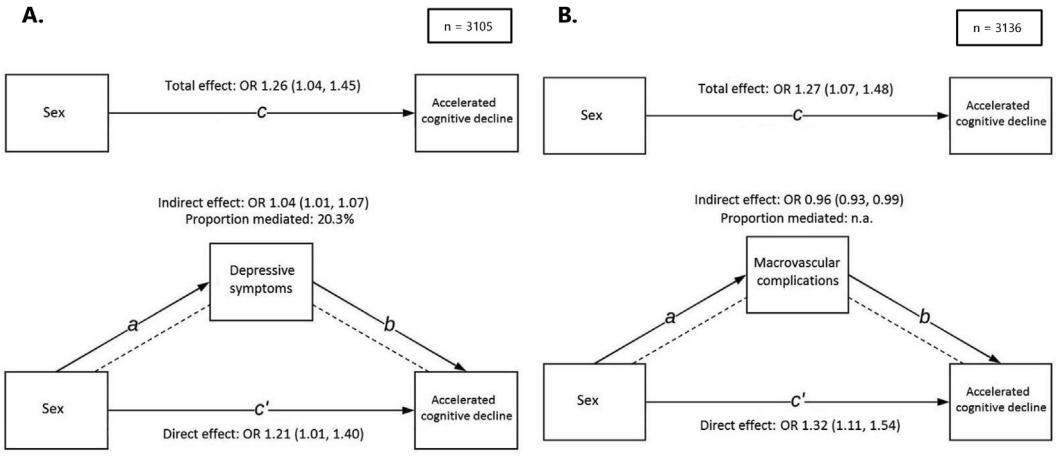

Figure 2 Causal mediation analysis of the effect of sex on ACD with mediator depressive symptoms (A) and macrovascular complications (B). The figure summarizes the results of CMA for the higher risk of females for ACD, with in panel A depressive symptoms as a mediator and in panel B macrovascular complications as a mediator. The total effect (c) is composed of an indirect effect (c') and direct effect (a^*b) of sex on ACD and all are presented in OR with 95% CI. The OR for pathway c slightly differs between panel A and B due to missing data on depressive symptoms (n = 31). Males denote the reference group. Panel A: shows depressive symptoms as mediator on the effect of sex on ACD. Females have an increased risk of ACD (total effect (c); OR 1.26 (1.04 − 1.05), which is composed of a direct effect of female sex on ACD (c') (OR 1.21 (1.01- 1.40) and an indirect effect of female sex through depressive symptoms on ACD (a^*b) (OR: 1.04 (1.01, 1.07)). The higher risk of females for ACD is for 20.3% explained by depressive symptoms. Panel B: shows macrovascular complications as mediator on the effect of sex on ACD. Females have an increased risk of ACD (total effect (c): OR 1.27 (1.07 − 1.48), which is composed of an direct effect of female sex on ACD (c') (OR 1.32 (1.11 − 1.54)) and an indirect negated effect of female sex through macrovascular complications (a^*b) (OR 0.96 (0.93-0.99). Proportion mediated could not be calculated here, since the direct effect (positive) and indirect effect (negative) are opposite in direction. CMA = Causal Mediation Analysis, ACD = accelerated cognitive decline, OR = odds ratio, 95% CI = 95% confidence interval. n.a. = not applicable.

generally not based on standardized cognitive testing. Of note, there also is a growing body of evidence suggesting that sex influences the diagnosis of dementia. By the time females are diagnosed with dementia, they already have a more severe disease burden and decline more rapidly compared to males [29,30]. The use of dementia diagnosis as an outcome might therefore underestimate the occurrence of cognitive decline in females.

We identified two significant mediators for the relationship between sex and ACD: depressive symptoms and macrovascular complications. The presence of depressive symptoms was a significant mediator for the relationship between sex and ACD and explained 20.3% of the higher risk of ACD for females. This finding is in line with the results of the ADVANCE trial [28]. The presence of anxiety and depression symptoms is more strongly associated with higher odds of cognitive decline or dementia in females than in males with T2D (ratio of OR, 1.28 [1.01, 1.63]). Depression is known to have a higher prevalence in females compared to males in people with and without T2D [31,32]. In general, depressive symptoms are associated with decreased processing speed, diminished attention and executive functioning [33–35]. These cognitive functions were measured with our A&E score and incorporated in the ACD outcome. The association between the baseline presence of depressive symptoms and subsequent cognitive decline should be interpreted with caution. It is not self-evident that the depressive symptoms have led to the accelerated cognitive decline; these could also be a sign of prodromal dementia [36].

Another identified mediator was the presence of macrovascular complications; more males had macrovascular complications increasing their risk of ACD. Despite this, fewer risk factors and vascular complications in females and similar glycemic control in both sexes, overall females still showed a higher overall risk of ACD.

A major share of the higher risk of ACD for females remained unexplained, after we investigated an extensive set of potential mediators. There were no sex differences in glycemic control nor in diabetes-complications such as diabetic foot, neuropathy, retinopathy and nephropathy. There were the expected sex differences in vascular risk factors. Females had a higher BMI, whereas males had a higher waist circumference, systolic blood pressure, more macrovascular complications and more frequently were current smokers [28,37–39]. However, these differences did not mediate the relationship between sex and ACD. Alternative explanations may include biological aspects or disparities in health care provision. Regarding biological aspects, exposure to endogenous estradiol in females seem to increase the risk of dementia, especially in the presence of diabetes [40]. Also, since our female participants were mostly post-menopausal (mean age >60), alternations in sex-hormones could play a role [41,42]. Furthermore, literature has suggested a genetically greater immune response [43] and a more prothrombotic state [44] in females with T2D compared to males. Both these phenomena potentially contribute to cerebral injury underlying ACD. With regard to sex differences in provision of healthcare, disparities between females and males could influence the risk of ACD. A recent review of De Ritter and colleagues [45] could not draw definite conclusions on sex-specific differences in diabetes management, due to a lack of available data on drug type, dosage, or adherence by sex in the reviewed literature.

Strengths of our study are the longitudinal design with a large sample size, with participants from multiple countries (Table A4). The cognitive outcome was based on repeated cognitive testing and consisted out of two complementary tests: one that measures general cognitive impairment (MMSE), and a composite score that captures more subtle cognitive changes as seen in T2D [20]. Additionally, our outcome was adjusted for relevant possible confounders such as age, race, level of education, test-retest interval and initial cognitive performance level. Performance on cognitive screening tests like MMSE are not influenced by sex [46]. The composite score was comprised of both a verbal and a visuospatial task. This is relevant, since on average females perform better on verbal memory tasks [47] and males perform better on visuospatial tasks [48]. However in this study, the average performance in females was worse on all cognitive tests compared to males. Another strength is the access to a comprehensive variety of standardized and detailed risk factor profiles, including lab measurements and information on treatment for all participants.

Several possible limitations of our study should be addressed. First, we studied a selected clinical trial population with T2D at elevated CV risk. The selection criteria for CAROLINA may affect generalizability of our findings for several reasons. Females are generally underrepresented in CV outcome trials [49], as was also the case in our cohort. Also, clinical trial participants are typically higher educated and more affluent than patients in routine care [50–52]. It is possible our participants were relatively protected to the rate of cognitive decline because of a more prosperous lifestyle and higher cognitive reserve than the overall general population with comparable levels of CV risk factors. Nevertheless, patient selection does not appear to have affected sex differences in risk factor profiles in our study, as they were compatible with known sex differences from population based cohort studies [39]. Moreover, the fact that the study population comprised patients at elevated cardiovascular risk may be considered an advantage for studying cognitive impairment, as it represents an at risk population for this outcome. Further, we aimed to investigate only subjects without cognitive impairment at baseline (MMSE $\geq$24), however this resulted in a higher proportion of females being excluded due to MMSE <24 at baseline compared to males (Figure A1). On the other hand, inclusion of subjects without cognitive impairment at baseline facilitated the possibility to capture cognitive decline over time. Furthermore, cognitive follow-up was only obtained from 78.7% of the eligible population (Figure A1). However, because there was no selective drop-out regarding sex, and adjusted females-

to-male differences of those with and without follow-up were comparable (Table A3), this will probably not have affected our findings. In a study of late-life outcomes, such as ACD, accounting for competing risk of death avoids overestimating the risk of ACD and helps to accurately identify participants at-risk for dementia [53]. Of note, we could not perform such analyses with our available data. Another limitation is that the trial did not capture some known risk factors, such as, APOE genotype, exercise-habits and sex-specific risk factors such as estimated lifetime exposure to estrogen, both endogenous (years of ovulation) and exogenous (years and timing of menopausal hormone therapy).

Conclusion

In a population with T2D at elevated CV risk, females had a higher risk of ACD compared to males. This sex difference should be acknowledged in clinical practice. Depressive symptoms partially mediated the higher risk of ACD in females. However, a major share of the higher risk of ACD in females remained unexplained after a careful evaluation of diabetes-related and vascular risk profile, vascular complications and treatment. Future research is therefore needed to unravel the causes of sex-specific ACD in T2D, in order to reveal possible sex-specific modifiable factors. This could eventually lead to improved personalized care and sex-specific recommendations for preventing cognitive dysfunction in T2D.

Ethics approval and consent to participate

The CAROLINA-COGNTION study protocol was approved by the institutional review board or independent ethics committee from each site. All participants gave written informed consent.

Consent for publication

All authors consented the publication to the Journal (Nutrition, Metabolism and Cardiovascular Diseases).

Availability of data and materials

The sponsor of the CAROLINA trial (Boehringer Ingelheim) is generally committed to responsible sharing of clinical study reports, related clinical documents, and patient-level clinical study data. Researchers are invited to submit inquiries via the Vivli website (https://vivli.org/).

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Author's contributions

CV: Conceptualization, Methodology, Software, Formal analysis, Writing - Original Draft, Visualization, **JJ:** Methodology, Writing - Review & Editing, **OEJ**: Resources, Writing - Review & Editing, Funding acquisition, **GJB:** Conceptualization, Methodology, Writing - Review & Editing, Supervision, Funding acquisition, **LGE:** Conceptualization, Methodology, Supervision, Writing - Review & Editing.

Declaration of competing interest

The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work. OEJ was previously employed by Boehringer Ingelheim.

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Appendix A. Supplementary data

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