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Effect of randomised blood pressure lowering treatment and intensive glucose control on dementia and cognitive decline according to baseline cognitive function and other subpopulations of individuals with type 2 diabetes: Results from the ADVANCE trial

Katie Harris [a,*], Jessica Gong [b,c], Stephen MacMahon [a,c], Ying Xu [a,d], Sultana Shajahan [a], Stephen Harrap [e], Neil Poulter [f], Michel Marre [g], Pavel Hamet [h], Giuseppe Mancia [i], Craig Anderson [a], Mark Woodward [a,c], John Chalmers [a]

[a] The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, Australia
[b] Department of Epidemiology and Public Health, University College London, London, UK
[c] The George Institute for Global Health, School of Public Health, Imperial College London, London, UK
[d] Centre for Health Systems and Safety Research, Australian Institute of Health Innovation, Macquarie University, Sydney, Australia
[e] Department of Anatomy and Physiology, University of Melbourne and Royal Melbourne Hospital, Parkville, Australia
[f] School of Public Health, Imperial College London, London, UK
[g] Clinique Ambroise Paré, Neuilly-sur-Seine, France & Institut Necker-Enfants Malades, INSERM, Université Paris Cité, Paris, France
[h] Montréal Diabetes Research Centre, Centre Hospitalier de l'Université de Montréal, Quebec, Montreal, Canada
[i] University of Milano-Bicocca, Milan, Italy

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ABSTRACT

Background and aims: Accumulating evidence indicates that reducing high blood pressure (BP) prevents dementia and mild cognitive impairment (MCI). Furthermore, although diabetes is a risk factor for dementia and MCI, there is uncertainty of the effect of intensive glucose control on these endpoints. This study aimed to determine the effects of BP-lowering (vs placebo) and intensive glucose-lowering (vs standard control) treatments according to baseline cognition and other characteristics on dementia and cognitive decline (CD) in people with type 2 diabetes mellitus (T2DM).

Methods: The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial involved 11,140 individuals with T2DM. The effects of BP-lowering and intensive glucose-lowering treatments were explored in subgroups of baseline Mini-Mental State Examination (MMSE), categorised as cognitively normal (scores ≥28) and cognitive impairment (scores <28). The primary outcome was a composite of dementia/CD that accounted for the competing risk of death. Multinomial regression models, adjusted for common cardiovascular risk factors, were used to estimate odds ratios (OR) with 95 % confidence intervals (CI) of the effects of the treatments on dementia/CD. Homogeneity of effects by subgroups were evaluated using interaction terms in the models. A two-sided p value <0.05 was regarded as statistically significant.

Results: BP-lowering treatment (vs. placebo) was associated with a lower odds of dementia/CD in participants with cognitive impairment (OR 0.76, 95 % CI (0.59–0.99)) but not in those cognitively normal (OR 1.05, 95 % CI (0.92–1.21); p for interaction 0.03). Those with a history of cardio-renal-metabolic syndrome did not experience a benefit of active BP lowering treatment compared with placebo on dementia/CD. There were no further subgroup effects of BP-lowering treatment. The effect of intensive glucose lowering (vs standard control) on the odds of dementia/CD did not vary by baseline cognition subgroup. However, it did vary by level of blood glucose at baseline (<7.9 mmol/L OR 1.12, 95 % CI (0.96–1.30) vs ≥ 7.9 mmol/L 0.87 (0.75–1.00); p for interaction 0.02) and duration of T2DM (<10 years OR 0.92 (0.81–1.05) vs ≥10 years 1.16 (0.97–1.38); p for interaction 0.04).

* Corresponding author at: The George Institute for Global Health AUSTRALIA, Level 18, International Towers 3, 300 Barangaroo Ave, Barangaroo NSW 2000, Australia.
E-mail address: kharris@georgeinstitute.org.au (K. Harris).

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Conclusions: This study suggests greater effects of BP-lowering treatment in those with early loss of cognitive function than in those cognitively normal. There were also differential effects of intensive glucose-lowering on dementia and CD according to levels of blood glucose and duration of diabetes in people with T2DM.
Clinical trial registration: ADVANCE is registered with ClinicalTrials.gov: number NCT00145925

Introduction

Reducing high blood pressure (BP) with antihypertensive agents is a much-researched strategy to prevent dementia and mild cognitive impairment (MCI) [1]. Meta-analyses, large observational studies and randomised controlled trials demonstrated that antihypertensive medications lowered the risk for dementia and cognitive decline (CD) compared to taking no antihypertensives or placebo [1–4]. However, there might be heterogeneity in the effects in relation to the effect of BP-lowering and the risk of dementia between subpopulations [5]. For example, the Whitehall II cohort study suggests that BP lowering may not prevent cognitive outcomes in older adults, as the positive associations of systolic BP ≥130 mmHg and risk of dementia at age 50 declined in those older than 60 years [6]. Although, there is less evidence per se for the effect of antihypertensives on dementia and further CD in those with existing MCI [7].

Although diabetes mellitus is another known cardiovascular (CV) risk factor for dementia and MCI [8], there is no significant difference for intensive compared with standard glucose control in preventing or delaying the onset of cognitive impairment [9]. However, poorer glycaemic control and longer duration of diabetes may increase the risk of dementia and MCI [10].

The primary aims of our study were therefore to determine the effects of BP-lowering (vs placebo) and intensive glucose-lowering (vs standard control) on a composite outcome of dementia and/or CD between groups defined by baseline levels of cognition among people with type 2 diabetes mellitus (T2DM). Secondary aims were to (1) explore the effects of BP-lowering and intensive glucose-lowering treatments on dementia/CD across other subpopulations based on risk factors explored in our previous work [11], (2) explore interaction effects between BP lowering and intensive glucose lowering treatments on dementia /CD and (3) evaluate potential differences in treatment effects on systolic and diastolic BP, blood glucose, and glycated haemoglobin, by baseline cognition and among other important subgroups.

Methods

Study design

Data are from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, for which the main results have been reported [12,13]. In brief, a total of 11,140 participants (age ≥55 years) with a diagnosis of T2DM (from age ≥30 years) and a history of major macro- or microvascular disease, or with at least one other CV risk factor, were recruited from 215 centres across 20 countries in Asia, Australia, Europe, and North America between 2001 and 2003. Participants were randomised using a factorial 2 × 2 design to a perindopril/indapamide combination BP lowering treatment or matching placebo, and gliclazide-based intensive glucose lowering therapy (target HbA_1C ≤48 mmol/mol [6.5 %]) or standard glucose control therapy based on guideline recommendations [13]. The median follow-up duration was 4.4 years and 5.0 years for the BP-lowering and intensive glucose-lowering arms, respectively. At the follow up study visits information was collected on BP, blood glucose and glycated haemoglobin, enabling the differences in these (continuous) measures to be studied by BP lowering and glucose control treatment groups, respectively.

Outcome

The primary outcome for the present study was a composite of dementia /CD. This was defined as a nominal endpoint that incorporated the competing risk of death: (i) alive at the end of the study (had neither dementia nor CD nor death during the study); (ii) dementia /CD during the study, regardless of whether the participant died before the end of follow-up; (iii) death preceding any dementia /CD during the study [11].

Individuals with a prior or current diagnosis of moderate or severe dementia were excluded from entry to the trial. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE) at baseline and at two-yearly intervals during 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 3-point decrement in MMSE score at any point during the study. When an individual scored <24 on the MMSE, or when the research physician or nurse coordinator suspected dementia, the individual was referred to a qualified specialist for a diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). 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 standardised across all study centres. Both CD and dementia were prespecified secondary outcomes in ADVANCE.

Exposures

The primary exposures in the present study were the ADVANCE randomised treatment effects: randomised BP-lowering treatment effect (active vs placebo) and randomised intensive glucose treatment effect (intensive vs standard glucose control).

Subgroups

The primary study subgroup was cognitive function defined by MMSE scores at baseline, and categorised as cognitively normal (MMSE ≥28) or cognitive impairment (MMSE<28) [14,15].

We also considered subgroups of several important CV risk factors that were collected on participants at study baseline as secondary analyses. These subgroups were selected based on our previous publication that explored the effect of risk factors on dementia/CD [11]. These were: age (<65 vs. ≥65 years), sex (women vs. men), region of residence (Asian vs. non-Asian country), age at completion of highest education (<18 vs. ≥ 18years), systolic BP (SBP) (<140 vs. ≥140 mmHg), estimated glomerular filtration rate (eGFR; ≥60 vs. <60 mL/min/1.73m^2), albumin-to-creatinine ratio (ACR; <30 μg/mg, ≥30 μg/mg), blood glucose (<7.9 vs. ≥7.9 mmol/L), total cholesterol (<5.5 vs. ≥5.5 mmol/L), HbA_1C (<7 % vs. ≥7 %), duration of T2DM (<10 vs. ≥10 years), waist circumference (low risk <94 cm for men and <80 cm for women vs. moderate/high risk ≥94 cm for men and ≥80 cm for women), body mass index (BMI; <25 kg/m^2, ≥25 kg/m^2), waist to height ratio (<0.5, ≥0.5), smoking (never vs. ever smoked), alcohol consumption (not current vs. current drinker), exercise (self-reported as participating in none/mild vs. moderate/vigorous levels of >15 min at least once per week), anxiety/depression (without vs. with symptoms of anxiety or depression according to self-report at study baseline on the anxiety/depression dimension of the 3-level version of the EuroQol 5 dimensions (EQ-5D) questionnaire), history of stroke or transient ischaemic attack (TIA; no vs. yes), history of myocardial infarction (no

Table 1
Baseline characteristics of participants in ADVANCE by randomised blood pressure treatment and baseline MMSE category.

Baseline variable	Placebo		Active	
	MMSE < 28	MMSE ≥ 28	MMSE < 28	MMSE ≥ 28
n	*1239*	*4330*	*1204*	*4359*
MMSE	25.6 (1.8)	29.3 (0.8)	25.6 (2.0)	29.3 (0.8)
Age (years)	67.3 (6.5)	65.3 (6.4)	67.4 (6.3)	65.4 (6.3)
≥65 years (n (%))	847 (68.4)	2447 (56.5)	826 (68.6)	2487 (57.1)
Women (n (%))	613 (49.5)	1756 (40.6)	578 (48.0)	1785 (40.9)
Asian region (n (%))	461 (37.2)	1605 (37.1)	455 (37.8)	1614 (37.0)
SBP (mmHg)	146.6 (22.3)	144.5 (20.9)	147.4 (23.2)	144.4 (21.4)
≥140 mmHg (n (%))	737 (59.5)	2480 (57.3)	723 (60.0)	2492 (57.2)
eGFR mL/min/1.73 m^2	72.2 (17.7)	75.3 (17.4)	72.2 (17.4)	75.0 (17.6)
<60 mL/min/1.73 m^2 (n (%))	338 (27.3)	864 (20.0)	292 (24.3)	907 (20.8)
ACR μg/mg	67.7 (138.0)	47.7 (107.7)	60.3 (125.6)	50.8 (111.6)
ACR ≥30 μg/mg (n (%))	408 (32.9)	1217 (28.1)	391 (32.5)	1247 (28.6)
Fasting Blood Glucose (mmol/L)	8.5 (2.9)	8.4 (2.7)	8.8 (3.0)	8.5 (2.7)
≥ 7.9 mmol/L (n (%))	618 (49.9)	2161 (49.9)	645 (53.6)	2245 (51.5)
Total Cholesterol (mmol/L)	5.3 (1.2)	5.2 (1.2)	5.3 (1.3)	5.2 (1.2)
≥5.5 mmol/L (n (%))	491 (39.6)	1570 (36.3)	469 (39.0)	1629 (37.4)
HbA1c (%)	7.6 (1.6)	7.5 (1.5)	7.7 (1.7)	7.5 (1.5)
≥ 7 % (n (%))	725 (58.5)	2465 (56.9)	729 (60.5)	2529 (58.0)
Waist Circumference (cm)	98.1 (12.9)	98.5 (13.2)	98.4 (13.2)	98.7 (13.0)
Moderate/High risk (n (%))	1002 (80.9)	3400 (78.5)	989 (82.1)	3444 (79.0)
BMI kg/m^2	28.1 (4.9)	28.4 (5.2)	28.2 (5.3)	28.4 (5.2)
BMI ≥ 25 kg/m^2 (n (%))	896 (72.3)	3137 (72.4)	864 (71.8)	3186 (73.1)
Waist to height ratio	0.60 (0.07)	0.59 (0.08)	0.60 (0.07)	0.59 (0.08)
Waist to height ratio ≥0.5 (n (%))	1171 (94.5)	3947 (91.2)	1124 (93.4)	4024 (92.3)
Smoking (ever smoked (n (%))	478 (38.6)	1867 (43.1)	461 (38.3)	1866 (42.8)
Alcohol (current drinker (n (%))	309 (24.9)	1382 (31.9)	307 (25.5)	1395 (32.0)
Exercise (moderate/ vigorous) (n (%))	483 (39.0)	2073 (47.9)	500 (41.5)	2054 (47.1)
Anxiety/Depression symptoms (n (%))	382 (30.8)	1168 (27.0)	410 (34.1)	1152 (26.4)
Education (years)	16.0 (7.1)	19.2 (7.3)	15.8 (6.8)	19.1 (7.1)
≥ 18 years (n (%))	375 (30.3)	2189 (50.6)	387 (32.1)	2205 (50.6)
Diabetes Duration (years)	8.0 (6.6)	7.9 (6.2)	8.1 (6.6)	8.0 (6.3)
≥ 10 years (n (%))	465 (37.5)	1619 (37.4)	436 (36.2)	1606 (36.8)
History of Stroke (n (%))	191 (15.4)	521 (12.0)	198 (16.4)	526 (12.1)
History of myocardial infarction (n (%))	141 (11.4)	514 (11.9)	153 (12.7)	525 (12.0)
History of retinal disease (n (%))	102 (8.2)	302 (7.0)	104 (8.6)	285 (6.5)
History of macrovascular disease (n (%))	407 (32.8)	1383 (31.9)	419 (34.8)	1378 (31.6)
History of microvascular disease (n (%))	170 (13.7)	414 (9.6)	144 (12.0)	424 (9.7)
Cardio-renal-metabolic syndrome (n (%))	121 (9.8)	331 (7.6)	110 (9.1)	332 (7.6)

Values in table are mean (standard deviation), otherwise indicated as n (%).
MMSE category:.
MMSE ≥ 28 – cognitively normal.
MMSE < 28 – cognitive impairment.
Albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate (eGFR).
Cardio-renal-metabolic syndrome defined as CKD stage 3 and above (eGFR <60) with a history of macrovascular disease.

vs yes), history of retinal disease (no vs yes), history of macrovascular disease (no vs yes), history of microvascular disease (no vs yes) and history of cardio-renal-metabolic syndrome which comprised chronic kidney disease stage 3 and above (eGFR <60) with a history of macrovascular disease.

Statistical analysis

Participant baseline characteristics are presented by randomised BP treatment (active vs. placebo) and baseline cognition (MMSE) category (<28 vs. ≥28), and similarly by glucose control (intensive vs standard) and baseline cognition category. Continuous variables are presented as mean (standard deviation), and categorical and categorised continuous variables as number (percentage).

Treatment effects on the dementia/CD outcome are estimated for subgroups defined by MMSE, age, sex, region, education, SBP, eGFR, ACR, blood glucose, total cholesterol, HbA1c, diabetes duration, waist circumference, BMI, waist to height ratio, smoking, alcohol, exercise, anxiety/depression, history of stroke, history of myocardial infarction, history of retinal disease, history of macrovascular disease, history of microvascular disease and history of cardio-renal-metabolic syndrome. Separate analyses were conducted on each of the randomised treatment arms, (1) the effect of BP-lowering treatment vs placebo were obtained from database locked at the end of the follow up after 4.4 years (median) and (2) intensive glucose control vs standard control at the end of 5 years (median) of follow up. Odds ratios adjusted for confounding variables (aOR) with 95 % confidence intervals (CI) were extracted from multinomial logistic regression models (that incorporated death as a competing risk), with the subgroup effect for the interaction terms obtained for the variable of interest and randomised treatment.

As sensitivity analyses for the primary study subgroup, multiple adjusted treatment effects on dementia/CD risk were also estimated by continuous MMSE using penalized smoothing splines, and further categorisation of MMSE (≥28, 24–27, ≤23) in multinomial logistic regression models.

The interaction effects between BP-lowering treatment and intensive glucose control on dementia/CD was assessed by examining the effect of BP-lowering treatment by intensive and standard glucose control subgroups, and similarly the effect of intensive glucose control by active BP lowering treatment and placebo subgroups.

For baseline cognition subgroups and any subgroups that demonstrated a significant interaction effect on the size of the effects of treatment, the target risk factor for the specific treatment (i.e. systolic and diastolic BP for BP lowering treatment vs placebo, and HbA1c and fasting blood glucose for intensive glucose control vs standard control) was explored in the respective subgroups. The mean difference (active/intensive – placebo/standard) for each of the continuous measures between treatment group arms according to subgroup category were plotted and visually inspected for any differences.

All reported p values are two-sided, with the 5 % threshold used to determine statistical significance. Since multiple statistical tests were undertaken, the reader is cautioned about drawing inferences from marginal levels of significance. All analyses were performed in R Studio Version 4.3.1 (R Core Team, 2023).

Results

Of the 11,140 participants in ADVANCE, 8 had missing a MMSE score at baseline and were excluded from analyses. In the 11,132 participants included in these analyses, participants with cognitive impairment were typically older, female, had less education (i.e. were younger at completion of education) and were less frequently smokers and alcohol

Table 2
Baseline characteristics of participants in ADVANCE by randomised glucose control treatment and baseline MMSE category.

Baseline variable	Standard		Intensive	
	MMSE < 28	MMSE ≥ 28	MMSE < 28	MMSE ≥ 28
n	*1190*	*4375*	*1253*	*4314*
MMSE	25.7 (1.9)	29.3 (0.8)	25.6 (1.9)	29.3 (0.8)
Age (years)	67.4 (6.5)	65.4 (6.3)	67.3 (6.3)	65.3 (6.4)
≥65 years (n (%))	814 (68.4)	2501 (57.2)	859 (68.6)	2433 (56.4)
Women (n (%))	590 (49.6)	1765 (40.3)	602 (48.0)	1773 (41.1)
Asian region (n (%))	446 (37.5)	1621 (37.1)	470 (37.5)	1598 (37.0)
SBP (mmHg)	147.0 (22.1)	144.5 (21.1)	146.9 (23.3)	144.4 (21.2)
≥140 mmHg (n (%))	721 (60.6)	2491 (56.9)	739 (59.0)	2481 (57.5)
eGFR mL/min/1.73 m^2	71.8 (17.8)	75.0 (17.4)	72.5 (17.4)	75.3 (17.6)
<60 mL/min/1.73 m^2 (n (%))	320 (26.9)	910 (20.8)	310 (24.7)	859 (19.9)
ACR μg/mg	67.0 (132.7)	49.2 (112.3)	61.5 (132.0)	49.3 (106.7)
ACR ≥30 μg/mg (n (%))	410 (34.5)	1228 (28.1)	389 (31.0)	1234 (28.6)
Fasting Blood Glucose (mmol/L)	8.6 (2.9)	8.4 (2.7)	8.7 (3.0)	8.5 (2.7)
≥ 7.9 mmol/L (n (%))	625 (52.5)	2204 (50.4)	638 (50.9)	2201 (51.0)
Total Cholesterol (mmol/L)	5.3 (1.2)	5.2 (1.2)	5.2 (1.2)	5.2 (1.2)
≥5.5 mmol/L (n (%))	476 (40.0)	1584 (36.2)	484 (38.6)	1616 (37.5)
HbA1c (%)	7.6 (1.6)	7.5 (1.5)	7.6 (1.7)	7.5 (1.5)
≥ 7 % (n (%))	700 (58.8)	2528 (57.8)	754 (60.2)	246 (57.2)
Waist Circumference (cm)	97.9 (12.9)	98.5 (13.0)	98.5 (13.2)	98.8 (13.2)
Moderate/High risk (n (%))	969 (81.4)	3417 (78.1)	1022 (81.6)	3424 (79.4)
BMI kg/m^2	28.2 (5.2)	28.3 (5.2)	28.2 (5.0)	28.4 (5.2)
BMI ≥ 25 kg/m^2 (n (%))	870 (73.1)	3158 (72.2)	890 (71.0)	3165 (73.4)
Waist to height ratio	0.60 (0.07)	0.59 (0.08)	0.60 (0.07)	0.59 (0.08)
Waist to height ratio ≥0.5 (n (%))	1118 (93.9)	3998 (91.4)	1177 (93.9)	3973 (92.1)
Smoking (ever smoked (n (%))	458 (38.5)	1867 (42.7)	482 (38.5)	1866 (43.3)
Alcohol (current drinker (n (%))	309 (26.0)	1418 (32.4)	307 (24.5)	1359 (31.5)
Exercise (moderate/ vigorous) (n (%))	497 (41.8)	2066 (47.2)	486 (38.8)	2061 (47.8)
Anxiety/Depression symptoms (n (%))	389 (32.7)	1170 (26.7)	403 (32.2)	1150 (26.7)
Education (years)	16.0 (7.2)	19.2 (7.3)	15.7 (6.7)	19.2 (7.1)
≥ 18 years (n (%))	352 (29.6)	2198 (50.2)	410 (32.7)	2196 (50.9)
Diabetes Duration (years)	8.0 (6.6)	7.9 (6.3)	8.1 (6.6)	7.9 (6.3)
≥ 10 years (n (%))	438 (36.8)	1624 (37.1)	463 (37.0)	1602 (37.1)
History of Stroke (n (%))	187 (15.7)	518 (11.8)	202 (16.1)	530 (12.3)
History of myocardial infarction (n (%))	128 (10.8)	538 (12.3)	166 (13.2)	501 (11.6)
History of retinal disease (n (%))	102 (8.6)	290 (6.6)	105 (8.4)	298 (6.9)
History of macrovascular disease (n (%))	400 (33.6)	1395 (31.9)	426 (34.0)	1366 (31.7)
History of microvascular disease (n (%))	162 (13.6)	422 (9.6)	154 (12.3)	417 (9.7)
Cardio-renal-metabolic syndrome (n (%))	122 (10.3)	357 (8.2)	109 (8.7)	305 (7.1)

Values in table are mean (standard deviation), otherwise indicated as n (%).
MMSE category:.
MMSE ≥ 28 – cognitively normal.
MMSE < 28 – cognitive impairment.
Albumin-to-creatinine ratio (ACR), estimated glomerular filtration rate (eGFR).
Cardio-renal-metabolic syndrome defined as CKD stage 3 and above (eGFR <60) with a history of macrovascular disease.

drinkers than those cognitively normal (Tables 1 and 2).

At the end of the BP-treatment arm (median 4.4 years), 1286 had dementia/CD (13 dementia alone, 63 dementia and CD, and 1210 CD alone), 806 had died, and 9040 were alive without dementia/CD (Supplementary Table 1). The effect of BP lowering treatment, compared to placebo, on dementia/CD was (aOR 95 %CI) 0.98 (0.87, 1.10).

At the end of follow-up of the intensive glucose-control follow up (median 5 years), 1827 participants had dementia/CD (21 dementia alone, 88 dementia and CD, and 1718 CD alone), 928 had died, and 8377 participants were alive without dementia/CD. The effect of intensive glucose, compared to standard control, on dementia/CD was (aOR 95 % CI) 1.00 (0.90, 1.11).

BP-lowering (vs placebo) treatment reduced the odds of dementia/CD in participants with cognitive impairment (aOR 0.76, 95 %CI 0.59–0.99) (Fig. 1), whereas there was no significant effect in those cognitively normal (aOR 1.05, 95 %CI 0.92–1.21; p for interaction 0.03). This is also reflected when considering MMSE as a continuous function, such that there was separation between the treatment effects for MMSE score 25–28 with a lower risk of dementia/CD in the active treatment arm compared to placebo, with overlap for MMSE≥28 (Supplementary fig. 1). When considering further categorisation of MMSE (≥28, 24–27, ≤23), the effect of blood pressure lowering treatment was 0.68 (0.50, 0.92) for those with MMSE 24–27, and 1.24 (0.59, 2.58) for those with MMSE ≤23, however there were only 212 participants with MMSE ≤23 resulting in wide confidence intervals around the estimated aOR (Supplementary Table 2). Furthermore, those with cardio-renal-metabolic syndrome did not experience a benefit of active BP lowering treatment compared with placebo on dementia/CD aOR 1.46 95 %CI (0.99, 2.15), compared to those with no history of cardio-renal-metabolic syndrome aOR 0.93 95 %CI (0.82, 1.06) (p for interaction 0.03). No significant differences were observed in the odds of dementia/CD for BP-lowering treatment (vs. placebo) within any of the other subgroups (Fig. 1).

The effect of intensive versus standard glucose control on the odds of dementia/CD was not significantly modified by baseline cognitive function: cognitive impairment (aOR 1.19, 95 %CI 0.96–1.48) versus cognitively normal (aOR 0.95, 95 %CI 0.84–1.07; p for interaction 0.07) (Fig. 2). There were some significant differences observed in the odds of dementia/CD for intensive-glucose treatment (vs. standard control) in several subgroups. In those with impaired blood glucose (≥7.9 mmol/L), the odds of dementia/CD was lower in those randomised to intensive control compared to standard glucose control (aOR 0.87, 95 %CI 0.75–1.00), whereas there was no significant difference in those with normal blood glucose (<7.9 mmol/L) (aOR 1.12, 95 %CI 0.96–1.29; p for interaction 0.02). There was also a statistically significant interaction in the effects of glucose lowering treatment by duration of T2DM ($p = 0.04$), such that the adjusted odds of dementia/CD was 0.92 (95 % CI 0.81–1.05) in those with T2DM of <10 years compared with an odds of 1.16 (95 % CI 0.97–1.38) in those with T2DM of ≥10 years.

There were no significant differences in the odds of dementia/CD for BP-lowering treatment (vs. placebo) by glucose treatment (p for interaction 0.99): intensive control (aOR 0.98, 95 % CI 0.82–1.16) and by standard control (aOR 0.98, 95 % CI 0.82–1.16). Correspondingly, in the glucose treatment arm, there were no significant differences in the odds of dementia/CD for intensive vs. standard glucose control by BP-lowering treatment (p for interaction 0.45): active treatment (aOR 1.04, 95 %CI 0.90–1.21) and placebo (aOR 0.96, 95 %CI 0.83–1.11).

We found a significant overlap in the difference of the SBP and DBP trajectories between active and placebo BP lowering treatment groups between cognitive impairment (MMSE<28) at baseline and cognitively normal (MMSE≥28) at baseline subgroups (Supplementary fig. 2). There was overlap in the difference for HbA1c and glucose trajectories

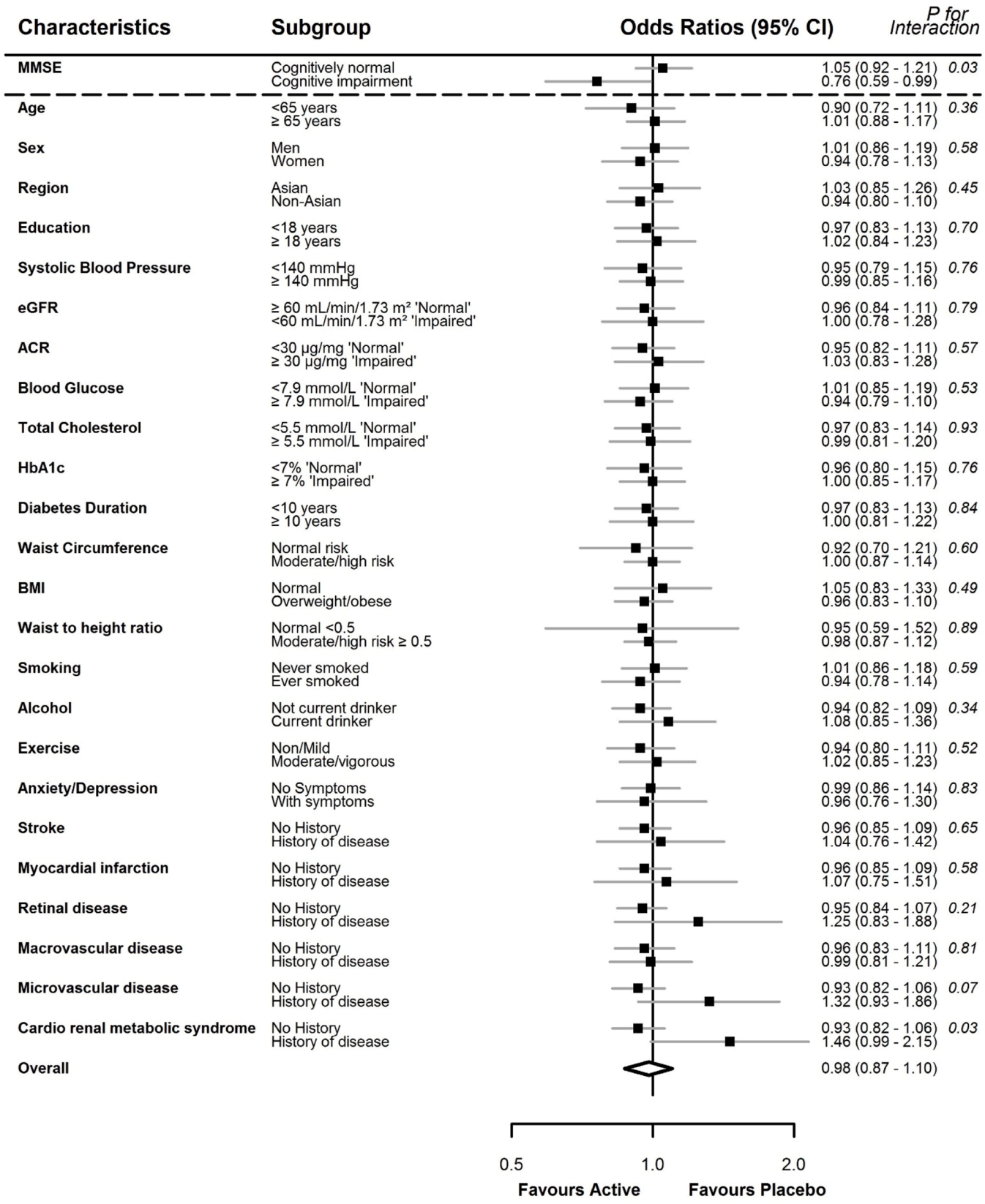

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Fig. 1. Effects of randomised blood pressure treatment on dementia/cognitive decline in subgroups of participants defined by characteristics at baseline.
MMSE categorisation: cognitively normal (MMSE ≥28) / cognitive impairment (MMSE<28).
Waist circumference: Normal risk <94 cm for men, <80 cm for women. Moderate/High risk ≥94 cm for men, ≥80 cm for women. Body mass index (BMI): Normal <25 kg/m2, overweight/ obese ≥25 kg/m2.
Multi-adjusted models adjusted (apart from when considered as the subgroup variable) for sex (women vs men), age, region (Asian vs non-Asian), age at completion of education, MMSE score, systolic blood pressure, total cholesterol, glycated haemoglobin (HbA1C), diabetes duration, waist circumference, smoking, alcohol consumption, exercise, depression/anxiety, blood glucose, estimated glomerular filtration rate (eGFR), albumin-to-creatinine ratio (ACR). Waist circumference was not included in models for body mass index (BMI) or waist to height ratio. Coefficients calculated as the interaction term between the subgroup variable and blood pressure treatment, in models excluding adjustment the corresponding variable. Models for history of stroke, myocardial infarction, retinal disease, macrovascular disease, microvascular disease and cardio renal metabolic syndrome were adjusted for sex (women vs men), age, region (Asian vs non-Asian) and age at completion of education, coefficients calculated as the interaction term between the subgroup variable and blood pressure treatment.

between intensive and standard glucose control between MMSE (Supplementary fig. 3 panels A and B) and diabetes duration subgroups (Supplementary fig. 3 panels C and D). There was separation by the baseline glucose subgroups such that those with impaired glucose at baseline had a bigger change in HbA1c and glucose trajectories between intensive and standard control compared with the change for those with normal glucose at baseline (Supplementary fig. 3 panels E and F).

Discussion

In this study of participants with T2DM with a history of major macro- or microvascular disease, or at least one further CV risk factor, there was no overall effect of BP lowering treatment vs placebo nor intensive glucose control vs standard control on the composite outcome of dementia/CD whilst accounting for the competing risk of death. However, we did observe that those with cognitive impairment at baseline had a lower risk of dementia/CD when taking randomised BP-lowering treatment as compared to placebo. In those cognitively normal at baseline, no significant effect of BP-lowering treatment was observed for dementia/CD. The effect of intensive glucose control (vs. standard control) on the odds of dementia/CD showed differential effects by level of blood glucose and duration of T2DM. Surprisingly, those with impaired glucose at baseline favoured intensive glucose control, though for those with normal glucose at baseline showed a tendency for standard control on the odds of dementia/CD. For those with <10 years diabetes duration there was a tendency to favour intensive control and the converse for those with longer diabetes duration on the odds of dementia/CD.

In our study, we observed that BP-lowering lowered the risk of dementia/CD in those with already impaired cognition, as indicated by an MMSE score of <28 at baseline, suggesting that treatment may slow the progression of CD when underlying pathological damage has begun to manifest. Moreover, the SPRINT-MIND (Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension) study demonstrated that intensive long-term BP control significantly reduced the combined rate of dementia and MCI [16]. However, our study was in participants who all had T2DM, whereas diabetes patients were excluded from SPRINT-MIND. Our results on BP-lowering treatment did not show significant benefits in ameliorating the risk of dementia/CD overall, which is similar to the ACCORD-MIND (Action to Control Cardiovascular Risk in Diabetes - Memory in Diabetes) study in T2DM that was unable to demonstrate a difference between intensive and conventional antihypertensive therapies on CD [17]. However when ADVANCE was merged with four other randomized double-blind placebo-controlled trials (HYVET (Hypertension in the Very Elderly Trial), PROGRESS (Perindopril Protection Against Recurrent Stroke Study), SYST-EUR (SYSTolic Hypertension in EURope trial), SHEP (Systolic Hypertension in the Elderly Program)) of BP lowering treatment, in a single-stage individual patient data meta-analysis, this demonstrated that BP-lowering treatment was effective for lowering the risk of incident dementia [1].

We note that the subgroup analyses based on baseline cognitive status in PROGRESS reported opposite findings [18]. The protective effect of active BP in reducing CD or dementia was observed in those who did not have baseline cognitive impairment, but not in those with baseline cognitive impairment. However, PROGRESS participants had a history of stroke or TIA within the previous 5 years [19].

We found that those with cardio-renal-metabolic syndrome did not experience a benefit of active BP lowering treatment compared with placebo on dementia/CD. Individuals with cardio-renal-metabolic syndrome are likely to have a higher level of risk factors and established disease [20]. Furthermore, those with cognitive impairment at baseline had a higher rate of cardio-renal-metabolic syndrome, which is in line with previous studies and maybe due to higher levels of small-vessel cerebrovascular disease [20]. Therefore, those with cardio-renal-metabolic syndrome may have more advanced conditions, whose cause is multifactorial, that doesn't confer a benefit of BP lowering treatment for dementia/CD. Indeed, further research is warranted to determine the effects of blood pressure lowering treatment in frailer older adults with multiple chronic conditions [21].

Overall, intensive glucose control was not associated with dementia/CD in ADVANCE. A potential explanation is that severe hypoglycaemia can result in irreversible neuronal cell death and accelerate CD and thus, a greater number of episodes of hypoglycaemia requiring hospitalisation or emergency room visits increases the risk of dementia [22]. The excess of hospitalisations due to severe hypoglycaemia in the intensive glucose control group in ADVANCE (1.1 % vs. 0.7 %; OR 1.52, 95 % CI 1.01–2.28; $p = 0.04$) [13] might have weakened any potential cognitive protective effect of intensive glucose control. A further ADVANCE study also demonstrated a relationship in the opposite direction, such that after adjustment for several covariates the risk of severe hypoglycaemia in patients with severe cognitive dysfunction was more than twofold higher than in patients with normal cognitive function [14]

In the present study, ADVANCE participants with T2DM duration <10 years showed a tendency to favour intensive glucose control compared with standard control with a lower risk of dementia/CD. The association between T2DM duration and increased risk of microvascular events previously shown in ADVANCE [23], and the reported link between small vessel disease in the heart and brain and dementia [24], is consistent with our observed interaction between T2DM duration and glucose lowering treatment and dementia./CD risk reduction, On the other hand, those whose T2DM was diagnosed >10 years before enrolment in the trial may have had established cerebral small vessel diseases that could not be reversed.

Differences in systolic and diastolic BP between BP lowering intervention and placebo arms were apparent by 6 weeks and these BP differences were sustained throughout the ADVANCE trial [12]. Furthermore, there was a significant reduction in HbA1c and blood glucose among those undergoing intensive control as compared with standard control, as previously reported [13]. Our present study extends these findings to show there were no differences in systolic and diastolic BP reductions due to BP lowering treatment by baseline cognition subgroups. There were also no differences in HbA1c and glucose reductions due to glucose control by baseline cognition and diabetes duration subgroups, there was however a bigger reduction in HbA1c and glucose for those with impaired glucose levels compared to normal glucose levels at baseline. The excess benefit gained in those who had greater intensity of hyperglycaemia, that is in those with a higher glucose level

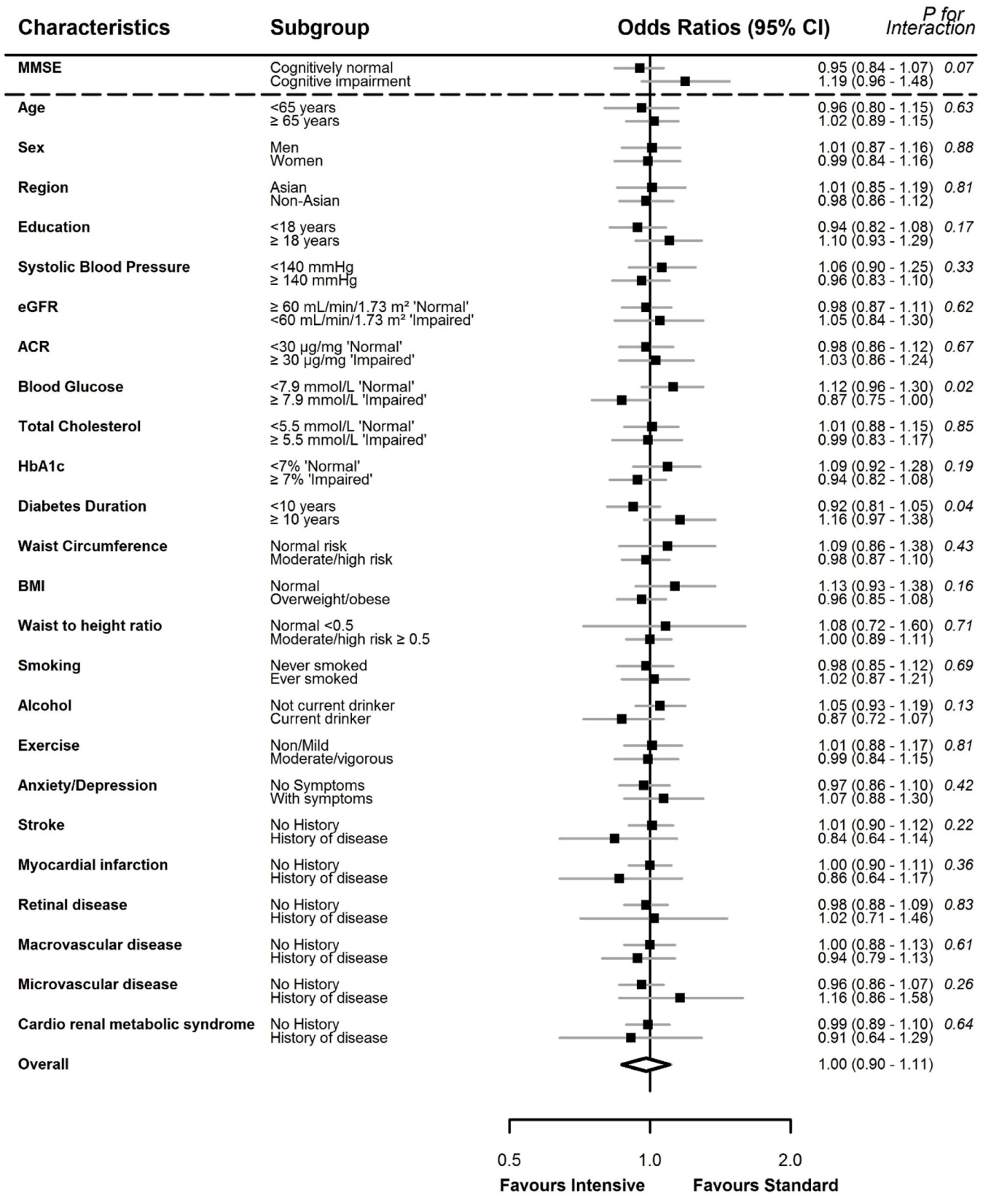

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Fig. 2. Effects of randomised glucose treatment on dementia/cognitive decline in subgroups of participants defined by characteristics at baseline.
MMSE categorisation: cognitively normal (MMSE ≥28) / cognitive impairment (MMSE<28).
Waist circumference: Normal risk <94 cm for men, <80 cm for women. Moderate/High risk ≥94 cm for men, ≥80 cm for women. Body mass index (BMI): Normal <25 kg/m2, overweight/ obese ≥25 kg/m2.
Multi-adjusted models adjusted (apart from when considered as the subgroup variable) for sex (women vs men), age, region (Asian vs non-Asian), age at completion of education, MMSE score, systolic blood pressure, total cholesterol, glycated haemoglobin (HbA1C), diabetes duration, waist circumference, smoking, alcohol consumption, exercise, depression/anxiety, blood glucose, estimated glomerular filtration rate (eGFR), albumin-to-creatinine ratio (ACR). Waist circumference was not included in models for body mass index (BMI) or waist to height ratio. Coefficients calculated as the interaction term between the subgroup variable and blood pressure treatment, in models excluding adjustment the corresponding variable. Models for history of stroke, myocardial infarction, retinal disease, macrovascular disease, microvascular disease and cardio renal metabolic syndrome were adjusted for sex (women vs men), age, region (Asian vs non-Asian) and age at completion of education, coefficients calculated as the interaction term between the subgroup variable and glucose treatment.

or to a lesser extent in those with elevated HbA_1c ≥7 %, may be due to an increased risk of dementia that was more notable in those with T2DM with higher glucose levels and thus the benefit was more evident [25]

There were some differences in participant baseline lifestyle characteristics in our study based on baseline cognition, specifically participants with cognitive impairment were less frequently (ever) smokers and (current) alcohol drinkers than those cognitively normal. Current alcohol drinking participants may have had a change in behaviour due to cognitive impairment, however the observation for smokers is unclear. Alcohol and smoking status were self-reported in ADVANCE, which is a notoriously inaccurate methodology [26] and under reporting maybe a consequence of participants having cognitive impairment at baseline. However, the effect of BP lowering treatment and intensive glucose control on dementia/CD were not modified by alcohol and smoking status in our study.

This study utilised a large and well-characterised international cohort of patients with T2DM that was strengthened by having a prospective design, randomised assignment to treatment, adjudicated endpoints for dementia and CD, and data on death enabling this competing risk to be included in multinomial logistic regression models [11]. Whilst we considered patients with T2DM from a clinical trial population that might be perceived to lack generalizability, ADVANCE participants have been shown to be broadly generalisable to patients with T2DM in community practice [27]. We considered the effects of multiple testing to be a limitation, as was the measurement of cognitive function on the MMSE which is insensitive for MCI and of specific cognitive domains, especially executive function [28]. Nevertheless, the 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 clinical trials and other interventions. As ADVANCE was powered to detect treatment effects on major macrovascular and microvascular events jointly as well as separately, there may have been limited power to determine a significant treatment effect for dementia and CD.

In summary, our study showed evidence of a differential benefit of BP-lowering treatment in those with cognitive impairment compared to those cognitively normal. It also provides evidence of differential effects of intensive glucose control on dementia and CD according to the initial level of glucose and the time since diagnosis of diabetes. Further trial and meta-analyses are recommended to more reliably ascertain the effects of BP-lowering and intensive glucose control treatments on dementia and cognitive decline in subpopulations of people with T2DM.

CRediT authorship contribution statement

Katie Harris: Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Jessica Gong:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Stephen MacMahon:** Writing – review & editing, Conceptualization. **Ying Xu:** Writing – original draft, Investigation. **Sultana Shajahan:** Writing – review & editing, Conceptualization. **Stephen Harrap:** Writing – review & editing. **Neil Poulter:** Writing – review & editing. **Michel Marre:** Writing – review & editing. **Pavel Hamet:** Writing – review & editing. **Giuseppe Mancia:** Writing – review & editing. **Craig Anderson:** Writing – review & editing, Writing – original draft. **Mark Woodward:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **John Chalmers:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J. C. reports research grants from Servier and from the National Health and Medical Research Council (NHMRC) of Australia, for the ADVANCE trial and for the ADVANCE-ON study, all before 2014, and Program Grant APP1149987 from the NHMRC for 2019–2023 for "Clinical, Public Health and Policy Interventions to Combat Cardiovascular Diseases". M. W. reports consultancy fees from Amgen, Kirin and Freeline and is supported by NHMRC grants APP1149987 and APP1174120. In the past 24 months G.M. has received compensations as speaker/chairman/consultant from: Berlin Chemie, IPCA Laboratories, Medtronic Inc USA, Menarini Int, Merck Healthcare KGaA, Omnicuris, Recordati, Sanofi, Servier, Sun Laboratories. N.P. has received personal speaker fees from Servier, Takeda and Novo Nordisk, and advisory board activities from AstraZeneca and Novo Nordisk, and has received grants for his research group relating to diabetes mellitus from Diabetes UK, NIHR Efficacy and Mechanism Evaluation Programme (EME), Julius Clinical and the British Heart Foundation with a pending grant from Novo Nordisk. N.P. holds no stocks or shares in any such companies. C.A. is on the Advisory Board for AstraZeneca Australia.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2024.100372.

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