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Randomized Control Trials

Aronia melanocarpa extract supplementation affects brain vascular function and cognitive performance: A randomized, double-blind, placebo-controlled, cross-over study in older adults with overweight or obesity

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SUMMARY

Background and Aims: Dietary anthocyanins are recognized for their potential beneficial effects on cognitive performance. It remains unclear which mechanisms underlie these effects. This study aimed to investigate the effects of anthocyanin-rich Aronia Melanocarpa extract (AME) on (brain) vascular function and cognitive performance in adults at increased risk of cognitive impairment.
Methods: Thirty healthy older adults (age: 65 ± 6 years old) with overweight or obesity (BMI: 28.3 ± 2.7 kg/m^2) were included in a randomized, double-blind, placebo-controlled cross-over study of 6 weeks (40 mg anthocyanins/day). At the end of each study period, cerebral blood flow (CBF), a marker of brain vascular function, was assessed using arterial spin labeling magnetic resonance imaging (ASL-MRI). Additionally, cognitive performance was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB), cerebral perfusion with transcranial Doppler ultrasound, and peripheral vascular function through endothelial function and retinal microvascular caliber measurements.
Results: AME supplementation did not affect CBF in predefined brain regions, but regional CBF decreased in one cluster located in the right insular cortex (treatment effect 4.4 ± 3.6 mL/100 g/min; p = 0.004), compared to placebo. Furthermore, cognitive performance was improved on the spatial working memory test, reflecting the executive function domain as the between errors and total errors were reduced by 20 % (−3; 95 % CI: −5 to −1; p = 0.006). Memory and psychomotor speed did not change, while cerebral perfusion and peripheral vascular function measurements were also not affected.
Conclusions: Six weeks of AME supplementation improved executive functioning in older adults with overweight or obesity. Although CBF decreased in the right insular cortex, the relevance remains unclear. CBF in predefined brain regions and other potential underlying mechanisms were not affected..
Clinical Trial Registry: This trial was registered at clinicaltrial.gov as NCT 05268133.

1. Introduction

The demographic shift towards an older population translates to a higher prevalence of age-associated co-morbidities, such as cardiovascular disease (CVD) and cognitive impairment. In fact, by 2050, the number of people aged 65 and older is expected to double to 1.6 billion [1]. Impaired vascular function has emerged as an important common denominator of age-related conditions [2]. Dietary interventions that could target these age-related conditions are therefore of great interest. Compared to the wealth of knowledge about the impact of dietary interventions on peripheral vascular function and CVD risk [3,4], not much is however known about diet-induced effects on vascular function in the brain and cognitive performance. Given the role of brain vascular function in the onset of cognitive decline and dementia [5,6], this could be of relevance for dietary intervention strategies.

In recent years, there has been a growing focus on the potential cognitive benefits of dietary anthocyanins [7]. These water-soluble

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flavonoids are important antioxidants, which are thought to be responsible for the beneficial health effects of berries, such as blueberries, bilberries and chokeberries [8]. Previously, we have reported beneficial effects of an anthocyanin-rich Aronia melanocarpa extract (AME) on cognitive performance. Specifically, in an intervention study with healthy middle-aged adults, daily 90 mg AME intake (providing 16 mg anthocyanins) for 24 weeks improved psychomotor speed as compared to a placebo [9]. Moreover, in a short-term trial involving healthy young adults we have also observed enhanced attention and psychomotor speed after one week of high dose AME supplementation (daily 750 mg providing 180 mg anthocyanins) [10]. Effects of berry anthocyanins have already been systematically reviewed, and we have concluded that dietary anthocyanins may improve cognitive performance [11]. Furthermore, this systematic review also focused on mechanisms underlying beneficial effects of berry anthocyanins on peripheral vascular function [11]. Effects on vascular function in the brain are however not clear. In a review by Rees et al. [12], mixed results on flavonoid-rich foods on brain vascular function were reported, which could be explained by differences in study design, flavonoid sources, dosage, and the focus on specific predefined brain areas. Further, in a trial by Wood et al. [13], a 12-week supplementation with wild blueberry (300 mg anthocyanins) improved endothelial function and cognitive performance, but cerebral blood flow (CBF) - a marker of brain vascular function [14] - did not change. CBF was however indirectly assessed using transcranial Doppler ultrasound. Well-controlled studies using more sensitive methods to directly assess (regional) CBF, including arterial spin labeling (ASL) magnetic resonance imaging (MRI), are still missing.

Therefore, in this randomized, double-blind, placebo-controlled cross-over study, the aim was to investigate effects of six weeks of 160 mg AME supplementation (40 mg 13cyanins) on brain vascular function, quantified as CBF using ASL-MRI. Older adults with overweight or obesity were included as they are at increased risk of cognitive impairment [15]. Moreover, cognitive performance was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB), while cerebral perfusion and different characteristics of the peripheral vascular tree (i.e., endothelial function and retinal microvascular calibers) were also quantified as secondary study outcomes.

2. Methods

2.1. Study population

Apparently healthy older men and postmenopausal women were recruited through local advertisements and social media. Moreover, study participants who participated in our previous trials that gave permission to be contacted for future studies were approached. Participants were invited for a screening visit to evaluate their eligibility by means of a medical questionnaire and an MRI safety screening list. In addition, anthropometrics and office blood pressure were measured, and a fasting blood sample was collected. Participants were eligible if they met the following inclusion criteria: aged 55–75 years old; body mass index (BMI) between 25 and 35 kg/m^2 (overweight or obese); fasting plasma glucose <7.0 mmol/L; fasting serum total cholesterol (TCH) < 8.0 mmol/L; fasting serum triacylglycerol (TAG) < 4.5 mmol/L; systolic blood pressure (SBP) < 160 mmHg; diastolic blood pressure (DBP) < 100 mmHg; stable body weight (<3 kg weight gain or loss within three months); and no blood donation from eight weeks before the start and during the study. Exclusion criteria were medical conditions that interfered with study endpoints (such as CVD or type-1 or type-2 diabetes); use of medication or dietary supplements that may influence study endpoints (such as medication to treat blood pressure, lipid or glucose metabolism); current smoker or smoking cessation <12 months; abuse of alcohol (more than 20 alcoholic units per week) or drugs; MRI contraindications; left-handedness; allergy to study product; and participation in another trial within one month before screening. All participants gave written informed consent before data collection. The study was approved by the Medical Ethics Committee of University Hospital Maastricht and Maastricht University (METC azM/UM) and performed at the University of Maastricht between June 2022 and August 2023 in accordance with the Declaration of Helsinki. The study was registered online at ClinicalTrials.gov (NCT 05268133).

2.2. Study design

A randomized, double-blind, placebo-controlled, cross-over study was performed. Participants were allocated to six weeks of AME or placebo intervention in a random order, separated by a wash-out period of at least six weeks. The study duration was based on a previous study that observed the most pronounced change in cognitive performance following an intervention duration of six weeks [9]. At baseline and after six weeks of both intervention and placebo, participants visited the Metabolic Research Unit Maastricht (MRUM). At baseline and during the follow-up study visits, anthropometric parameters were assessed and fasted blood samples were collected. Subsequently, at both follow-up study visits, vascular and retinal microvascular measurements were carried out, followed by assessments of cognitive performance (CANTAB). Next, at the Scannexus research facility, brain vascular function was quantified using ASL-MRI. Finally, various questionnaires on mood, quality of life, sleep, stress, and dietary intake were completed.

All study visits were performed in the morning in quiet and darkened rooms that were temperature controlled at 20 °C, in a fasted state, and occurred at the same time of the day. Participants received a list of anthocyanin-rich foods to refrain from during the study period. In addition, they were instructed to arrive in a fasted state in the MRUM the morning of the study visits and to abstain from vigorous physical activity and alcohol consumption for two days prior to the visits.

An electronic data capture system (Castor EDC, Amsterdam, the Netherlands) was used for data collection and the study was monitored by the Clinical Trial Center Maastricht (CTCM). Randomization was carried out by an independent researcher using Castor EDC, including random and concealed block sizes, and stratification for sex.

2.3. Intervention

During the six-week intervention period with AME, participants consumed one capsule with 200 mL water per day before breakfast providing 160 mg AME (BioActor BV, Maastricht, the Netherlands). The AME contained 40 mg (25 %) anthocyanins, consisting of 17 % cyanidin-3-galactoside and 8 % other cyanidin-3-glycosides (i.e., cyanidin-3-arabinoside, cyanidin-3-xyloside, and cyanidin-3-glucoside) and was kindly provided by BioActor BV (Brainberry®; Maastricht, the Netherlands). For the dosage, we focused on a comparable study in terms of intervention and peripheral vascular outcomes that observed improved FMD after 12 weeks of intervention with 30 mg anthocyanins [16]. Capsules containing 160 mg cellulose were used as placebo. Both the AME and placebo capsules were opaque (Swedish orange) and identical in appearance. The jars were blinded, displaying only the participant number and the intervention period (e.g., PP01 period 1) on

the label. Participants were instructed to note daily capsule intake and any deviations in a supplementation logbook. The capsule jars each contained 60 capsules of which 42 had to be consumed (one capsule/day for 6 weeks), to allow for the determination of compliance. Remaining capsules at the end of each intervention period were returned to the study facility to check compliance, which was considered valid if > 85 %.

2.4. Brain vascular function

After 15 min of rest in a supine position, MRI measurements were carried out with a 3 T MAGNETOM Prisma Fit MRI-system and a 64-channel head-neck coil (Siemens Medical Solution, Erlangen, Germany) at the Scannexus research facility in Maastricht. First, a high-resolution anatomical 3D magnetization-prepared rapid acquisition with gradient echo (MPRAGE) scan was performed (TR 2400 ms, TE 2.19 ms, TI 1040 ms, 1.0 mm isotropic resolution, 8° flip angle and 160 sagittal slices), and a labeling plane was placed perpendicular to the vertebral and carotid arteries, based on an angiogram. Pseudo-continuous ASL (pCASL) was used to measure CBF, as previously described [17]. In short, a background-suppressed segmented three-dimensional gradient and spin echo readouts were used (TR 4300 ms, TE 13.6 ms, GRAPPA 2, labeling duration 1750 ms, post-labeling delay 2000 ms, segmentation factor 6, ten label-control repetition with 19 slices each and 3.0 mm isotropic voxel resolution). Individual pCASL-images were distortion corrected with TopUp using M_0 images with opposite phase-encoding direction. CBF quantification was performed following the ASL White Paper [18], using FSL (Version 6.0) and the BASIL toolbox (Version 4.0.15) [19,20]. Furthermore, the used labeling efficacy was 0.64 (four background suppression pulses; 0.934), the gray matter T_1 was 1330 ms, and hemoglobin blood concentrations of participants measured during the visits were used as a correction. CBF was averaged in predefined regions: whole-brain, gray-matter, cortical and subcortical after Boundary-Based co-registration to the MPRAGE image, which was segmented using Volbrain [19]. Observed minimal detectable changes in CBF were approximately 6 mL/100 g/min (95 % confidence).

2.5. Cognitive performance

Cognitive performance was assessed in a quiet room using validated and computerized assessments from CANTAB on a digital touchscreen tablet (iPad, 5th generation, Apple) [21]. The attention and psychomotor speed, memory, and executive function domains were assessed, of which an overview is provided in Table S1. In short, the motor screening task (MOT) was used first to get familiarized with the CANTAB system but not used for further analyses. Attention and psychomotor speed were measured with the five-choice reaction time (RTI) test. Memory was assessed with the delayed matching to sample (DMS) test and the paired associates learning (PAL) test. Executive function was determined with the multitasking (MTT) and the spatial working memory (SWM) test.

2.6. Questionnaires

Mood was assessed with the single-item Affect grid [22], non-specific stress with the 10-item Perceived Stress Scale (PSS) [23], quality of life (QOL) with a 32-item QOL-questionnaire [24], and sleep quality with the Pittsburgh Sleep Quality Index (PSQI) [25]. A validated food frequency questionnaire (FFQ) was completed at the end of each intervention period to estimate dietary intake during both 6-week periods, based on the Dutch Food Composition Database [26].

2.7. Vascular endothelial function

All endothelial function measurements were carried out after a 15-min acclimatization period in supine position. Office brachial systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) were determined in fourfold, of which the first measurement was disregarded, and the three remaining measurements were averaged (Omron Intellisense M7, Nieuwegein, the Netherlands). Using the mean SBP and DBP, mean arterial pressure (MAP) was determined.

Ultrasound echography in B-mode using a 13-MHz transducer (MyLab Gamma, Esaote, Maastricht, the Netherlands) with continuous recording was used to assess FMD [27]. After 3 min of a baseline resting period, distal hypoxia was induced by inflating a pneumatic cuff around the forearm to 200 mmHg for 5 min, followed by 5 min of a post-occlusive reactive hyperemia response. The FMD was analyzed using a custom-written Matlab program with automated edge-detection and wall tracking (MyFMD; Dr. AP. Hoeks, Dept of Biomedical Engineering, Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands). The FMD response was quantified as the maximal percentage brachial artery diameter change post-occlusion relative to the baseline brachial artery diameter. The minimal detectable change in FMD in the present study population was approximately 4 %-point.

Furthermore, ultrasound echography was used to determine the carotid artery reactivity (CAR) response to a cold pressure test. The left common carotid artery was visualized proximal to the bulbous. The test consisted of a 1-min baseline period and 3 min of immersion of the left hand in an ice water bucket (4 °C). Images were analyzed using MyFMD software as described above. The baseline carotid artery diameter was averaged over the first minute and diameters were averaged per 20-s intervals during immersion. From this, the maximal percentage change in post-immersion diameter relative to baseline was determined [28]. The observed minimal detectable change in CAR was about 5 %-point.

2.8. Cerebral perfusion

Transcranial Doppler (TCD) ultrasound measurements (MultiDop T, DWL, Compumedics Germany CmbH, Singen, Germany) were carried out to assess cerebral perfusion, which is an indirect measurement of CBF. Two 2-MHz ultrasound probes were placed on the left and right temporal bone acoustic window to locate the middle cerebral artery using a DiaMon probe holder (DWL, Compumedics Germany CmbH, Singen, Germany). Readings of blood flow velocity (BFV) - with an observed minimal detectable change of approximately 15 cm/s - and pulsatility index (PI) were continuously collected for 5 min at baseline, while the participant was seated.

2.9. Retinal microvascular calibers

Retinal images of the optic disc were taken using a fundus camera (Topcon TRC-NW-300, TopCon Co., Tokyo, Japan) [27]. Retinal microvascular calibers were determined using Interactive Vessel Analyzer software (IVAN, University of Wisconsin, Wisconsin, USA). The diameters of three arteriolar and three venular segments were determined, and images from both study periods were analyzed simultaneously to ensure that the selected segments were identical in all images of a participant. Using the Parr-Hubbard formula [29], the mean central retinal arteriolar and

venular equivalents (CRAE and CRVE) and the arteriolar-to-venular ratio (AVR) were calculated. Retinal AVR showed a minimal detectable change of 0.04.

2.10. Statistical analyses

Data are presented as means ± standard deviations (SDs) unless indicated otherwise. Non-normally distributed outcomes were reported as median and interquartile ranges (IQR). To detect a 7.5 % change in the primary study outcome parameter CBF, a within-subject variability of 12 %, a power of 90 % and a two-sided alpha of 0.05, it was calculated that a total of 27 study participants were required [30]. To account for a drop-out rate of 10 %, a total of 30 study participants were included. The main hypothesis for the cognitive outcomes was that executive function would improve. A sample size of 27 participants was also sufficient to achieve a power >80 % to detect changes of at least 5 % within the executive function domain, using a two-sided alpha of 0.05.

For regional CBF outcomes, voxel-wise comparison was performed after co-registration to the Montreal Neurological Institute (MNI; 2 mm) using a repeated measures mixed effects analysis with a general linear model with a single-group paired difference (FLAME stage 1 and 2), a Z-threshold of 2.3 ($p < 0.05$) and a voxel connectivity of 26. Family-wise error correction was performed based on smoothness estimates. Voxel-wise interference was performed on the whole-brain, excluding cerebellum, without selection of predefined brain regions. The location of significant clusters in the Harvard–Oxford (sub)cortical structural atlas was determined using Atlasquery.

For all outcomes, linear mixed models with random-intercept were performed. Period, sex, and intervention were used as fixed factors, study participant as random factor. Three-way (intervention*period*sex) and two-way (intervention*period, intervention*sex, period*sex) interactions were included to test for significance but omitted from the model if not significant following a top-down approach. Baseline values were included as covariate if the outcome was also measured at baseline. Carry-over effects were determined by including intervention order as fixed factor, which was not significant for any outcome and therefore omitted from the model. Statistical analyses were performed using IBM SPSS Statistics (26.0, IBM Corporation, Armonk, NY, USA). For all analyses, p-values <0.05 were considered statistically significant.

3. Results

3.1. Study participants

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study is shown in Fig. S1. In total, thirty-nine participants were assessed for eligibility, of which nine were excluded based on BMI ($n = 1$), blood pressure ($n = 1$), fasting plasma glucose ($n = 2$) or serum total cholesterol concentrations ($n = 1$), intake of medication interfering with the study outcomes ($n = 2$), non-MRI compatible implants ($n = 1$), or personal reasons ($n = 1$). As a results, thirty participants were included, and no participants dropped out during the study. For one participant, MRI measurements could not be performed due to unforeseen claustrophobia, and MRI data from three study participants were excluded from the analyses due to insufficient quality. Data from one participant were excluded for the two cognitive tests in the executive function domain (MTT and SWM) due to a measurement error during the execution of these tests. Furthermore, four FMD and sixteen CAR measurements could not be analyzed due to problems with the recording of the echo images. Lastly, retinal microvascular calibers could not be analyzed for six participants due to insufficient image quality.

Baseline characteristics can be found in Table 1. Participants (17 men and 13 women) were 65 years old (range: 55–74) and had an average BMI of 28.3 ± 2.7 kg/m^2. No serious adverse events or protocol deviations were reported, and the study product was well-tolerated. Compliance was also excellent based on the number of returned capsules with a median of 100 % (IQR: 98–100 %).

3.2. Anthropometrics and blood pressure

Anthropometric and blood pressure measurements including body weight, waist and hip circumferences (WC and HC), waist-hip-ratio (WH-ratio), office blood pressure (SBP, DBP, MAP) and HR can be found in Table 2. Body weight, WC and WH remained stable during the whole study and changes did not differ between groups (all $p < 0.05$). Similarly, blood pressure and HR were not significantly different after AME supplementation as compared to placebo. Furthermore, no significant differences in energy and nutrient intake, as assessed with the FFQ, were observed following the AME and placebo periods (Table S2).

3.3. Brain vascular function

As compared to placebo, AME did not affect whole-brain and gray matter CBF, and the CBF in cortical and subcortical brain regions also did not change (Table 3 and Fig. S2). In the voxel-wise analysis, significantly lower regional CBF was observed in one cluster following AME supplementation, compared to placebo (Table 3). This cluster had a volume of 992 mm^3 (124 voxels) and CBF decreased by 4.4 ± 3.6 mL/100 g brain tissue/min (Peak MNI coordinates: X = 29, Y = 29.7, Z = 64; p = 0.004). Based on the Harvard–Oxford atlas, the average probability of location was the right insular cortex (30.8 %), temporal lobe (9.8 %), frontal orbital cortex (4.0 %), and planum polare (1.8 %) (see Fig. 1).

3.4. Cognitive performance

Results of the cognitive performance assessments following AME and placebo supplementation are summarized in Table 4. Within the domain of executive function, significant improvements in cognitive performance were observed. Specifically, a reduction of 20 % (−3; 95 % CI: −5 to −1; p = 0.006) in between errors (incorrectly revisiting an already opened box) and a similar reduction of 20 % (−3; 95 % CI: −5 to −1; p = 0.006) in total errors (overall count of incorrect box opening) were observed on the spatial working memory test after AME supplementation, as compared to placebo. These results indicate that errors were not repeated within the same trial. No differences between AME supplementation and placebo were observed for tests

Table 1
Baseline participant characteristics[a].

	Participants
Men/Women (%)	57/43
Age (years)	65 (range: 55–74)
BMI (kg/m^2)	28.3 ± 2.7
Glucose (mmol/L)	5.9 ± 0.4
TAG (mmol/L)	1.5 ± 0.6
TCH (mmol/L)	5.6 ± 1.1

Abbreviations: BMI: body mass index; TAG: triacylglycerol; TCH: total cholesterol.
[a] Values are means ± SDs unless indicated otherwise; n = 30.

Table 2
Anthropometrics following AME and placebo supplementation in older adults[a].

	AME		Placebo		Intervention effect[b]
	Baseline	After 6 weeks	Baseline	After 6 weeks	
Body weight (kg)	85.3 ± 8.7	85.3 ± 8.7	85.4 ± 9.0	85.2 ± 9.4	0.2 [-0.4 – 0.7], p = 0.498
WC (cm)	98 ± 7	99 ± 7	99 ± 7	99 ± 7	0 [-1 – 1], p = 0.401
HC (cm)	110 ± 8	110 ± 7	110 ± 7	110 ± 7	0 [-2 – 1], p = 0.413
WH ratio	0.89 ± 0.09	0.90 ± 0.08	0.90 ± 0.08	0.90 ± 0.08	0.01 [0.01–0.02], p = 0.259
SBP (mmHg)	130 ± 15	125 ± 17	130 ± 17	127 ± 13	−2 [-5 – 2], p = 0.367
DBP (mmHg)	81 ± 9	79 ± 8	81 ± 10	79 ± 8	−1 [-3 – 1], p = 0.222
MAP (mmHg)	98 ± 10	94 ± 10	97 ± 11	95 ± 9	−1 [-3 – 1], p = 0.183
HR (bpm)	64 ± 9	64 ± 9	62 ± 8	64 ± 9	−1 [-4 – 2], p = 0.576

Abbreviations: BMI: body mass index; DBP: diastolic blood pressure; HC: hip circumference; HR: heart rate; MAP: mean arterial pressure; SBP: systolic blood pressure; WC: waist circumference; WH: waist-hip ratio.
[a] Values are means ± SDs; n = 30.
[b] Linear mixed model analysis with random-intercept. Time, period, sex, and intervention were used as fixed factors, and participant as random factor. P-values for the intervention effect between AME and placebo intervention (mean difference [95 % CI]) were reported.

Table 3
Cerebral blood flow (CBF, mL/100 g brain tissue/min) following AME and placebo supplementation in older adults[a].

	AME	Placebo	Intervention effect[b,c]
Whole brain CBF	41.8 ± 9.2	42.1 ± 8.5	−0.4 [-5.0 – 4.3], p = 0.875
Gray matter CBF	51.5 ± 10.9	51.9 ± 10.3	−0.4 [-6.0 – 5.3], p = 0.895
Cortical CBF	55.6 ± 11.7	56.1 ± 11.1	−0.5 [-6.6 – 5.6], p = 0.862
Subcortical CBF	33.8 ± 8.2	34.3 ± 8.4	−0.6 [-5.1 – 3.9], p = 0.785
Cluster 1 CBF	36.3 ± 7.9	40.6 ± 7.7	−4.4 ± 3.6, p = 0.004

Abbreviations: CBF: cerebral blood flow.
[a] Values are means ± SDs; n = 26.
[b] Linear mixed model analysis with random-intercept for regional approach. Period, sex, and intervention were used as fixed factors, and participant as random factor. P-values for the intervention effect between AME and placebo intervention (mean difference [95 % CI]) were reported.
[c] For voxel-wise comparison, repeated measured effects analysis using a general linear model with a single group paired difference (FLAME stage 1 and 2) were applied and family-wise corrected. P-values for the intervention effect between AME and placebo intervention (mean difference ± SD) were reported.

representing the attention and psychomotor speed domain, and the memory domain (all p > 0.05).

Besides cognitive performance, other perceivable benefits were also investigated by means of questionnaires. Mood, quality of life, stress, and sleep quality did not differ between AME and placebo (all p > 0.05) (Table S3).

3.5. Cerebral perfusion and peripheral vascular function

In Table 5, effects of AME supplementation on cerebral perfusion and vascular function are shown. There were no changes in BFV and PI as measured by transcranial Doppler ultrasound. Also, no significant effects on vascular endothelial function were observed. Specifically, there was no change in FMD and CAR between interventions. Moreover, no differences in retinal microvascular calibers (i.e., CRAE, CRVE and AVR) were observed after AME supplementation as compared to placebo (all p > 0.05).

4. Discussion

In this randomized, double-blind, placebo-controlled, crossover study involving thirty older adults with overweight or obesity, we examined effects of AME supplementation on brain vascular function, quantified as CBF with ASL-MRI. No serious adverse events were reported, the study product was well-tolerated, and compliance was considered excellent. We observed that AME supplementation did not affect CBF in predefined brain regions, but voxel-wise analyses revealed a decreased CBF in one brain cluster located in the right insular cortex. Furthermore, cognitive performance was improved in the executive function domain, but performance within the domains of memory and psychomotor speed did not change. No effects were observed on characteristics of the peripheral vascular tree, blood pressure and anthropometric measurements.

Regional increases in CBF were not observed, which is in line with findings observed in a long-term blueberry intervention study by Wood et al. [13], where transcranial Doppler ultrasound was used as an indirect measure of CBF. However, this method primarily assesses perfusion rather than blood flow [31], does not capture regional CBF, and was also unaffected in the current trial.

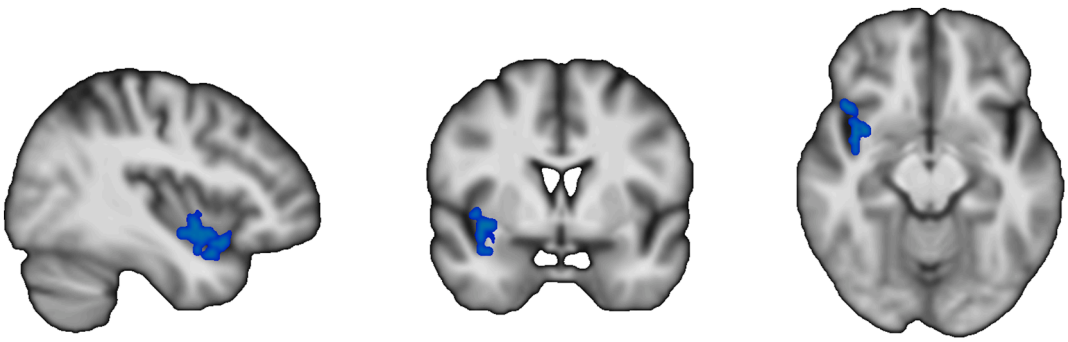

Fig. 1. Results of voxel-wise comparisons including all acquired cerebral blood flow (CBF) data in the 3-dimensional Montreal Neurological Institute (MNI) template in older adults. CBF decreased in one cluster following AME as compared to placebo (family-wise error corrected, n = 26). This cluster had a volume of 992 mm^3 (124 voxels) and CBF decreased by 4.1 ± 3.5 mg/100 g brain tissue/min (Peak MNI coordinates: X = 29, Y = 29.7, Z = 64; P = 0.004). Based on the Harvard–Oxford atlas, the average probability of location was the right insular cortex (30.8 %), temporal lobe (9.8 %), frontal orbital cortex (4.0 %), and planum polare (1.8 %).

Table 4
Cognitive performance following AME and placebo supplementation in older adults[a].

	AME	Placebo	Intervention effect[b]
Attention and psychomotor speed			
RTI — movement time (ms) [c]	335 ± 68	325 ± 62	10 [-10 – 29], p = 0.325
RTI — reaction time (ms) [c]	399 ± 46	404 ± 45	−6 [-14 – 3], p = 0.186
Memory			
DMS — total correct (%) [c]	82.8 ± 8.2	84.7 ± 7.4	−1.9 [-6.0 – 2.2], p = 0.350
PAL — first attempt memory score [c]	11.2 ± 3.4	12.0 ± 3.8	−0.8 [-2.1 – 0.5], p = 0.199
PAL — total errors [c]	16 ± 11	17 ± 13	−1 [-5 – 3], p = 0.704
Executive function			
MTT — incongruency cost [d]	130 ± 76	113 ± 51	16 [-11 – 43], p = 0.232
MTT — median latency (ms) [d]	801 ± 111	798 ± 107	1 [-27 – 29], p = 0.932
MTT — multitasking cost [d]	292 ± 144	258 ± 120	33 [-28 – 94], p = 0.278
MTT — total errors [d]	8 ± 11	7 ± 8	0 [-3 – 4], p = 0.875
SWM — between errors [d]	12 ± 8	15 ± 9	−3 [-5 to −1], p = 0.006
SWM — total errors [d]	12 ± 8	15 ± 9	−3 [-5 to −1], p = 0.006
SWM — strategy score [d]	7.5 ± 3.2	7.5 ± 3.1	−0.1 [-0.9 – 0.7], p = 0.822

Abbreviations: DMS: delayed matching to sample test; MTT: multitasking test; PAL: paired associates learning test; RTI: reaction time test; SWM: spatial working memory test.
[a] Values are means ± SDs.
[b] Linear mixed model analysis with random-intercept. Period, sex, and intervention were used as fixed factors, and participant as random factor. P-values for the intervention effect between AME and placebo intervention (mean difference [95 % CI]) were reported.
[c] n = 30.
[d] n = 29.

Table 5
Cerebral perfusion and peripheral vascular function following AME and placebo supplementation in older adults[a].

	AME	Placebo	Intervention effect[b]
Cerebral perfusion			
BFV (cm/s) [d]	42.74 ± 11.58	42.81 ± 14.93	0.24 [-4.49 – 4.97], p = 0.915
PI [d]	0.90 ± 0.19	0.89 ± 0.15	0.01 [-0.07 – 0.09], p = 0.773
Vascular endothelial function			
Baseline brachial artery diameter (mm) [c]	3.6 ± 0.7	3.6 ± 0.6	0.0 [-0.1 – 0.1], p = 0.519
FMD% [c]	3.8 ± 1.9	4.2 ± 1.9	−0.4 [-1.3 – 0.4], p = 0.327
Baseline carotid artery diameter (mm) [d]	6.7 ± 1.2	6.7 ± 1.1	−0.0 [-0.4 – 0.3], p = 0.801
CAR% [d]	3.3 ± 2.1	4.2 ± 2.3	−0.9 [-2.5 – 0.8], p = 0.295
Retinal microvascular calibers			
CRAE (μM) [e]	120 ± 17	122 ± 18	−2 [-5 – 0], p = 0.071
CRVE (μM) [e]	224 ± 16	222 ± 26	3 [-4 – 9], p = 0.398
Retinal AVR [e]	0.53 ± 0.06	0.54 ± 0.07	−0.01 [-0.02 – 0.00], p = 0.107

Abbreviations: AVR: arteriolar-to-venular ratio; BFV: blood flow velocity; CAR: carotid artery reactivity; CRAE: central retinal arteriolar equivalent; CRVE: central retinal venular equivalent; FMD: brachial artery flow-mediated vasodilation; PI: pulsatility index.
[a] Values are means ± SDs.
[b] Linear mixed model analysis with random-intercept. Period, sex, and intervention were used as fixed factors, and participant as random factor. P-values for the intervention effect between AME and placebo intervention (mean difference [95 % CI]) were reported.
[c] n = 26.
[d] n = 14.
[e] n = 24.

Thus, the focus should preferably be on direct methods to assess regional CBF, such as ASL-MRI. For example, Bowtell et al. [32] already assessed CBF using ASL-MRI and observed significant increases in parietal and occipital lobes after 12 weeks of blueberry supplementation (387 mg anthocyanins) in older adults [32]. It is important to highlight that the anthocyanin dosage used was tenfold higher and the study duration was twice as long, compared to this study. Furthermore, CBF was only quantified in predefined brain regions, which is an important limitation as other brain regions may have been missed. To the best of our knowledge, we were the first to investigate effects of an anthocyanin-rich intervention on CBF using a voxel-wise approach, and we expected to observe increased CBF in brain regions that are important for cognitive processes based on previous dietary intervention studies performed within our research group [30,33]. However, the dosage used here may not have been sufficient to result already in improved (brain) vascular function within a period of six weeks. Indeed, even though cognitive improvements have already been observed at a lower dosage, earlier trials with anthocyanins observing improvements in vascular function had a longer intervention period (12–24 weeks) and/or a higher dosage (302–364 mg) [13,16,34,35]. Furthermore, the composition of the intervention product plays a crucial role in the effectiveness of the intervention [36]. For instance, the antioxidant capacity in dietary extracts can be lower as compared to whole foods due to the absence of other (synergistic) compounds and variations in metabolite concentrations or compositions.

Instead of an increased regional CBF, we observed a significantly decreased CBF in a cluster located mainly in the right insular cortex. The underlying relevance of this finding remains unclear. The insula consists of four functionally distinct regions, which are activated by sensorimotor and olfactogustatory processing, regulation of negative emotions, and cognitive functions [37]. Possibly, a reduced CBF in this brain region might relate to an inhibitory control towards insular cortex-related functionalities, such as motivational decision-making, emotional processing and stress responses [38]. This reduction may affect the regulation of negative emotions, but this was not translated into an immediate functional benefit such as improved quality of life, mood, stress, or sleep within the duration of the study. Known physiological

mechanisms involved in blood flow changes include neurovascular coupling and synaptic plasticity of neuronal cells [39]. It has been suggested that neurovascular coupling could be irregular, absent or inverted in specific brain regions, which might indicate that blood flow may not directly reflect metabolic activity [40]. As such, it remains unclear what the implications of a decreased CBF in this specific brain region are.

Cognitive performance within the domain of executive function was improved as total errors and between errors were significantly reduced on the SWM test following AME supplementation, as compared to the placebo. These outcomes reflect improved spatial working memory and visuospatial information manipulation, which are required for cognitive tasks involving navigation, word or object recognition and problem-solving. Implementation of strategic thinking and multitasking, such as response inhibition were however not differentially affected. Improvements in similar outcomes within the domain of executive function have already been observed before in multiple anthocyanin intervention studies. Specifically, an acute blueberry intervention study in middle-aged adults noted improvements in the number of errors and response times on the Go/No-Go task [41]. In a long-term setting, an improved accuracy on task switching was also observed after 12 weeks of blueberry powder supplementation in older adults [13]. Furthermore, improved lexical access and inhibitory control were reported after 12 weeks of blueberry supplementation in middle-aged adults with subjective cognitive decline [42]. In contrast to the current study involving older adults, our recently completed AME trials involving healthy young and middle-aged adults did not show improvements in executive functioning, although attention and psychomotor speed was beneficially affected [9,10]. Based on the expected development and decline of cognitive abilities during the lifespan, different age groups could show varying effects within different cognitive domains. Indeed, attention and psychomotor speed starts declining more rapidly in adulthood, compared to memory and executive functioning [43]. Besides ageing, other risk factors such as overweight or obesity are known to be associated with impairments in executive function [44,45]. The combination of these risk factors, as seen in our study population, may also result in a greater decline in executive function, compared to other cognitive domains. Therefore, there may be more room for improvement within the executive function domain.

We did not observe significant improvements in vascular endothelial function, as assessed by FMD and CAR, or retinal microvascular calibers in this study. Moreover, blood pressure was not affected. This is in line with our previous studies on short-term [10] and long-term [9] AME supplementation in healthy adults. However, others have reported beneficial effects of anthocyanin supplementation on (peripheral) vascular function, especially regarding endothelial function [11]. For example, Istas et al. [16] observed improvements in FMD after 12 weeks of AME supplementation in healthy men. Similarly, 12 weeks of blueberry supplementation increased FMD in overweight and obese middle-aged adults [35]. As discussed before, it is however important to note that besides differences in the involved target population, there are also relevant disparities in the intervention duration and anthocyanin dosage, which could explain the contradictory results observed.

As CBF was not increased in brain regions that are important for cognitive processes, and the (peripheral) vascular function measurements that were included in this study remained unchanged, other underlying mechanisms must be involved in the regulation of AME-induced beneficial effects on cognitive performance. In vitro studies have shown that cyanidin-3-glucosides are able to pass the blood–brain barrier (BBB) in a time-dependent manner using a hCMEC/D3 cell human model [46]. Further, various anthocyanin metabolites can cross the BBB, which was determined both through intravenous injections [47] and dietary supplementation [48–50] in several animal studies. However, due to the invasive nature of measuring BBB passage, this has not been confirmed in humans yet. In the brain, anthocyanins may have direct effects, due to the antioxidant, anti-neuroinflammatory and anti-apoptotic properties of anthocyanins [51]. Potentially, these beneficial traits could play a role in the observed improvement in cognitive performance. Indeed, a link between neurodegeneration and neuroinflammation and cognitive performance has already been elucidated [52].

Strengths of this study were the randomized, double-blind, placebo-controlled cross-over design. We also included a gold standard non-invasive direct assessment of brain vascular function, through ASL-MRI. Furthermore, standardized and validated measurements for cognitive performance and various potential mechanisms of action, such as characteristics of the peripheral vascular tree, were incorporated. The present study was powered based on the primary outcome parameters CBF and cognitive performance, while we chose not to perform power calculations for the secondary outcomes. Another limitation is that anthocyanin metabolites in blood were not measured due to practical limitations, which could have provided more insight into the bioavailability and compliance of the intervention, as well as additional mechanistic insights. Furthermore, we chose to focus on a heterogenous study population consisting of apparently healthy older adults with overweight or obesity. Further studies are thus needed to assess effects in specific target groups, such as individuals with subjective or mild cognitive impairments.

In conclusion, six weeks of AME supplementation resulted in improved executive functioning in healthy older adults with overweight or obesity. However, memory and psychomotor speed did not change. Besides a statistically significant decrease in CBF in the right insular cortex, the relevance of which remains unclear, regional CBF in predefined brain regions and other potential mechanisms underlying the observed improvements in cognitive performance were not affected. Future research focusing on higher anthocyanin dosages and longer intervention durations is recommended to further elucidate dietary anthocyanin-induced cognitive benefits in humans.

Author contributions

Conceptualization: SA, JP, and PJJ; Methodology: SA, JP, and PJJ; Formal analysis: SA, KMR, and PJJ; Writing – original draft preparation: SA; Writing – review and editing: JP, KMR, and PJJ; Visualization: SA and KMR. PJJ had primary responsibility for final content. All authors have read and agreed to the published version of the manuscript.

No one eligible for authorship has been excluded from the list of authors.

Ethical approval and trial registration

The study protocol was reviewed and approved (NL-004153) by the Medical Ethics Committee of University Hospital Maastricht and Maastricht University (METC azM/UM), and was prospectively registered on ClinicalTrials.gov (NCT 05268133; https://clinicaltrials.gov/study/NCT05268133).

Declaration of generative AI and AI-assisted technologies

No generative AI or AI-assisted technologies were used in the writing, editing, or preparation of this manuscript.

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Conflict of interest

SA is an employee of BioActor BV. All other authors declare no conflict of interest.

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Data availability

Data presented in this manuscript are available from the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2025.106561.

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