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Effect of renin-angiotensin system antihypertensive medication use on cognitive function in diabetes mellitus with obesity or overweight: An ancillary study to the Action for Health in Diabetes (Look AHEAD) trial

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Abstract

Aim: To determine whether antihypertensive medication (AHM) acting through the renin angiotensin system (RAS-AHM), compared with other AHM, can mitigate effects on cognitive function and risk for impairment in a population with type 2 diabetes mellitus (T2DM).

Materials and Methods: This secondary analysis of the randomized controlled Action for Health in Diabetes (Look AHEAD) study included 712 community-dwelling participants who were followed over 15 years. Logistic regression was used to relate RAS-AHM use to cognitive impairment, and linear regression was used to relate RAS-AHM use to domain-specific cognitive function after adjusting for potential confounders.

Results: A total of 563 individuals reported RAS-AHM use and 149 reported other-AHM use during the study. RAS-AHM users have college or higher education (53%), had higher baseline glycated haemoglobin (57 mmol/mol), and reported higher diabetes medication use (86%), while other-AHM users were more likely to be White (72%), obese (25%) and to have cardiovascular history (19%). RAS-AHM use was not associated with a reduced risk of dementia compared with other-AHM use. We did observe better executive function (Trail Making Test, part B, $P < 0.04$), processing speed (Digit Symbol Substitution Test, $P < 0.004$), verbal memory (Rey Auditory Verbal Learning Test-delayed recall, $P < 0.005$), and composite score ($P < 0.008$) among RAS-AHM users compared with other-AHM users.

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Conclusion: In this sample of adults with T2DM, free of dementia at baseline, we observed a slower decline in processing speed, executive function, verbal memory, and composite score among RAS-AHM users.

KEYWORDS
antihypertensive medications, cognitive decline, cognitive impairment, dementia, obesity, overweight, renin angiotensin system, type 2 diabetes

1 | INTRODUCTION

The recent Lancet Commission on dementia reported that approximately 40% of dementia cases are potentially preventable.[1] Modifiable risk factors included physical activity, type 2 diabetes mellitus (T2DM), obesity and hypertension.[1] T2DM has been associated with increased dementia risk.[1,2] This risk is associated with T2DM duration[3] and severity, based on T2DM complications[4]; however, glycaemic control has not been shown to alter dementia risk.[5] T2DM has been associated with cognitive decline in memory, attention, processing speed, and executive function tests.[6]

There is evidence for the involvement of the renin angiotensin system (RAS) in Alzheimer's disease (AD) pathogenesis,[7-10] resulting in an increased interest in the effect of antihypertensive medication (AHM) acting via the RAS (RAS-AHM), specifically angiotensin-converting enzyme (ACE) inhibitors and angiotensin 1 receptor blockers (AT1RBs), on AD risk. Several observational studies[11-13] have shown a beneficial effect of these medications on AD. The Ginkgo Evaluation of Memory Study[13] demonstrated that blood pressure control only partially mediated the beneficial effect, suggesting other mechanisms need to be explored. However, two recent meta-analyses[14,15] found no evidence that the RAS-AHM class was more effective in dementia risk reduction than non-use or other AHM classes.[14,15] It is important to note that most observational studies had a short follow-up, and only one studied the relationship between mid-life exposure and late-life dementia risk.

The RAS plays a vital role in T2DM. Specifically, T2DM-related micro- and macrovascular complications are associated with overexpression of angiotensin II (ANGII) and overactivation of AT1R.[16] Additionally, ANGII increases aldosterone production, impairing insulin signalling and worsening insulin resistance.[16] Treatment with AHM acting via the RAS system (RAS-AHM; ACE inhibitors, AT1RBs) has been shown to improve glucose metabolism, delay insulin resistance, and prevent T2DM-associated vascular complications in numerous clinical trials.[16] However, only one study has evaluated the effect of RAS-AHM on dementia risk in participants with T2DM and hypertension; this study found that, over a 12-year follow-up period, 2377 ACE inhibitor users had 26% lower all-cause dementia risk when compared with non-ACE inhibitor users and that 1780 AT1RB users had 40% lower all-cause dementia risk when compared non-AT1RB users.[17] There are currently no studies evaluating the effect of RAS-AHM on cognitive function in participants with T2DM.

The Action for Health in Diabetes (Look AHEAD) trial evaluated the effect of intensive lifestyle modification on cardiovascular outcomes in people with T2DM and overweight or obesity at study entry,[18] and ancillary studies designed to determine whether these interventions influenced cognitive outcomes did not result in decreased risk of cognitive impairment[19] or preserved cognitive function.[20]

Our study aimed to determine whether RAS-AHM use reduced the risk of cognitive impairment or slowed cognitive decline compared with other-AHM use using the Look AHEAD study, which is suitable to evaluate our aims and interactions between lifestyle intervention and medication effect on cognitive outcomes.

2 | MATERIALS AND METHODS

2.1 | Participants and study design

This study was a secondary analysis of cognitive data of the randomized controlled Look AHEAD trial. The Look AHEAD trial was a multicentre, single-blinded randomized controlled trial that recruited 5145 individuals from 16 centres across the United States from 2001 to 2004 who were overweight or obese and had T2DM.[18] At enrolment, participants were 45 to 76 years of age with body mass index (BMI) 25 kg/m^2 (≥27 kg/m^2 if on insulin), glycated haemoglobin (HbA1c) levels <97 mmol/mol, systolic/diastolic blood pressure <160 / <100 mmHg and triglyceride levels <6.77 mmol/L, and reported consuming ≤14 alcoholic drinks per week. The local institutional review boards approved the protocols, and all participants provided written informed consent. Participants were randomly assigned with equal probability to a multidomain intensive lifestyle intervention (ILI),[21] which included frequent group or individual sessions focused on diet modification and physical activity, designed to induce and maintain an average weight loss ≥7%, or to a diabetes support and education (DSE) control intervention,[22] which consisted of group sessions featuring standardized protocols focused on improving diet, physical activity and social support.[23] Medical history and medications were assessed at initial and annual follow-up visits, and weight, height and blood pressure were measured. The trial and both intervention arms were stopped in September 2012 after 9.6 years due to futility. Despite more weight loss and better glycaemic control, there was no difference in the primary composite outcome of cardiovascular events between the ILI and DSE groups.[23] The mean length of the

intervention for participants was 9.8 years. The study continued as an observational cohort through to 2021.

2.2 | Variables

2.2.1 | Exposure assessment

The Look AHEAD trial did not regulate medication management. Detailed information about medication use was collected at each visit by asking participants to bring in all prescribed medications, prescriptions and over-the-counter medications. Our secondary analysis included medications that were coded into drug classes; the AHM drug class consisted of an angiotensin receptor 1 blocker (AT1RB; candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) or an ACE inhibitor (benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril). As these medications act via the RAS, they were grouped into the RAS-AHM group. We classified users of all other AHM groups, including diuretics, beta receptor blockers, calcium channel blockers and alpha 1 receptor blockers, as other-AHM users. Participants were assigned to the RAS-AHM group if they reported RAS-AHM use at any visit but not other-AHM use. Similarly, participants were assigned to the other-AHM group if they reported other-AHM use at any visit but not RAS-AHM use. Participants who used both types of AHMs, concurrently or at different visits, were excluded from this analysis.

The ACE inhibitors and AT1RBs were further divided into those that cross the blood-brain barrier (BBB-C; captopril, fosinopril, lisinopril, perindopril, ramipril, trandolapril, candesartan, telmisartan, valsartan) and those that do not cross the blood-brain barrier (BBB-NC; benazepril, enalapril, moexipril, quinapril, eprosartan, irbesartan, losartan, olmesartan). This classification was used to address findings from previous studies and a recent meta-analysis[24] that the use of blood-brain barrier-crossing RAS-AHM in cognitively normal older adults decreased the rate of cognitive decline. The classification was primarily based on reviews of the literature and medication package inserts.

We did not, however, further divide RAS-AHM and other-AHM users by intervention, DSE versus ILI.

2.2.2 | Outcome: Cognitive assessment and dementia diagnosis

Cognitive assessments were conducted between August 2009 and February 2020 in various ancillary studies, Look AHEAD Physical and Cognitive Function (August 2009 to June 2012, N = 977), Look AHEAD M&M/Brain (November 2011 to August 2013, N = 601), and Look AHEAD-C (August 2013 to December 2014, N = 3075). The same cognitive protocol was applied in the Look AHEAD-MIND study (May 2018 to February 2020, N = 2451), allowing for a total of four possible cognitive assessments at Years 8 to 9, 10 to 11, 12 to 14, and 15 to 18 after randomization.

Cognitive testing included the Rey Auditory Verbal Learning Test (RAVLT) to assess verbal learning and memory,[25] the Digit Symbol Substitution Test (DSST) to assess attention and processing speed,[26] the Modified Stroop Colour and Word Test (Stroop) to assess interference,[27] and the Trail-Making Test Parts A and B (TMT, Part A and B) to assess attention, processing speed and executive function, respectively.[28] The Modified Mini Mental State Examination (3MSE)[29] assessed global cognitive function.

When a participant scored below the prespecified age- and education-specific cut-off point, it triggered the administration of the Functional Assessment Questionnaire (FAQ)[30] to by a friend or family member previously identified by the participant to assess functional status and performance on instrumental activities of daily living to help identify cognitive impairment. Two masked adjudicators independently reviewed all Look AHEAD cognitive test and depression scores, FAQ, and medical and health information to classify participants as not impaired, as having mild cognitive impairment (MCI),[31] or as having probable dementia.[19,32] Due to the relatively small number of dementia cases, we created a group called "cognitively impaired" into which participants diagnosed with MCI (N = 34, 4.8 %) or probable dementia (N = 13, 1.8%) were grouped.

2.2.3 | Covariates

Based on previous literature, we assessed baseline covariates possibly related to T2DM, AHM use, or dementia. These included baseline age, sex, race, education (high school or less, college graduate, post-college), body mass index (BMI; ≥25 to <30 kg/m^2, ≥30 to <40 kg/m^2, ≥40 kg/m^2), smoking status (never, past, present), alcohol consumption status (units/week, 1 to 3/week, 4+/week), HbA1c (<53 mmol/mol, 53 - 74 mmol/mol, >75 mmol/mol0), mean systolic (SBP) and diastolic blood pressure (DBP) throughout the study, serum creatinine, history of hypertension, apolipoprotein (*APOE*) e4 genotype (no e4, one e4, two e4 alleles), Beck Depression Index (0-10, ≥11), and history of cardiovascular disease (CVD). History of CVD included self-report of myocardial infarction, coronary artery bypass graft, carotid endarterectomy, lower leg angioplasty, aortic aneurysm, congestive heart failure, or history of stroke. APOE ε4 carrier status was determined for participants who provided consent (80% of women vs. 86% of men; $P < 0.001$) using TaqMan genotyping (rs7412 and rs429358). We also included the study site and intervention.

2.3 | Statistical analyses

Participants who completed a cognitive evaluation and reported AHM use were eligible for inclusion. The sample was defined by having an adjudicated cognitive status; thus, all participants were alive and had not been lost to follow-up. All contributed to the analysis, except that in the analysis for risk of cognitive impairment, participants were censored when they were diagnosed with MCI or dementia.

The clinical trial concluded in 2012, but cognitive assessments occurred in four ancillary observational studies using identical protocols between 2009 and 2020: counting from the original randomization during Years 8 to 9, 10 to 11, 12 to 14, and 15 to 18 provided us with four timepoints.

Participant characteristics were compared using *t*-tests and ANOVA for continuous variables and chi-squared tests for categorical variables for included versus excluded participants. We identified potential confounders significantly related to AHM use at a significance level of $P \leq 0.05$ and included them in the analyses. Analyses were adjusted for baseline age, sex, education, race/ethnicity, intervention, BMI, SBP, HbA1c, use of any diabetes medication, and CVD.

After adjusting for potential confounders, logistic regression was used to relate RAS-AHM to cognitive impairment. Repeated measures of linear regression to account for within-subject correlation was used to evaluate associations between RAS-AHM and cognitive function after adjusting for potential confounders. We also explored the effect of RAS-AHM based on medication type (ACE inhibitor) and blood-brain barrier crossing status on dementia risk (using logistic regression analysis) and cognitive function (using the repeated measures linear regression model). To evaluate the potential role of the intervention and SBP on the effect of AHM on cognitive impairment, we added an interaction term between AHM use and intervention arm; and AHM use and SBP to the fully adjusted model.

Cognitive function test scores were treated as continuous variables and were standardized (*z*-scores) by subtracting scores from the overall cohort-wide mean of the initial assessments and dividing this by their standard deviation (SD).[33] Domain-specific scores were formed by taking the average *z*-scores for tests in each domain. The primary cognitive measure used in the Look AHEAD studies is a composite of the average of these domain scores.[34]

All analyses were performed in SAS 9.4 (SAS Institute, Cary, North Carolina) for Windows.

3 | RESULTS

3.1 | Participants

The analysis included 712 participants with an adjudicated cognitive status who used either RAS-AHM (N = 563) or other-AHM (N = 149; Figure 1). RAS-AHM users were more likely to have a college or higher education (53%), higher baseline HbA1c level (57 mmol/mol), and higher diabetes medication use (86%), while other-AHM users were more likely to be White (72%), to be obese (25%) and to have a history of CVD (19%; Table 1). The racial difference could be attributable to guidelines since RAS-AHM have been found to be less effective in African-American populations; thus, they may be less often prescribed in African-American populations.[35] The higher prevalence of CVD among other-AHM users could be partially explained by the beta-blockers which mainstay medication for CVD.

Forty-seven participants developed cognitive impairment (MCI, n = 34 [4.8%] or dementia, n = 13 [1.8%]) during an average of 14.8 years of follow-up (Table 1). The cognitive characteristics from the first measured visit [means (SD)] 3MSE, TMT part A and part B times (seconds), Stroop, DSST, RAVLT delayed, and composite scores were indicative of a high functioning sample (Table 2). RAS-AHM users performed significantly better at the first visit on TMT part B, DSST, RAVLT delayed, and composite score (Table 2).

3.2 | Association between RAS-AHM use and cognitive impairment

Among the RAS-AHM users, 7.5% were diagnosed with either MCI or dementia (cognitive impairment), while of the other-AHM users, 10.1% were diagnosed with MCI or dementia (cognitive impairment; Table 1). In the fully adjusted model, there was no significant risk reduction for cognitive impairment among RAS-AHM users compared with other-AHM users (odds ratio [OR] 0.62, 95% confidence interval [CI] 0.29-1.31; $P = 0.21$ [Table 3]).

A total of 101 participants reported ACE inhibitor use and 15 participants reported AT1RB use. In the unadjusted model, there was a significant 73% lower risk of cognitive impairment among ACE inhibitor users compared with other-AHM users (OR 0.27, 95% CI 0.08-0.97; $P = 0.04$); however, after adjusting for potential confounders, this differential in risk was no longer significant (OR 0.30, 95% CI 0.07-1.25; $P = 0.10$) (Table 3). Due to the small number of AT1RB users, we did not perform a subanalysis for this medication group.

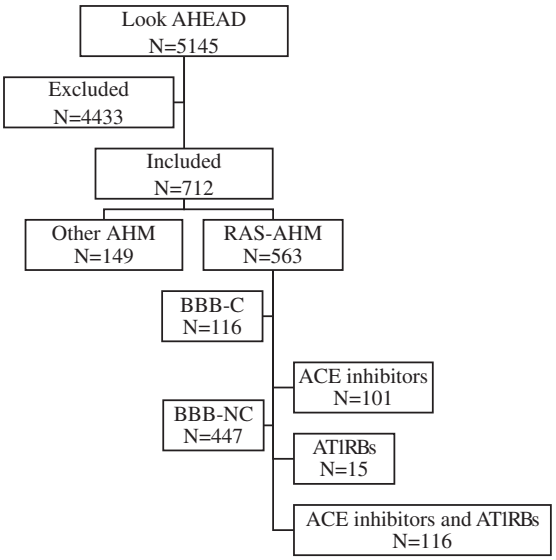

FIGURE 1 Flow of participants. Excluded: no cognitive examination or no reported antihypertensive medication (AHM) use or AHM groups were switched during the span of the study. Included: All four cognitive evaluations and reported use of AHM with no switch of AHM group during the span of the study. RAS-AHM (AHM acting via the renin angiotensin system) included: angiotensin-converting enzyme (ACE) inhibitors and angiotensin 1 receptor blockers (AT1RBs). Other AHM included: diuretics, beta receptor blockers, calcium channel blockers, and alpha 1 receptor blockers. Blood-brain barrier crossing (BBB-C) and non-crossing (BBB-NC)

TABLE 1 Baseline characteristics of participants with cognitive assessments (antihypertensive medication [AHM] acting through the renin angiotensin system compared with other AHM)

	Overall, N = 712 Mean (SD)	RAS-AHM, N = 563	Other-AHM, N = 149	*P* value
Intervention assignment, n (%)				0.43
DSE	1064 (49.9)	558 (50.9)	506 (48.8)	
ILI	1069 (50.1)	539 (49.1)	530 (51.2)	
Age group, n (%)				**<0.001*****
45-54 years	245 (34.4)	210 (37.3)	35 (23.5)	
55-64 years	370 (52.0)	294 (52.2)	76 (51.0)	
65-76 years	97 (13.6)	59 (10.5)	38 (25.5)	
Sex, n (%)				0.40
Male	256 (36.0)	198 (35.2)	58 (38.9)	
Female	456 (64.0)	365 (64.8)	91 (61.1)	
Race/ethnicity				**<0.001*****
African-American	72 (10.1)	50 (8.9)	22 (14.8)	
American-Indian	72 (10.1)	65 (11.6)	7 (4.7)	
Hispanic	97 (13.6)	89 (15.8)	8 (5.4)	
Non-Hispanic White	456 (64.0)	349 (62.0)	107 (71.8)	
Other	15 (2.1)	10 (1.8)	5 (3.4)	
Education level, n (%)				0.79
High school or lower	324 (46.4)	258 (46.6)	66 (45.8)	
College graduate	242 (34.7)	189 (34.1)	53 (36.8)	
Post college	132 (18.9)	107 (19.3)	25 (17.4)	
BMI, n (%)				0.80
≥25 to <30 kg/m^2	141 (19.8)	113 (20.1)	28 (18.8)	
≥30 to <40kg/m^2	436 (61.2)	346 (61.5)	90 (60.4)	
≥40 kg/m^2	135 (19.0)	104 (18.5)	31 (20.8)	
Mean (SD) BMI, kg/m^2	34.9 (5.7)	34.8 (5.7)	35.3 (5.9)	0.31
HbA1c, n (%)				0.08
<53 mmol/mol	301 (42.3)	245 (43.5)	56 (37.6)	
53 - 74 mmol/mol	352 (49.4)	267 (47.4)	85 (57.1)	
>75 mmol/mol	59 (8.3)	51 (9.1)	8 (5.4)	
Mean (SD) HbA1c, %	7.19 (1.14)	7.24 (1.17)	7.00 (0.99)	**0.01****
Blood pressure, mmHg*				
SBP	124.4 (14.9)	124.1 (14.8)	125.2 (15.1)	0.45
DBP	69.6 (9.1)	69.7 (9.2)	69.5 (8.7)	0.88
History of CVD: yes, n (%)	50 (7.0)	25 (4.4)	25 (16.8)	**0.001*****
Dyslipidaemia: yes, n (%)	453 (63.6)	352 (62.5)	101 (67.8)	0.24
Total cholesterol, mmol/L	5.01 (0.98)	5.01 (0.97)	5.03 (1.02)	0.86
HDL, mmol/L	1.14 (0.32)	1.13 (0.32)	1.16 (0.31)	0.42
LDL, mmol/L	2.95 (0.83)	2.94 (0.82)	2.97 (0.88)	0.76
Triglycerides, mmol/L	2.09 (1.43)	2.9 (1.41)	2.08 (1.52)	0.88
Kidney disease: yes, n (%)	43 (6.0)	32 (5.7)	11 (7.4)	0.44
Serum creatinine, mmol/L	68.97 (15.91)	68.97 (15.91)	15.03 (15.03)	0.05*
Smoking status, n (%)				0.23
Never	1072 (50.3)	555 (50.7)	517 (50.0)	
Past	977 (45.9)	499 (45.6)	478 (46.2)	

(Continues)

TABLE 1 (Continued)

	Overall, N = 712 Mean (SD)	RAS-AHM, N = 563	Other-AHM, N = 149	*P* value
Present	81 (3.8)	41 (3.7)	40 (3.9)	
Alcohol intake, n (%)				0.74
None/week	1458 (68.5)	724 (66.2)	734 (71.0)	
1-3/week	427 (20.1)	229 (20.9)	198 (19.2)	
4+/week	243 (11.4)	141 (12.9)	102 (9.9)	
APOE carrier status, n (%)				0.20
No e4 alleles	438 (77.7)	344 (79.1)	94 (72.9)	
1 e4 allele	110 (19.5)	81 (18.6)	29 (22.5)	
2 e4 alleles	16 (2.8)	10 (2.3)	6 (4.7)	
Beck Depression Index score, n (%)				0.44
0-10	549 (85.5)	429 (85.0)	120 (87.6)	
≥11	93 (14.5)	76 (15.0)	17 (12.4)	
Cognitive status, n (%)				**0.05***
Normal	665 (93.4)	531 (94.3)	134 (89.9)	
MCI	34 (4.8)	35 (4.4)	9 (6.0)	
Dementia	13 (1.8)	7 (1.2)	6 (4.0)	
Diabetes medication, n (%)				
Any medication	596 (85.0)	482 (86.5)	114 (79.2)	**0.03***
Insulin	74 (10.8)	59 (10.8)	15 (11.0)	0.95
Biguanides	422 (60.8)	341 (61.8)	81 (57.0)	0.30

P < 0.05*; *P* < 0.01**; *P* < 0.001***.

Abbreviations: AHM, antihypertensive medication; APOE, apolipoprotein ε4; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DSE, diabetes support and education; HbA1c, glycated haemoglobin; ILI, intensive lifestyle intervention; MCI, mild cognitive impairment; RAS-AHM, antihypertensive medication acting through the renin angiotensin system; SBP, systolic blood pressure.

TABLE 2 Cognitive characteristics from the first visit with cognitive measures

	Overall, N = 712 Mean (SD)	RAS-AHM, N = 563 Mean (SD)	Other-AHM, N = 149 Mean (SD)	*P* value
3MSE	91.8 (6.8)	91.9 (6.9)	91.3 (6.3)	0.34
TMT, part A	37.3 (20.3)	36.6 (20.8)	40.2 (18.0)	0.07
TMT, part B	106.6 (68.5)	102.3 (66.8)	123.4 (72.9)	**0.002****
Stroop	32.3 (15.6)	31.8 (15.0)	34.2 (17.4)	0.12
DSST	41.5 (10.7)	42.3 (10.8)	38.4 (9.7)	**<0.001*****
RAVLT delayed	41.4 (9.5)	42.0 (9.4)	39.0 (9.9)	**0.002****
Composite *z*-score	-0.037 (0.79)	0.009 (0.78)	-0.220 (0.78)	**0.003****

P < 0.05*; *P* < 0.01**; *P* < 0.001***.

Abbreviations: 3MSE, Modified Mini Mental Status Exam; AHM, antihypertensive medication; DSST, Digit Symbol Substitution Test; RAS-AHM, antihypertensive medication acting through the renin angiotensin system; RAVLT, Rey Auditory Verbal Learning Test; Stroop, Modified Stroop Colour and Word Test; TMT, part A, and B, Trail Making Test Parts A and B.

Of the 563 RAS-AHM users, 116 were receiving BBB-C and 447 BBB-NC medications. In the fully adjusted models, BBB-C was not superior in risk reduction to BBB-NC or other-AHM use; BBB-NC was not superior to other-AHM use (Table 3).

The results were not altered after adjusting interaction terms for intervention arm.

3.3 | Association between RAS-AHM use and cognitive function

In fully adjusted models, RAS-AHM users had significantly better cognitive function when compared with other-AHM users for TMT, part B (β = −16.4 [5.60]; *P* = 0.004), DSST (β = 2.6 [0.90]; *P* = 0.005),

RAVLT, delayed recall (β = 2.3 [0.81]; $P = 0.005$) and composite score (β = 0.17 [0.06]; $P = 0.008$ [Table 4]).

The ACE inhibitor-user group performed significantly better on 3MSE, TMT part A and B, DSST, RAVLT delayed recall and composite score in the unadjusted model compared with other-AHM users; however, this comparison was no longer significant after adjustment (Table 4).

In the fully adjusted model BBB-C RAS-AHM performed significantly better than other-AHM on TMT, part B (β = −18.9 [7.3]; $P = 0.01$), Stroop (β = −4.8 [1.9]; $P = 0.01$), DSST (β = 2.7 [1.2], $P = 0.02$), RAVLT, delayed recall (β = 3.7 [1.1], $P = 0.001$) and composite score (β = 0.26 [0.08]; $P = 0.002$ [Table 4]). While BBB-NC RAS-AHM performed significantly better than other-AHM on TMT, part B (β = −15.8 [5.8], $P = 0.006$); DSST (β = 2.5 [0.9], $P = 0.006$); RAVLT, delayed recall (β = 1.9 [0.83], $P = 0.02$) and composite score (β = 0.15 [0.07], $P = 0.03$ [Table 4]). BBB-C performed significantly better than BBB-NC in the fully adjusted model RAS-AHM on Stroop ($P = 0.02$) and RAVLT, delayed recall ($P = 0.04$).

The results were not altered after adjusting interaction terms for time (Figure 2).

4 | DISCUSSION

In this first large secondary longitudinal study of nondemented, community-dwelling participants of the Look AHEAD clinical trial who had T2DM with overweight or obesity, we evaluated associations between the use of RAS-AHM and the risk of cognitive impairment and cognitive function with regard to key domains of cognition, including psychomotor speed, executive function, verbal learning and memory, and global cognitive function.

Our study did not find a risk reduction for cognitive impairment among RAS-AHM users compared with other-AHM users. However, we found that RAS-AHM users, over a mean 14.8-year follow-up, had a significantly slower decline in processing speed, executive function, verbal memory, and composite score measures, which have been associated with cognitive decline in T2DM, compared with other-AHM users, and this was not explained by a deleterious effect of any specific medication group within the other-AHM class (Supporting information Table S1).

The RAS has been shown to be important in both T2DM and obesity. T2DM-associated micro- and macrovascular complications have been linked with angiotensin II (ANGII), which has vasoconstrictive properties, and with overexpression resulting in overactivation of angiotensin 1 receptor.[16] ANGII also increases aldosterone production, resulting in impaired insulin signalling and worsening insulin resistance. Treatment with medication acting via the RAS-AHM has been shown to improve glucose metabolism, delay insulin resistance and prevent T2DM-associated vascular complications in numerous clinical trials[16]; thus, benefits on cognitive function could be either a downstream effect on improved vascular function or improved glucose metabolism or other unmeasured effects.

We could not replicate the study findings of Kuan et al,[17] who reported 26% dementia risk reduction among ACE inhibitor users compared with non-ACE inhibitor users and 40% dementia risk reduction among AT1RB compared with non-AT1RB users. Methodological differences could explain this; specifically, the study by Kuan et al had a larger sample size, and ACE or AT1RB medication use was only required for 180 days, allowing a larger sample size. Additionally, they compared ACE inhibitor users with individuals who reported use of AT1RBs and other-AHM and they did not control for blood pressure or renal function.

The literature suggests that AT1RBs are superior to ACE inhibitors for reducing cognitive decline in people with hypertension and MCI[36]; thus, we stratified our analysis of RAS-AHM by grouping medications according to their medication class but were only able to evaluate ACE inhibitor use and cognitive impairment risk since only a few participants reported use of AT1RBs. The lack of ACE inhibitor use

TABLE 3 Logistic regression results: association between type of antihypertensive medication use and cognitive impairment

	Cognitive impairment (MCI or dementia)					
	Unadjusted		Adjusted for demographics[a]		Adjusted for demographics and health characteristics[b]	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
RAS-AHM vs other AHM	0.54 (0.28-1.02)	0.06	0.73 (0.36-1.50)	0.39	0.62 (0.29-1.31)	0.21
ACE inhibitors vs other AHM	0.27 (0.08-0.97)	0.04*	0.36 (0.10-1.35)	0.13	0.30 (0.07-1.25)	0.10
BBB-C vs BBB-NC	0.53 (0.18-1.56)	0.10	0.54 (0.18-1.63)	0.40	0.57 (0.19-1.76)	0.30
BBB-C vs Other AHM	0.32 (0.10-0.99)		0.44 (0.13-1.45)		0.39 (0.11-1.34)	
BBB-NC vs Other AHM	0.60 (0.31-1.15)		0.80 (0.39-1.66)		0.67 (0.32-1.43)	

[a]Adjusted for baseline age, sex, education, and race/ethnicity.
[b]Adjusted for baseline age, sex, education, race/ethnicity, study intervention, BMI, SBP, HbA1c, use of diabetes medication, CVD.
Abbreviations: ACE, angiotensin-converting enzyme; AHM, antihypertensive medication; BBB-C, blood-brain barrier crossing; BBB-NC, blood-brain barrier non-crossing; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; OR, odds ratio; SBP, systolic blood pressure.

TABLE 4 Linear regression results: association between type of antihypertensive medication use and cognitive function

		Cognitive function					
		Unadjusted		Adjusted for demographics[a]		Adjusted for demographics and health characteristics[b]	
Outcome	Medication group (reference is other AHM)	Beta (SE)	*P* value	Beta (SE)	*P* value	Beta (SE)	*P* value
RAS vs. other AHM							
3MSE	RAS-AHM	0.64 (0.61)	0.30	0.75 (0.54)	0.16	0.75 (0.56)	0.18
TMT, part A	RAS-AHM	−3.3 (1.7)	0.05	−2.4 (1.6)	0.13	−3.0 (1.6)	0.07
TMT, part B	RAS-AHM	−17.0 (5.8)	**0.003****	−14.9 (5.4)	**0.006**	−16.4 (5.6)	**0.003****
Stroop	RAS-AHM	−2.9 (1.4)	0.04*	−1.9 (1.4)	0.18	−2.0 (1.5)	0.18
DSST	RAS-AHM	3.1 (0.95)	**0.001*****	2.4 (0.87)	**0.006**	2.6 (0.90)	**0.004****
RAVLT delayed	RAS-AHM	3.5 (0.86)	**<0.0001*****	2.2 (0.79)	**0.006**	2.3 (0.81)	**0.005****
Composite *z*-score	RAS-AHM	0.22 (0.07)	**0.003****	0.16 (0.06)	**0.01**	0.17 (0.06)	**0.008****
ACE inhibitors vs. other AHM							
3MSE	ACE inhibitors	1.7 (0.73)	**0.02***	1.5 (0.68)	**0.03**	1.3 (0.71)	0.07
TMT, part A	ACE inhibitors	−4.0 (1.9)	**0.03**	−2.3 (1.9)	0.23	−2.3 (2.0)	0.24
TMT, part B	ACE inhibitors	−17.2 (7.7)	**0.03**	−8.7 (7.1)	0.22	−9.7 (7.5)	0.20
Stroop	ACE inhibitors	−3.2 (2.0)	0.11	−1.7 (2.0)	0.40	−1.4 (2.1)	0.51
DSST	ACE inhibitors	2.6 (1.2)	**0.03**	1.7 (1.1)	0.12	2.2 (1.1)	0.06
RAVLT delayed	ACE inhibitors	3.1 (1.3)	0.01	1.4 (1.2)	0.22	1.4 (1.2)	0.25
Composite *z*-score	ACE inhibitors	0.24 (0.09)	**0.008**	0.15 (0.08)	0.07	0.16 (0.08)	**0.05**
BBB-C RAS / BBB-NC RAS vs. other AHM							
3MSE	BBB-C	0.73 (0.81)	0.57	1.2 (0.71)	0.24	1.2 (0.72)	0.26
	BBB-NC	0.61 (0.63)		0.63 (0.55)		0.63 (0.57)	
TMT, part A	BBB-C	−3.5 (2.2)	0.14	−4.0 (2.1)	0.16	−4.6 (2.1)	0.09
	BBB-NC	−3.3 (1.7)		−2.0 (1.6)		−2.6 (1.7)	
TMT, part B	BBB-C	−16.3 (7.7)	**0.01**	−17.4 (7.1)	**0.02**	−18.9 (7.3)	**0.01**
	BBB-NC	−17.2 (6.0)		−14.2 (5.5)		−15.8 (5.8)	
Stroop	BBB-C	−5.2 (1.9)	**0.03**	−4.8 (1.9)	**0.02**	-4.8 (1.9)	**0.03**
	BBB-NC	−2.3 (1.5)		−1.1 (1.5)		−1.2 (1.5)	
DSST	BBB-C	2.6 (1.3)	**0.004**	2.6 (1.1)	**0.02**	2.7 (1.2)	**0.02**
	BBB-NC	3.3 (1.0)		2.3 (0.89)		2.5 (0.9)	
RAVLT delayed	BBB-C	5.1 (1.2)	**<0.0001**	3.6 (1.0)	**0.003**	3.7 (1.1)	**0.0022**
	BBB-NC	3.0 (0.89)		1.8 (0.8)		1.9 (0.83)	
Composite *z*-score	BBB-C	0.27 (0.10)	**0.008**	0.26 (0.08)	**0.008**	0.26 (0.08)	**0.007**
	BBB-NC	0.17 (0.04)		0.08 (0.03)		0.04 (0.03)	

[a]Adjusted for baseline age, sex, education, and race/ethnicity.

[b]Adjusted for baseline age, sex, education, race/ethnicity, study intervention, BMI, SBP, HbA1c, use of diabetes medication, CVD.

Abbreviations: 3MSE, Modified Mini Mental Status Exam; AHM, antihypertensive medication; AT1RB, angiotensin 1 receptor blocker; BBB-C, blood-brain barrier crossing; BBB-NC, blood-brain barrier non-crossing; BMI, body mass index; CVD, cardiovascular disease; DSST, Digit Symbol Substitution Test; HbA1c, glycated haemoglobin; RAS-AHM, antihypertensive medication acting through the renin angiotensin system; RAVLT, Rey Auditory Verbal Learning Test; Stroop, Modified Stroop Colour and Word Test; TMT, part A, and B, Trail Making Test Parts A and B.

and cognitive impairment could be partially explained by the small number of participants, evident in large CIs. An additional explanation could be the demographic differences among AHM-user groups, especially in race, sex, BMI and CVD, which are essential determinants of dementia risk.

In our study, we replicated the findings of Ho et al[24] whose meta-analysis of 14 cohort studies evaluated the effects of RAS-AHM in hypertensive participants, stratified by their BBB status, on seven cognitive domains. In our research, similarly to Ho et al, we found that users of BBB-C RAS-AHM did perform better on verbal memory

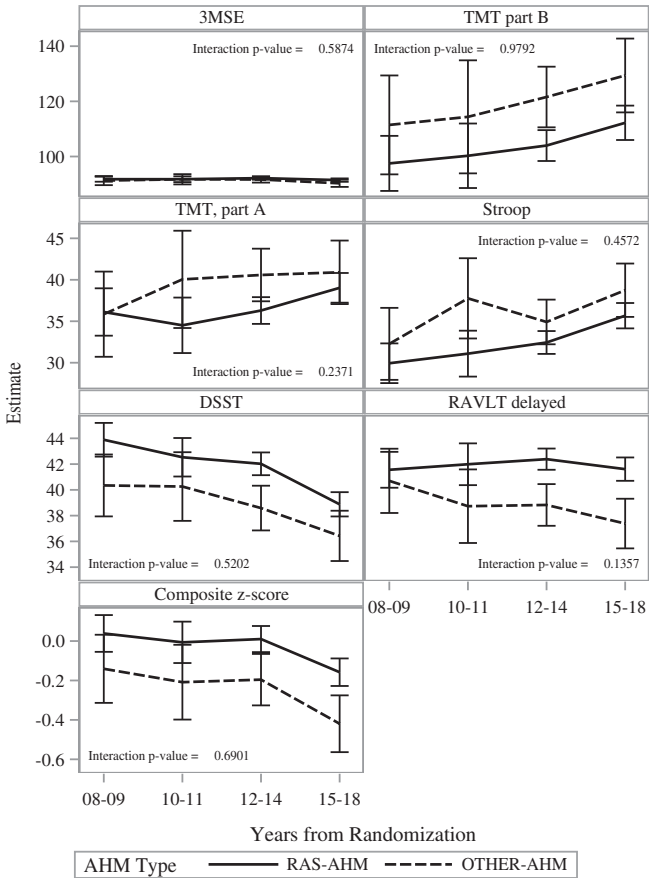

FIGURE 2 Cognitive trajectories over time by antihypertensive medication (AHM) use. Estimates are from unadjusted mixed models to account for correlation within subject. 3MSE, Modified Mini Mental State Examination; DSST, Digit Symbol Substitution Test; RAS-AHM, AHM acting via the renin angiotensin system; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trail-Making Test.

when compared with other-AHM and BBB-NC RAS-AHM users. Furthermore, we found that both BBB-NC and BBB-C medication users performed better in processing speed, executive function, and composite score than other-AHM users and that BBB-C was superior to BBB-NC in measures of executive function.

We cannot ignore the potential role of diabetes medication in AD pathology, especially metformin, which has been reported to decrease dementia risk by reducing vascular risk and to provide neuroprotection independently of glycaemic control[37]; however, both AHM-user groups reported a similar frequency of metformin use.

This study has several strengths. First, it included a large, well-characterized cohort of volunteers followed for 14.8 years and included a detailed cognitive evaluation. Second, medication use was visually validated. Third, we were able to create an RAS-AHM medication group to draw a conclusion about its effect by excluding those who switched to the other-AHM group or reported concomitant use of other AHM at any visit. The exclusion from our analysis of users of multiple AHM at the time of medication recording may at the same time be a weakness, however, because users of multiple AHM may have represented a hypertensive group that was more challenging to control. Such individuals should therefore be included in future studies.

This study also had some limitations. First, we could not account for history of hypertension, including length, severity, and AHM use. Second, with our long follow-up period, we could not create a clear RAS-AHM-user group who reported only RAS-AHM use the whole time. Third, the observational cohort design has limitations inherent to such studies, and we could not account for unknown or unmeasured confounders nor make assumptions regarding causality. Fourth, we did not have baseline cognitive evaluations since this was not part of the original study assessments. However, the mean age at enrolment was 58.6 years, and screening was rigorous, including an evaluation by a behavioural psychologist or interventionist to confirm the participant understood intervention requirements, and those with issues likely to impair adherence were excluded before enrolment. Thus, the likelihood is low that participants had cognitive impairment at baseline. Additionally, of the 2133 participants included in our study who were followed for over 15 years and underwent cognitive adjudication, only 40 (1.9%) were diagnosed with dementia and 163 (7.6%) with MCI, reinforcing the low likelihood of having cognitive impairment in this at-risk population at baseline. Fifth, like most randomized clinical trials, our study population was highly educated and predominantly White, limiting its generalizability. Sixth, although medications were visually inspected during visits, we did not determine medication adherence and did not have information on prior use of these medications. Seventh, as in all observational studies, our results may also be vulnerable to confounding. We sought to address confounding by adjusting for the average SBP during the investigation and evaluated for interaction terms between SBP and AHM use in our models. We also adjusted for history of CVD, all implicated in cognitive impairment and the main indications for using RAS-AHM. Eighth, another potential limitation is survival bias; however, we could not evaluate the competing effect of mortality and dementia due to large intervals between cognitive assessments.

In summary, this longitudinal analysis found that RAS-AHM use in participants with T2DM and with overweight or obesity and at higher risk for cognitive decline was associated with slower decline over long-term performance on processing speed, executive function, verbal memory, and composite score. These findings could add additional information with regard to use of RAS-AHM in patients with T2DM who have overweight or obesity. However, the study findings need to be replicated in a larger sample to understand the mechanisms by which RAS-AHM use may affect cognitive impairment and function of patients with T2DM who are at increased risk of dementia and cognitive decline.

AUTHOR CONTRIBUTIONS

Whitney Wharton—Study concept or design; Analysis or interpretation of data; Drafting/revision of the manuscript for content, including medical writing for content.

Andrea Anderson—Analysis or interpretation of data; Drafting/revision of the manuscript for content, including medical writing for content. Kathleen M. Hayden—Major role in the acquisition of data;

Analysis or interpretation of data; Drafting/revision of the manuscript for content, including medical writing for content. Owen T Carmichael—Analysis or interpretation of data; Drafting/revision of the manuscript for content, including medical writing for content. Jeanne M Clark—Major role in the acquisition of data; Drafting/revision of the manuscript for content, including medical writing for content. Jose Luchsinger—Major role in the acquisition of data; Drafting/revision of the manuscript for content, including medical writing for content. Mark Espeland—Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data; Drafting/revision of the manuscript for content, including medical writing for content.

Sevil Yasar—Study concept or design; Analysis or interpretation of data; Drafting/revision of the manuscript for content, including medical writing for content.

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CONFLICT OF INTEREST

Jose Luchsinger reports stipend from Wolters Kluwer as Editor-in-Chief of the journal *Alzheimer's Disease and Associated Disorders*, Royalties from Springer as Editor of the book Diabetes and the Brain. He also received grants supporting this work, R01AG058571, and K24AG045334. Mark Espeland reports grant funding from the NIH (R01AG064440; U24AG057437; P30AG049638; R01AG050657), the Department of Health and Human Services (HHSN271201700002C), and the Alzheimer's Association (POINTER-19-611 541). Whitney Wharton, Andrea Anderson, Owen Carmichael, Jeanne Clark and Sevil Yasar have no financial disclosures to disclose relevant to this study.

DATA AVAILABILITY STATEMENT

Data sharing not applicable no new data generated

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SUPPORTING INFORMATION

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

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