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ORIGINAL ARTICLE

WILEY

Sex differences in risk factors for cognitive decline and dementia, including death as a competing risk, in individuals with diabetes: Results from the ADVANCE trial

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Abstract

Aim: To estimate the associations between risk factors and cognitive decline (CD)/dementia, and the sex differences in these risk factors in individuals with type 2 diabetes, while accounting for the competing risk of death.

Materials and Methods: The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial of 11,140 individuals with type 2 diabetes was used to estimate the odds of CD/dementia using multinomial logistic regression.

Results: During a median 5-year follow-up, 1827 participants (43.2% women) had CD/dementia (1718 with CD only; 21 with dementia only; 88 with CD and dementia), and 929 (31.0% women) died without CD/dementia. Women had lower odds of CD/dementia than men (odds ratio [OR] [95% confidence interval], 0.88 [0.77, 1.00]); older age, higher total cholesterol, HbA1c, waist circumference, waist-to-height ratio, moderately increased albumin-creatinine ratio, stroke/transient ischaemic attack and retinal disease were each associated with greater odds of CD/dementia; higher years at education completion, baseline cognitive function, taller stature and current

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alcohol use were inversely associated. Higher waist circumference (women-to-men ratio of ORs [ROR], 1.05 [1.00, 1.10] per 5 cm) and presence of anxiety/depression (ROR, 1.28 [1.01, 1.63]) were associated with greater ORs for CD/dementia in women than men.

Conclusions: Several risk factors were associated with CD/dementia. Higher waist circumference and mental health symptoms were more strongly associated with CD/dementia in women than men. Further studies should examine the mechanisms that underlie these sex differences.

KEYWORDS
cohort study, randomized trial, type 2 diabetes

1 | INTRODUCTION

Diabetes, cognitive dysfunction and dementia each account for a large portion of the global health burden,[1–3] and the growing prevalence of these conditions can have substantial impacts on the ageing population.[4,5] Cognitive dysfunction has been increasingly recognized as a major co-morbidity in people with diabetes.[6] People with diabetes also have an increased risk of dementia,[7–11] as well as accelerated cognitive decline (CD) than those without diabetes.[12]

Despite these consistent associations, the extent to which explanatory factors contribute to the excess risk of CD and dementia in type 2 diabetes remains uncertain,[6] and recommendations to guide clinicians in managing and preventing cognitive dysfunction in people with diabetes are scarce.[3] While risk factor modification is important in preventing CD and dementia,[13] the effect of the risk factors may be modified by sex, and the manifestations can be different.[14,15] A series of recent publications highlighted the need to better characterize the effects of risk factors on CD and dementia by sex.[14–17] In general populations, women also exhibit greater deterioration of cognition,[18] and the transition from normal cognition to dementia may be more abrupt compared with men at an older age.[19] Diabetes has also been associated with a greater relative risk of vascular dementia in women than men.[11] The risk of cognitive impairment may be higher in women than men in diabetes,[20] although the literature is sparse.

Diabetes is also associated with nearly double the risk of premature death compared with people without diabetes.[21] Competing risk of death has only been accounted in a number of studies,[9,10,22,23] despite CD and dementia requiring a follow-up measurement, which death may preclude. Death as a competing risk should therefore be examined to avoid biased estimates, particularly in people with diabetes given their heightened risk of CD, dementia and death.

This study sought to provide estimates of relative risks between common cardiometabolic and lifestyle risk factors and CD/dementia, while considering death as a competing risk. We used data from a large, well-characterized, international cohort of people with type 2 diabetes, from a randomized control trial. We also explored the effect modification of sex on these risk factors for CD/dementia, and the effects of randomized treatments by sex were additionally prespecified.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

Data for the present study were taken from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial; the main results have been previously reported.[24] In brief, ADVANCE was a 2-by-2 randomized factorial trial that investigated the effects of blood pressure-lowering treatment and intensive glucose control. From 2001 to 2003, a total of 11,140 participants (aged ≥55 years) were recruited from 215 centres across 20 countries in Asia, Australia, Europe and North America. All participants had a diagnosis of type 2 diabetes (from the age of ≥30 years), with a history of major macrovascular or microvascular disease, or with at least one other cardiovascular risk factor. Participants were randomized to perindopril/indapamide combination blood pressure lowering compared with matching placebo; and gliclazide-based intensive glucose therapy (target HbA1c ≤ 48 mmol/mol [6.5%]) compared with standard glucose control therapy based on routine guidelines.[24] The median follow-up of the intensive glucose arm was 5.0 years.[24,25] All participants provided written informed consent, and ethical approvals were obtained in all study centres.

2.2 | Putative risk factors

Several major cardiometabolic and lifestyle risk factors for CD and dementia were selected, based on previous publications in general and diabetes populations, tempered by the availability of appropriate variables in ADVANCE.[6,13] At study induction, participants responded to a series of questionnaires soliciting information on demographic and lifestyle variables, including age, sex, region of residence (categorized as Europe, Asia, Australia/New Zealand and North America[25]), ethnicity, age at highest education attainment, physical activity (self-

reported participating in mild, moderate or vigorous exercise >15 min at least once per week[26]), alcohol intake (current or non-current drinker, with a current drinker defined as currently drinking alcohol once a week or more) and cigarette smoking (never or ever smoker, with an ever smoker further categorized into either a current or former smoker). Blood pressure (systolic and diastolic blood pressure), serum total cholesterol and HbA1c were measured using standard protocols.[24] Hypertension was defined as currently treated hypertension at study baseline. Urinary albumin-to-creatinine ratio (ACR) was measured based on single-spot urine samples taken at a random time of day. ACR was categorized into normal: <30 μg/mg; moderate: ACR ≥30, ≤300 μg/mg; and severe: ACR >300 μg/mg. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equation[27] and categorized as normal: eGFR <60 mL min^{-1} (1.73 $m)^{-2}$; mild to moderate reduction: eGFR ≥60, <90 mL min^{-1} (1.73 $m)^{-2}$; and severe reduction: eGFR ≥90 mL min^{-1} (1.73 $m)^{-2}$. Weight, height and waist circumference were measured, and body mass index (BMI) (weight [kg]/{height $[m]^2$}) was calculated. Waist circumference was included as a continuous variable, as well as categorical variable, based on cut-offs provided by the World Health Organization (WHO).[28] Symptoms of anxiety or depression were self-reported at study baseline, based on the anxiety/depression dimension of the three-level version of the EuroQol 5 Dimensions (EQ-5D) questionnaire.[29] History of macrovascular disease (stroke, transient ischaemic attack [TIA] or myocardial infarction) and microvascular disease were recorded at baseline. A history of retinal disease was recorded as positive if the participant was receiving retinal photocoagulation therapy, or had macular oedema, proliferative retinopathy or blindness believed to be caused by diabetes.

2.3 | Assessment of cognitive function and dementia

The primary outcome for the current study is a composite of CD or dementia. Individuals with a prior or current diagnosis of dementia did not enter the study. Cognitive function was evaluated using the mini-mental state examination (MMSE)[30] at baseline and was subsequently administered at 2-year intervals during the follow-up on three occasions. Original translated versions of the MMSE questionnaire were used; if a language was not available in the original version, a contextually appropriate translation of the MMSE was then arranged.

CD was recorded if there was at least a three-point decrement in MMSE score at any point during the study.[31] At each follow-up, when an individual scored less than 24 on MMSE, or where the physician or nurse suspected dementia, the individual was referred to a qualified specialist with expertise in making dementia diagnoses, based on the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).[32] The clinical assessment for dementia included an interview with both the patient and a close friend or a relative, wherever possible. These clinical evaluation methods were standardized across all study centres. Both CD and dementia were prespecified secondary outcomes in ADVANCE.[24,25]

2.4 | Statistical analyses

Baseline characteristics by sex (women vs. men) were summarized as mean and standard deviation (SD) for continuous variables, and number with percentages for categorical variables.

Multinomial regression models were used to estimate the odds ratios (ORs) with 95% confidence intervals (CIs) for outcomes specified as: 0, had neither CD nor dementia nor died during the study (reference category); 1, CD or dementia during the study, regardless of whether the participant died before the end of follow-up; and 2, death preceding any CD or dementia during the study, included as a competing risk. The association of each risk factor with CD or dementia was assessed in basic models adjusted for age, sex, region, age at completion of highest level of education and the treatments randomly allocated in the randomized controlled trial. Multiple adjusted models were fit, additionally adjusting for MMSE score, systolic blood pressure, total cholesterol, HbA1c, ACR, eGFR, diabetes duration, waist circumference, smoking, alcohol consumption and physical activity. Models for past medical history (stroke/TIA, myocardial infarction and retinal disease) remained with only basic adjustments. The effects of randomized treatments in association with CD/dementia were also assessed.

To address potential effect modification by sex, we investigated the association between risk factors and CD/dementia by sex, and models with interaction terms between each risk factor and sex were used to obtain the women-to-men ratio of odds ratios (ROR) with 95% CIs.

The benefit of incorporating death as a competing risk to CD or dementia was assessed by comparing the chosen multinomial models with logistic regression models, where the outcome was specified as: 0 (had neither CD nor dementia during the study [reference category]); or 1 (had CD or dementia during the study). Individuals who died were included in the reference category (i.e. "0") for the purpose of these analyses.

Because the current study focuses on CD and dementia as the primary outcome of interest, the results on death as the multinomial outcome are not included.

Complete case analyses were undertaken. All analyses were performed in R Studio version 4.0.3 (R Core Team, 2020). All *p*-values reported are two-sided, with the 5% threshold used to determine statistical significance.

3 | RESULTS

3.1 | Baseline characteristics

Table 1 presents the baseline characteristics of the 11,140 participants in ADVANCE, stratified by sex; 42.5% of the ADVANCE participants were women, and the mean age at study baseline was 65.8 years (SD = 6.4).

At study baseline, women had a lower age at completion of highest level of education by around 2 years on average compared

with men (17.2 vs. 19.4 years); the prevalence of treated hypertension was higher in women (72.9%) than men (65.6%); over half of all men and less than a quarter of women had ever smoked (55.9% vs. 23.1%); men were four times more probable to be a current drinker than women (43.7% vs. 12.5%); and while men were twice more probable to have had a history of myocardial infarction (15.8% vs. 6.9%), a higher percentage of women reported anxiety/depression symptoms than men (35.5% vs. 22.6%) (Table 1).

3.2 | Follow-up

The median follow-up of the 11,140 participants was 5.0 years, during which 1827 participants (43.2% women) had CD and/or dementia (CD only [n = 1718, 43.0% women]; dementia only [n = 21, 42.9% women]; CD and dementia [n = 88, 47.7% women]); 929 participants died (31.0% women) without having CD/dementia; and 8384 were alive without CD/dementia at the end of the study (43.6% women).

TABLE 1 Characteristics of participants in ADVANCE by sex

Characteristics	Sex		Total (n = 11,140)
	Women (n = 4733)	Men (n = 6407)	
Age (years)	65.7 (6.3)	65.9 (6.5)	65.8 (6.4)
Region of residence:			
Europe, n (%)	2214 (46.8)	2869 (44.8)	5083 (45.6)
Asia, n (%)	1926 (40.7)	2210 (34.5)	4136 (38.1)
Australia/New Zealand, n (%)	477 (10.1)	1008 (15.7)	1485 (13.3)
North America, n (%)	116 (2.45)	320 (4.99)	436 (3.91)
Age at completion of highest education (years)	17.2 (7.0)	19.4 (7.3)	18.4 (7.3)
MMSE score (points)	28.4 (2.1)	28.6 (1.8)	28.5 (1.9)
Blood pressure:			
Systolic blood pressure (mmHg)	145.3 (22.2)	144.8 (21.0)	145.0 (21.5)
Diastolic blood pressure (mmHg)	79.8 (11.0)	81.3 (10.9)	80.6 (10.9)
Treated hypertension, n (%)	3452 (72.9)	4203 (65.6)	7655 (68.7)
Total cholesterol (mmol/l)	5.55 (1.2)	4.93 (1.1)	5.20 (1.2)
HbA1c (mmol/mol)	59.5 (17.9)	58.0 (16.3)	58.6 (17.0)
HbA1c (%)	7.60 (1.6)	7.45 (1.5)	7.51 (1.6)
Albumin-to-creatinine ratio (μg/mg)	51.1 (112.6)	53.5 (116.8)	52.5 (115.0)
eGFR (mL min^{-1} (1.73 $m)^{-2}$)	72.7 (18.2)	75.8 (16.9)	74.4 (17.5)
Diabetes duration (years)	7.89 (6.19)	7.97 (6.47)	7.94 (6.35)
Body mass index (kg/m^2)	28.8 (5.7)	28.0 (4.7)	28.3 (5.2)
Waist circumference (cm)	95.6 (13.1)	100.7 (12.7)	98.6 (13.1)
Height (cm)	158.3 (6.5)	171.2 (7.2)	165.7 (9.4)
Waist-to-height ratio	0.60 (0.08)	0.59 (0.07)	0.59 (0.08)
Ever smoker, n (%)	1092 (23.1)	3582 (55.9)	4674 (42.0)
Current drinker, n (%)	593 (12.5)	2803 (43.7)	3396 (30.5)
Moderate to vigorous physical activity, n (%)	1901 (40.2)	3212 (50.1)	5113 (45.9)
Anxiety/depression, n (%)	1672 (35.5)	1441 (22.6)	3113 (28.1)
Stroke/transient ischaemic attack, n (%)	584 (12.3)	855 (13.3)	1439 (12.9)
Myocardial infarction, n (%)	325 (6.9)	1009 (15.8)	1334 (12.0)
Retinal disease, n (%)	340 (7.2)	455 (7.1)	795 (7.1)
Cognitive decline/dementia, n (%)	789 (16.7)	1038 (16.2)	1827 (16.4)
Cognitive decline only, n (%)	738 (15.6)	980 (15.3)	1718 (15.4)
Dementia only, n (%)	9 (0.2)	12 (0.2)	21 (0.2)
Cognitive decline and dementia, n (%)	42 (0.9)	46 (0.7)	88 (0.8)
Death, n (%)	288 (6.1)	641 (10.0)	929 (8.3)

Abbreviations: eGFR, estimated glomerular filtration rate; MMSE, mini-mental state examination.
Values are mean (standard deviation) unless stated.

Of those still being followed up at the end of the study, eight had missing MMSE values (Table 1).

3.3 | Comparative effects of putative risk factors on CD/dementia

After adjustment for confounding, women had a 12% lower risk of CD/dementia (OR, 0.88; 95% CI [0.77, 1.00]) compared with men. The risk of CD/dementia was lower among people in Australia/New Zealand in comparison with people in Europe (OR, 0.69; [0.58, 0.82]). Older age, higher total cholesterol, HbA1c, waist circumference, waist-to-height ratio, moderately increased ACR, prior stroke/TIA and retinal disease were each associated with a greater risk of CD/dementia; higher education, baseline cognitive function, taller stature and current alcohol use were inversely associated (Figure 1). Results from the basic models (Figure **S1**) for the association of each risk factor with CD/dementia were broadly similar to the multiple adjusted results. Alternative categorizations for comparison by smoking status, waist circumference and hypertension are also presented (Tables S1–S3). The estimates for waist circumference were no longer significant when categorized based on sex-specific cut-offs.

3.4 | Effect modification by sex

There was some evidence of effect modification by sex of common cardiovascular risk factors (Figure 2). Higher waist circumference (women-to-men ROR, 1.05, 95% CI [1.00, 1.10] per 5 cm increment) and presence of anxiety/depression symptoms (ROR, 1.28 [1.01, 1.63]) were more strongly associated with higher odds of CD/dementia in women than in men (Table 2).

The longitudinal change in MMSE over the study follow-up showed no difference by sex (slope for women = −0.04293; slope for men = −0.03891; difference in slopes = 0.001513 [*p*- value = .897]; Figure S2).

3.5 | Randomized treatment effects

There was no evidence that intensive glucose control (vs. standard control) or blood pressure lowering (vs. placebo) conferred a lower risk of CD/dementia, or evidence for any difference in the risk by sex (Table 3).

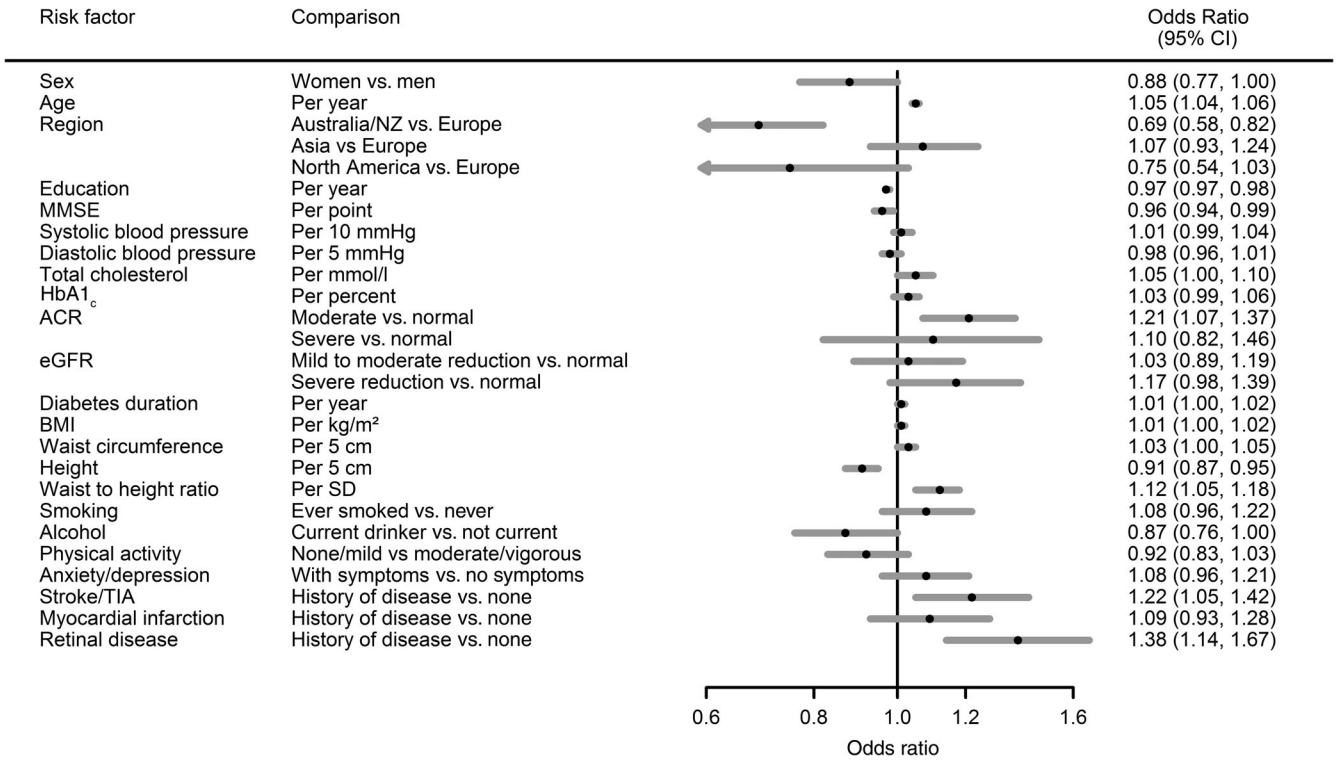

FIGURE 1 Odds ratios for the associations between risk factors and cognitive decline or dementia in ADVANCE, after multiple variable adjustments. All models are adjusted for sex, age, region, age at completion of highest education and randomized treatments. Models were additionally adjusted for mini-mental state examination (MMSE) score, systolic blood pressure, total cholesterol, HbA1c, albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate (eGFR), diabetes duration, waist circumference, smoking, alcohol use, physical activity and mental health symptoms. Models for stroke/transient ischaemic attack (TIA), myocardial infarction and retinal disease were kept basically adjusted for sex, age, region, age at completion of highest education and randomized treatments. All analyses accounted for the competing risk of death. ACR was categorized as normal: ACR < 30 μg/mg; moderate: ACR ≥ 30, ≤300 μg/mg; and severe: ACR > 300 μg/mg. eGFR was categorized as normal: eGFR < 60 mL min^{-1} $(1.73m)^{-2}$; mild to moderate reduction: eGFR ≥ 60, <90 mL min^{-1} $(1.73m)^{-2}$; and severe reduction: eGFR ≥ 90 mL min^{-1} $(1.73m)^{-2}$. BMI, body mass index

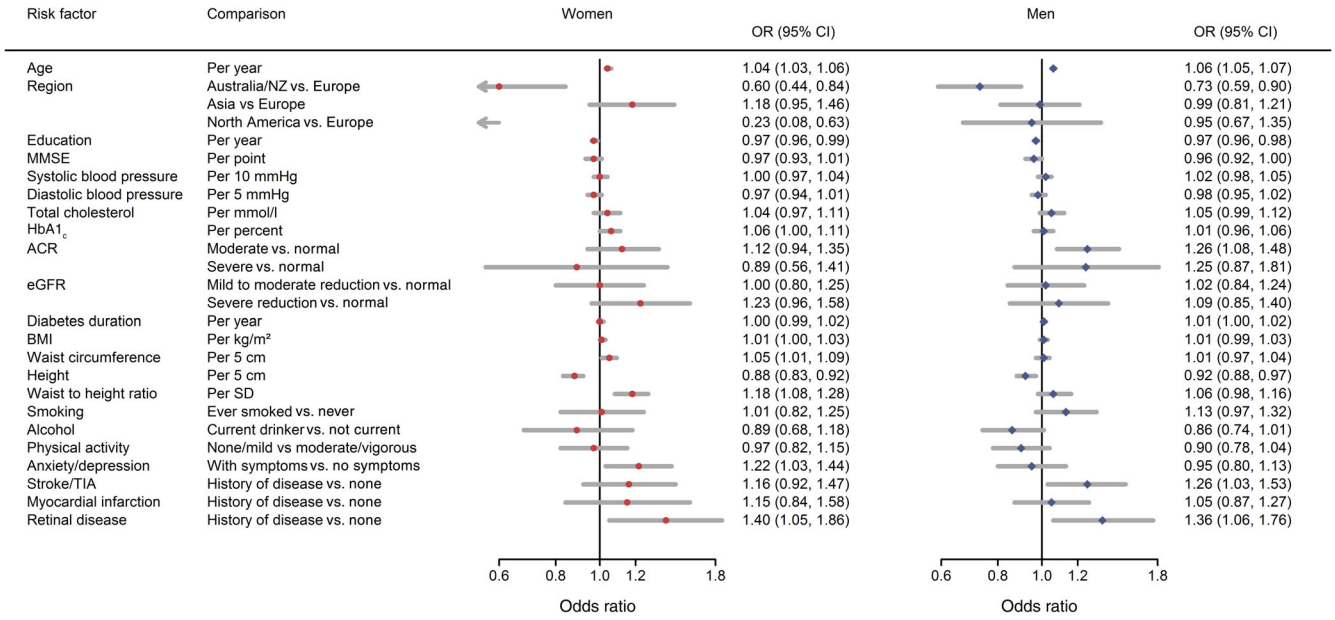

FIGURE 2 Association between risk factors and cognitive decline or dementia – disaggregated by sex (women and men). Multiple adjusted odds ratios (ORs) from multivariable model with interactions. All models adjusted for age, region, age at completion of highest education and randomized treatments. Models with the exceptions of past medical history (stroke/transient ischaemic attack [TIA], myocardial infarction and retinal disease) additionally adjusted for mini-mental state examination (MMSE) score, systolic blood pressure, total cholesterol, HbA1c, albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate (eGFR), diabetes duration, waist circumference, smoking, alcohol use, physical activity and mental health symptoms. Models for stroke/TIA, myocardial infarction and retinal disease were kept basically adjusted for sex, age, region, age at completion of highest education and randomized treatments. All analyses allowed for interactions with sex and accounted for the competing risk of death. ACR was categorized as normal: ACR < 30 μg/mg; moderate: ACR ≥ 30, ≤300 μg/mg; and severe: ACR > 300 μg/mg. eGFR was categorized as normal: eGFR < 60 mL min^{-1} (1.73 $m)^{-2}$; mild to moderate reduction: eGFR ≥ 60, <90 mL min^{-1} (1.73 $m)^{-2}$; and severe reduction: eGFR ≥ 90 mL min^{-1} (1.73 $m)^{-2}$. BMI, body mass index

3.6 | Multinomial regression versus logistic regression

A comparison of the results from the multinomial regression, which considers death as a competing risk, with traditional logistic regression that includes death as no-event, is included in Table S4.

4 | DISCUSSION

In our large, well-characterized cohort of individuals with type 2 diabetes, the risk of CD/dementia was greater in men compared with women. Older age, higher total cholesterol, HbA1c, waist circumference, waist-to-height ratio, moderately increased ACR, prior stroke/TIA and retinal disease were all associated with a greater risk of CD/dementia, while higher education, baseline cognitive function, taller stature and alcohol use were associated with a lower risk of CD/dementia. There were also risk variations by region. Mental health symptoms and higher waist circumference were associated with a greater risk of CD/dementia in women in comparison with in men. There was no evidence that randomized treatments ameliorated the overall risk of CD/dementia or by sex.

Increased HbA1c has been linked to diabetes-associated cognitive decrements, CD and dementia[6,12,33,34]; However, when treatments for improving glycaemic control were considered in observational studies, there was an indication that some glucose-lowering agents, such as metformin,[35] were associated with a lower risk of cognitive impairment and dementia.[35–38] Intervention studies, on the other hand, including our own results from the ADVANCE trial,[25] did not yield evidence for intensive glycaemic control ameliorating the risk of CD/dementia.[1,33,39] While the causative pathway between diabetes and dementia needs to be further determined,[40] a multifactorial pathogenesis has been suggested for CD and dementia in diabetes, involving abnormal insulin signalling, cerebrovascular injury and accelerated neurodegeneration, among many other putative biological mechanisms.[11,40] Insulin resistance can increase atherosclerosis, which subsequently may contribute to the vascular pathway, leading to cognitive impairment and dementia.[41] Endothelial dysfunction in diabetes may also play a role in precipitating neuronal toxicity, resulting in reduced cerebral blood flow and neuronal injury.[6] Further, insulin can modulate the clearance of beta amyloid, which is a hallmark in Alzheimer's disease (AD) neuropathology.[42] Previous neuropathological studies also suggested that diabetes may accelerate neurodegeneration via a non-vascular pathway, such that a lower threshold for amyloid is needed for AD to develop in diabetes,[43,44] and given sex differences could plausibly occur at any stage in these biological processes, possibly under the influence of sex hormones.

TABLE 2 Multiple adjusted women-to-men ratios of odds ratios (RORs) for association between risk factors and cognitive decline or dementia in ADVANCE

Characteristics	Comparison	Sex Women versus men ROR (95% CI)[a]
Age	Per year	0.98 (0.96, 1.00)
Region	Australia/New Zealand vs. Europe	0.83 (0.56, 1.23)
	Asia vs. Europe	1.19 (0.89, 1.60)
	North America vs. Europe	0.24 (0.08, 0.70)
Education	Per year	1.00 (0.98, 1.02)
MMSE	Per point	1.01 (0.95, 1.07)
Systolic blood pressure	Per 10 mmHg	0.99 (0.94, 1.04)
Diastolic blood pressure	Per 5 mmHg	0.99 (0.94, 1.04)
Total cholesterol	Per mmol/l	0.99 (0.90, 1.09)
HbA1c	Per percent	1.05 (0.98, 1.13)
ACR	Moderate vs. normal	0.89 (0.70, 1.13)
	Severe vs. normal	0.71 (0.39, 1.28)
eGFR	Mild to moderate reduction vs. normal	0.98 (0.73, 1.31)
	Severe reduction vs. normal	1.13 (0.79, 1.60)
Diabetes duration	Per year	0.99 (0.97, 1.01)
BMI	Per kg/m^2	1.01 (0.98, 1.03)
Waist circumference	Per 5 cm	1.05 (1.00, 1.10)
Height	Per 5 cm	1.00 (0.98, 1.02)
Waist-to-height ratio	Per SD	1.11 (0.98, 1.25)
Smoking	Ever smoked vs. never	0.90 (0.69, 1.16)
Alcohol	Current drinker vs. not current	1.04 (0.76, 1.43)
Physical activity	None/mild vs. moderate/vigorous	1.08 (0.87, 1.35)
Anxiety/depression	With symptoms vs. no symptoms	1.28 (1.01, 1.63)
Stroke/TIA	History of disease vs. none	0.92 (0.68, 1.25)
Myocardial infarction	History of disease vs. none	1.10 (0.76, 1.58)
Retinal disease	History of disease vs. none	1.03 (0.70, 1.51)

Abbreviations: ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; MMSE, mini-mental state examination; TIA, transient ischaemic attack.

All models adjusted for age, region, age at completion of highest education and randomized treatments. Models except for past medical history (stroke/TIA, myocardial infarction and retinal disease) additionally adjusted for MMSE score, systolic blood pressure, total cholesterol, HbA1c, ACR, eGFR, diabetes duration, waist circumference, smoking, alcohol use, physical activity and mental health symptoms; models for stroke/TIA, myocardial infarction, retinal disease adjusted for sex, age, region, age at completion of highest education and randomized treatments. All models allowed for interactions with sex. All analyses accounted for the competing risk of death.

[a]ROR above 1 indicates higher odds ratio for women, and ROR below 1 indicates the odds ratio is higher for men.

Previous studies have reported high blood pressure to be associated with CD and dementia in community-based populations.[45] However, our results do not support hypertension being a risk factor for CD/dementia in diabetes. Another observational study also suggested that hypertension following a diagnosis of diabetes is unlikely to account for the elevated dementia risk in diabetes.[46] The Systolic Blood Pressure Intervention Trial – The Memory and Cognition in Decreased Hypertension (SPRINT MIND) study, although excluding people with diabetes, showed that intensive blood pressure control significantly reduced the combined rate of mild cognitive impairment and dementia.[47] A recent meta-analysis, which included the ADVANCE trial, showed that intensive blood pressure lowering was associated with a lower risk of cognitive impairment or dementia,[48] although the populations included were not exclusively in diabetes. Intensive blood pressure lowering did not reduce the risk of CD or dementia in ADVANCE.[24,48] Similarly, the Action to Control Cardiovascular Risk in Diabetes – The Memory in Diabetes (ACCORD MIND) study in patients with type 2 diabetes did not show a difference between intensive versus conventional antihypertensive therapies in CD.[49] The specific associations between blood pressure and blood pressure-lowering treatments with CD/dementia in diabetes populations need to be further characterized.[50]

Although women had a lower risk of CD/dementia than men, mental health symptoms were associated with a greater relative risk of CD/dementia among women compared with men. In diabetes populations, depression is nearly twice as common compared with the general population.[51] Anxiety and depressive symptoms have been linked to an increased risk of CD and dementia[52,53]; and depressive symptoms have been reported to increase the risk of progression to dementia in those with mild cognitive impairment.[54] Previous studies in general populations have reported higher rates of affective disorders in women than in men,[55] and the risk of mild cognitive impairment was higher in women with depression than in men.[56] One plausible explanation could be that women are more probable to be prescribed with pharmacological treatments for depression, potentially presenting the problem of overtreatment.[57] The use of antidepressants has been linked to a greater risk of dementia,[58,59] with a case-control study reporting that the adverse effect of anticholinergic antidepressants on dementia risk did not attenuate after controlling for depression.[59] Furthermore, sex difference also exists in the metabolism of antidepressants.[60]

Higher waist circumference was found to be more strongly associated with CD/dementia in women compared with men. Central obesity has also been linked to CD in people with diabetes.[61] A recent meta-analysis found no evidence that higher waist circumference conferred a greater risk of all-cause dementia, and no sex difference was reported[62]; although the study populations included in this meta-analysis were not exclusively in diabetes. Obesity has previously been linked to insulin resistance,[63] which may increase the risk of dementia and CD in diabetes. Whether different body composition and fat distribution observed in women and men with diabetes,[20] partially driven by the influence of sex hormones on visceral obesity,[20] can explain

TABLE 3 Randomized treatment effects (intensive glucose control vs. standard control; blood pressure lowering vs. placebo) and the association with cognitive decline or dementia, by sex

			Basic model OR (95% CI)	Multiadjusted model OR (95% CI)	*p* for interaction – multiadjusted model
Intensive glucose control versus standard control					
	Intensive	Standard			
Women	50.2%	49.8%	0.98 (0.84, 1.15)	0.99 (0.85, 1.16)	.91
Men	49.9%	50.1%	0.98 (0.86, 1.13)	1.00 (0.87, 1.16)	
Overall	50.0%	50.0%	0.98 (0.89, 1.09)	1.00 (0.90, 1.11)	
Blood pressure lowering versus placebo					
	Active	Placebo			
Women	50.0%	50.0%	0.92 (0.77, 1.10)	0.93 (0.78, 1.12)	.52
Men	50.0%	50.0%	1.01 (0.86, 1.18)	1.01 (0.86, 1.19)	
Overall	50.0%	50.0%	0.97 (0.86, 1.09)	0.98 (0.87, 1.10)	

Note: Overall basic model adjusted for sex, age, region and age at completion of education.
Overall multiple adjusted models additionally adjusted for Mini-Mental State Examination score, systolic blood pressure, total cholesterol, HbA1c, albumin-to-creatinine ratio, estimated glomerular filtration rate, diabetes duration, waist circumference, smoking, alcohol use, physical activity and mental health symptoms. Sex-specific coefficients calculated as the interaction term between sex and randomized treatments.

the sex differences in obesity and CD/dementia, requires further investigation.

Sex hormones mediate the risk of CD and dementia,[14,17] and a decrease in cerebral glucose metabolism related to menopause also appears to represent a sex-specific pathophysiological mechanism of AD.[64] Importantly, sex hormones can have a range of impact on cardiometabolic health, including energy metabolism, body composition, vascular function and inflammatory responses.[20] Endocrine imbalances, such as hyperandrogenism in females and hypogonadism in males, are related to unfavourable cardiometabolic profiles, which may have a differential influence on cognition in women and men with diabetes.

Many of the risk factors identified for CD/dementia are also common diabetes-related co-morbidities and complications,[65,66] which are potentially modifiable. Although the risk of diabetes-related complications can be reduced with optimal glycaemic control,[66] evidence of diabetes-specific treatments lowering the risk of cognitive dysfunction in people with diabetes is limited,[3] such that whether good glycaemic control prevents or treats cognitive dysfunction in diabetes remains unclear.[3] While the directions of the epidemiological links, and the underlying pathophysiological mechanisms, need to be further determined, clinicians should be vigilant to recognize these risk factors for CD and dementia, and particular attention would be prudent in the case of specific combinations of risk factors.

4.1 | Strengths and limitations

To the best of our knowledge, this is the first study to systematically examine the effect of risk factors, and the sex differences in the effect of these risk factors, in association with the risk of CD/dementia, while incorporating death as a competing risk, in a large, well-characterized, international cohort of patients with type 2 diabetes. The strength of including the competing risk of death should be highlighted, as such a consideration directly addresses the elevated mortality rates in men because of other causes, and improves the estimation for CD/dementia risk by sex.[9,16,23] This study was further strengthened by its prospective design within a randomized controlled trial, and the results from ADVANCE are also broadly generalizable to patients with type 2 diabetes in community practice.[67]

The limitations of the current study were, first, we were unable to examine the effects of other risk factors for CD/dementia, including hearing loss, apolipoprotein E4 status, any early life exposures (e.g. nutrition) or any other unmeasured behavioural risk factors, as well as information on height loss in older life, and sex hormone levels, such that residual confounding may be possible. Second, the ADVANCE trial was not designed to assess CD/dementia as the primary outcome, and we had limited power to detect interactions (see Supplementary Material S1). Nevertheless, the effect sizes of the sex interactions are meaningful, and our analyses concentrate on estimation rather than significance. The median 5-year follow-up may not be sufficient for allowing CD or dementia to develop, given the long prodrome and slow development of these conditions. Third, considering that the onset of CD and dementia is highly insidious, we were unable to measure the duration of disease with any accuracy, precluding the use of any time-to-event analyses. Fourth, multiple testing of interactions can result in false positives, given that, for every 20 tests performed with a threshold of 5%, one significant test would be expected even if there were no real effects. We also acknowledge that we were unable to determine causality, and we are not intending to claim that between-person changes would necessarily reflect within-person changes. Fifth, lifestyle variables (physical activity, smoking and alcohol use) were self-reported, hence may be subjective

to reporting bias. Lastly, the use of MMSE for assessing specific cognitive domains has limitations, such that there is no component sensitive to assess executive function, and there is only one item to screen for visuospatial deficits in MMSE.[68] Nevertheless, MMSE is a valid and widely accepted screening tool for cognitive impairment, and as an operational tool to monitor cognitive change over time through serial administration during drug trials and other interventions.

In conclusion, while there is an urgent need for screening cognitive dysfunction in diabetes in routine practice,[4] early detection and management of modifiable risk factors and other comorbidities may slow the progression of CD and prevent or delay the onset of dementia in people with type 2 diabetes. Our findings may be useful for identifying high-risk individuals to participate in future trials. Specific mechanisms for the sex differences need to be further elucidated.

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CONFLICT OF INTEREST

HB reports personal fees from Nutricia Australia. MC reports honoraria for advisory boards or speaking at scientific meetings from Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, MSD, MundiPharma, Novartis, Novo Nordisk, Reata, Sanofi and Servier. PH is a member of College International de Recherche Servier. SH reports honoraria from Servier for speaking at scientific meetings. GM reports honoraria for participation in national or international meetings as chairman/lecturer from Boehringer Ingelheim, Daiichi Sankyo, Ferrer, Latin Pharma Medtronic, Menarini, Merck, Novartis, Recordati, Sanofi and Servier. JC reports research grants from the NHMRC and from Servier for the ADVANCE trial and ADVANCE-ON post-trial follow-up, and honoraria for speaking about these studies at scientific meetings, a research grant from Idorsia for the SPIRIT study of Resistant Hypertension, and support from NHMRC Program Grant (APP1149987). MW does consultancy for Amgen, Freeline and Kirin outside the submitted work. JG, KH, MH, SAEP, and SM have nothing to declare.

AUTHOR CONTRIBUTIONS

JC and SM conceived, designed and acquired the ADVANCE trial data. MW conceived this study. KH and JG conducted the statistical analyses, with advice from MW. JG wrote the initial drafts of the manuscript. All authors were involved in data interpretation. Drafts were revised for important scientific content by all authors. All authors gave final approval of the version to be published. MW is the guarantor of this work.

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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