Food & Function

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
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Cite this: *Food Funct.*, 2025, **16**, 8836

Cocoa flavanols alleviate early diastolic dysfunction by decreasing left atrial volume in a randomized double blinded trial in healthy older individuals

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Aims: Left atrial (LA) enlargement marks impaired cardiac filling and predicts future cardiovascular events. Dietary flavanols have been shown to reduce cardiovascular mortality, despite uncertain underlying mechanisms. In this study, we hypothesized that flavanol intake reduces LA volume in older individuals without cardiovascular diseases. *Methods*: In a substudy of the randomized, double-blinded Healthy Aging Through Dietary Intervention trial (NCT 05782309), we investigated the effects of cocoa flavanols on cardiac volumetry and diastolic function in healthy older individuals. LA and left-ventricular (LV) volumes as well as strain rates were measured by high-resolution cardiac magnetic resonance imaging before and after flavanol intake. *Results*: Sixty-three participants (59% male) aged ≥ 55 years received either 500 mg cocoa flavanols (containing 80 mg (−)-epicatechin) originating from cocoa extract (n = 30) or a control (n = 33) twice daily for 30 days. Flavanol intake counteracted subclinical cardiac dysfunction, evidenced by a 12.6 ± 3.5% reduction in maximal LA volume (p = 0.0063) and LA volume index (p = 0.0067) and ~4.4 ± 1.9% reduction in LV end-diastolic volume (LVEDV) (p = 0.049) and LVEDV index (p = 0.041). Flavanol intake did not influence strain, strain rate, and systolic function parameters, while the systolic blood pressure decreased by 7 mmHg [~4.7 ± 1.9% (p = 0.04)]. Blood pressure dynamics, gender or age of participants in the intervention group were not associated with LA volumetric changes. *Conclusion*: We provide evidence that cocoa flavanol intake mitigates early changes of diastolic dysfunction by reversing left atrial and left ventricular remodeling, thus providing novel insights into the mechanisms behind the beneficial cardiovascular effect of flavanol intake. The clinical trial registry number is NCT 05782309 (https://clinicaltrials.gov).

Received 16th June 2025,
Accepted 22nd September 2025

DOI: 10.1039/d5fo02589c

rsc.li/food-function

Introduction

The impaired relaxation pattern of the left ventricle is a common feature of the aging heart, causing increased filling pressures and consecutive LA remodeling and enlargement.[1] As these changes occur slowly and continuously, they are often not clinically visible in the early stages, and individuals remain asymptomatic. Clinical detection, especially of these incipient states, remains challenging.[2] To date, there is no known clinical, pharmacological or dietary intervention capable of reversing impaired cardiac relaxation patterns or diastolic dysfunction,[3] despite the possibility that up to 20% of individuals older than 45 years may experience some degree of diastolic dysfunction.[4] However, as filling pressures increase even further and the affected individuals transition from diastolic dysfunction to heart failure with preserved ejection fraction (HFpEF), they start experiencing the full spectrum of symptoms, including reduced exercise capacity, dyspnea, and edema accumulation. In addition to reflecting relaxation pressures in the left heart, LA enlargement has been verified and

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validated as a prognostic marker for future cardiovascular events in individuals with and without cardiovascular diseases.[5–7]

Dietary flavanols occur in various food groups, including fruits, tea, and cocoa-derived products.[8] The "COcoa Supplement and Multivitamin Outcomes Study (COSMOS)", a large-scale randomized clinical trial investigating the intake of cocoa flavanols from cocoa extract and multivitamins in over 20 000 individuals during a median follow-up of 3.6 years, showed a 27% reduction in cardiovascular death in the flavanol intake group.[9] Due to the growing evidence for cardiometabolic benefits of flavanols, the Academy of Nutrition and Dietetics released an intake recommendation of 400–600 mg of flavanols daily.[10] In fact, several vasoprotective properties, such as the improvement of endothelial dysfunction and blood pressure reduction by flavanol intake, are known.[11,12] Previously, we found that cocoa flavanols intake protected radial arteries against intima hyperplasia after catheterization-induced injury,[13] and improved cardiovascular fitness in healthy older individuals after a 30-day flavanol supplementation period.[14] In the present work, we sought to assess other potential mechanisms behind the beneficial cardiovascular effects of flavanols and hypothesized that 30-day intake of the same cocoa flavanol regimen would mediate beneficial changes in left atrial and left ventricular volumes, as surrogate parameters associated with diastolic dysfunction, and assessed using high-resolution CMR imaging, the gold standard method to assess cardiac volumetry,[15] in older, otherwise healthy individuals.

Methods

Study design and population

The present study represents a prespecified substudy of the randomized, double-blinded (participants and researchers), placebo-controlled, parallel-group Healthy Aging Through Dietary Intervention trial (clinicaltrials.gov registration number NCT 05782309). The original trial was performed in the Department of Cardiology of the University Hospital of Duesseldorf, Germany. Participants aged between 55 and 79 years were recruited from the local community *via* advertising banners in the hallways of the University Hospital of Duesseldorf and Heinrich-Heine University Duesseldorf. Participants received a 30-day intake of either a cocoa flavanols extract (2 × 500 mg daily per os, containing 80 mg of (–)-epicatechin per intake) or a control treatment (2 capsules, 2× day per os). Cocoa flavanols were defined as the sum of flavanol monomers and procyanidins with a degree of polymerization up to 7 (DP1–7), according to the AOAC2020.05 method[16] (SI Table S1). Flavanol monomers, including (–)-epicatechin, were assessed using AOAC2013.04 [17] (SI Table S1). While cocoa may contain flavanols with a degree of polymerization greater than 7, these procyanidins represent a smaller fraction of all procyanidins.[18] Theobromine (100 mg) and caffeine (30 mg) were included in equal amounts in both the intervention and control capsules to regulate for their influence on the study's endpoints. Their amount was lower than the proven one to induce cardiovascular effects.[19,20] Screened participants were excluded from the trial if they presented any cardiovascular, neurological, orthopedic, or metabolic disease or had any long-term drug intake. Treated hypertension was not considered an exclusion criterion. The primary endpoint of the Healthy Aging Through Dietary Intervention trial were changes in cardiopulmonary exercise capacity induced by 30-day cocoa flavanol intake. The results have been previously published by us.[14]

The current substudy analyzed changes in cardiac volumetry, as specified among the secondary endpoints of the Healthy Aging Through Dietary Intervention trial. The heart chamber volumes and diastolic cardiac function were assessed by high-resolution cardiac magnetic resonance (CMR) at baseline and after 30-day intake. The maximal left-atrial volume (LA_{max}) and the end-diastolic left-ventricular volume (LV_{EDV}) and their indexes (LAVI and LVI_{EDV}, respectively) normalized to body surface area (BSA) were defined as the primary endpoints of the current substudy. Systolic and diastolic blood pressures were defined as secondary endpoints of the present substudy. Upon enrollment, several baseline measurements were performed to warrant study eligibility. These included blood pressure, echocardiography, electrocardiography, physical examination, laboratory parameters electrolytes, blood count, and the HF parameter N-terminal pro b-type natriuretic peptide (NT-proBNP) *via* standardized venous punction from the cubital vein. All participants gave informed verbal and written consent before enrolment. The ethics committee of Heinrich-Heine University approved our study (Approval Number R5761R), which was carried out in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. The study was previously registered on clinicaltrials.gov (NCT 05782309). Study enrolment started in January 2019, and the measurements were completed by February 2021.

The data underlying this article will be shared on reasonable request to the corresponding author.

Randomization and intervention

Participants were randomized to the flavanol or control group with a double-blinded design. Randomization and allocation have been previously described in detail.[14] Briefly, the allocation was performed by an independent study nurse, and it was disclosed by telephone. In the flavanol group, capsule intake provided 1000 mg of cocoa flavanols containing 160 mg of (–)-epicatechin per day. The intake amount of flavanol was chosen based on a previous study, in which we showed that the maximum change in flow-mediated dilation (FMD) occurred at an intake amount of 820 mg flavanol, containing 112 mg (–)-epicatechin.[21] Participants from the control group received a flavanol-free, nutrient-matched control regimen. The detailed capsules composition is shown in SI Table S1. The capsules were sealed in containers, on which alphabetical codes were written double-blinded. Intake was per os and

twice daily (a total of 4 capsules per day) in both groups. Participants were instructed to ingest the capsules with meals (breakfast and dinner), as recommended in ref. 22. Mars, incorporated provided all capsules. Capsules containing cocoa flavanols were indistinguishable in appearance from the control capsules and were handed in non-transparent, sealed containers. This regimen was maintained for 30 days, and compliance was assessed by counting the left-over capsules and the documented intake directly by the subjects. Subjects were asked to continue their current lifestyle with the same level of activity and habitual diet until the follow-up date. The amount of flavanol intake within the habitual diet was not quantified. Measurements occurred before the first intake of test capsules (baseline) and one day after the last test capsules (follow-up). Unblinding was undertaken by an independent study nurse after the database release was approved and after the study was completed.

Cardiac magnetic resonance

CMR was performed on a 1.5 T MRI System (Achieva, Philips, Best Netherlands) using a 5-channel phased array coil as described previously.[23] After scout and reference scans, the functional and geometric assessment was performed using cine steady-state free precession images in standard long-axis geometries (two-, three- and four-chamber view) as well as in short-axis orientation with full ventricular coverage from base to apex (repetition time/echo time = 3.3/1.6 ms, flip angle = 60°, spatial resolution = 1.5 × 1.5 × 8 mm^3, 50 phases, two slices per breath-hold).

Dedicated software (Circle CVI 42, Circle Cardiovascular Imaging Inc., Calgary, AB, Canada) was used to automatically delineate ventricular and atrial contours and calculate volumes, strain, and strain rate. Volumes were further indexed to BSA (calculated automatically by the MRI system) to assess end-diastolic volume index (LVI_{EDV}), end-systolic volume index (LVI_{ESV}) and to assess the LV systolic functional parameters stroke volume index (SVi), cardiac index, and ejection fraction (EF). Global longitudinal strain (GLS), early and late longitudinal diastolic strain rate (GLSRe, GLSRa), as well as early and late circumferential diastolic strain rate (GCSRe, GCSRa) were derived from the integrated feature tracking algorithm. No significant manual corrections to the automated tracking were necessary.

Pulse wave velocity

Arterial pulse wave velocity (PWV) analysis was performed using applanation tonometry (SphygmoCor®, AtCor Medical, Australia). PWV was assessed *via* ECG-synchronized applanation tonometry of the left common carotid and femoral arteries. Distances were measured with a measuring band (difference in distance, Δd), and transit times were calculated from the latency between the R-wave and pulse wave onset (difference in time, Δt). PWV was then defined as PWV = $\Delta d/\Delta T$.

Blood pressure measurements

Peripheral blood pressure was measured automatically before CMR with an appropriate medical device (boso medicus, BOSCH + SOHN GmbH u. Co. KG). The measurement was performed on both brachial arteries in a supine position after 5 minutes of rest. The arithmetical mean was used for analyses.

Statistics

Data are presented as mean ± standard deviation (SD), unless otherwise stated. Baseline characteristics were compared either by unpaired *t*-test (normally distributed numerical data), Mann–Whitney *U* test (non-normally distributed numerical data), or Fisher's exact test (categorical data), as appropriate. Variables measured at baseline and follow-up were compared between the groups by repeated measurements two-way ANOVA with the Bonferroni *post hoc* test. To exclude an association between LA remodeling of the intervention group and gender, baseline blood pressure, and body-mass-index, we performed logistic regression analysis. We defined positive LA remodeling as a >15% reduction from initial LA volume, which has been previously used in clinical studies.[24] The sample size was calculated to correspond to the observed effects in FMD by a similar flavanol regimen, in which 30 days of flavanols induced a 30% improvement in flow-mediated dilation.[25] We used mean reference values for LA_{max} diameter according to Maceira *et al.*[26] of 73 ± 15 (SD) ml and expected a decrease in the intervention group of 17.5%. Considering an alpha level of 5% and a power of 80%, we calculated a sample size of 42. Including a drop-out rate of 10%, the final sample size was set for 47 participants. Since this was within our sample size initially calculated for analyses of flavanol on $VO2_{max}$, as the primary endpoint of the Healthy Aging Through Dietary Intervention trial,[14] no supplementary participants needed to be included for the current analysis.

P-Values <0.05 were considered statistically significant. Statistical analysis was performed using Prism 9 (GraphPad Software, San Diego, CA, USA).

Results

Baseline characteristics

Sixty-seven participants adhered to the criteria for inclusion. One participant did not consent to the study; two had contraindications for CMR. The remaining 64 participants were included in the study. Both the flavanol and the control capsules were well tolerated. Following the intervention, one participant from the flavanol group developed claustrophobia from the first CMR examination and was excluded from the final analysis. All other participants who were included followed the predetermined protocol up to the follow-up and were included in the study's final analysis. The flow chart of the study is shown in Fig. 1. Baseline characteristics showed no significant differences for age (p = 0.95), BMI (p = 0.15), and BSA (p = 0.79) between groups. Detailed baseline characteristics are shown in Table 1.

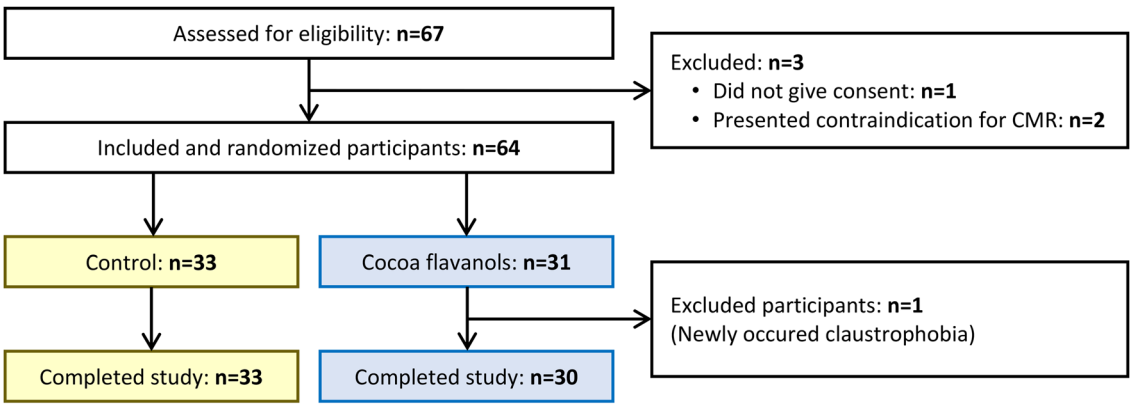

Fig. 1 CONSORT flow diagram.

Table 1 Baseline characteristics (N = 63). Values represent mean ± SD. (ACEI = angiotensin-converting-enzyme inhibitors, ARB = angiotensin receptor blockers, eGFR = estimated glomerular filtration rate, NT-proBNP = N-terminal pro–B-type natriuretic peptide)

Demographics	Control (n = 33)	Cocoa flavanols (n = 30)	p
Age, years	62.9 ± 6.5	63.0 ± 4.4	0.95
Male, n (%)	18 (55)	20 (63)	0.61
Height, cm	173.9 ± 8.3	177.6 ± 9.4	0.11
Weight, kg	81.1 ± 12.6	80.6 ± 13.4	0.87
Body mass index, kg m^{-2}	26.7 ± 3.1	25.5 ± 3.6	0.15
Body surface area, m^2	1.98 ± 0.2	2.0 ± 0.2	0.79
Systolic blood pressure, mmHg	138.6 ± 16.0	137.9 ± 15.3	0.87
Diastolic blood pressure, mmHg	80.7 ± 9.7	80.3 ± 8.1	0.85
Heart rate, 1 min^{-1}	65.5 ± 10.1	62.7 ± 8.0	0.23
Comorbidities			
Type 2 diabetes mellitus, n (%)	2 (6)	1 (3)	>0.9999
Hyperlipidemia, n (%)	7 (21)	5 (17)	0.75
Hypertension, n (%)	14 (42)	12 (40)	>0.9999
Antihypertensive medication			
ACEI or ARB, n (%)	13 (39)	11 (37)	>0.9999
Beta-Blocker, n (%)	2 (6)	0 (0)	0.49
Calcium antagonists, n (%)	3 (9)	1 (3)	0.61
Thiazide-type diuretics, n (%)	2 (6)	0 (0)	0.49
Laboratory values			
Hemoglobin, g dl^{-1}	14.0 ± 0.8	13.6 ± 2.5	0.77
eGFR, ml min^{-1}/173 m^2	86.3 ± 12.1	87.6 ± 14.4	0.72
NT-proBNP, pg ml^{-1}	84.3 ± 64.8	69.4 ± 54.5	0.25

Baseline cardiovascular function

CMR revealed similar LV systolic function at baseline between the two groups, mirrored by EF (65 ± 6.6% in the control *versus* 65.2 ± 7.1% in the flavanol group, p = 0.91), SV (94.7 ± 23.3 ml in the control *versus* 95.5 ± 17.6 ml in the flavanol group, p = 0.88) and CI (3.24 ± 0.78 l min^{-1} in the control *versus* 3.07 ± 0.56 l min^{-1} in the flavanol group, p = 0.34). In terms of afterload, blood pressure was comparable between groups (systolic BP: 137.2 ± 17.4 in the control *versus* 137.9 ± 15.3 mmHg in the flavanol group, p = 0.85; and diastolic BP: 80.7 ± 9.7 in the control *versus* 80.2 ± 8.1% in the flavanol group, p = 0.85). By applanation tonometry, we saw equivalent PWV of the two groups (9.0 ± 2.2 in the control *versus* 9.0 ± 2.2 m s^{-1} in the flavanol group, p = 0.64).

Analysis of cardiac volumes showed similar LA_{max} (p = 0.46), LAVI (p = 0.32), LV_{EDV} (p = 0.73), and LVI_{EDV} (p = 0.76). Longitudinal SRe and circumferential SRe were comparable (p = 0.48 and p = 0.90). Altogether, these baseline cardiac characteristics mirrored well-balanced groups.

Cocoa flavanols improve markers of diastolic function

LA_{max} decreased by ~12.6 ± 3.5% in the flavanol group (64.3 ± 17.9 ml at baseline *versus* 56.2 ± 19.5 ml at follow-up, Fig. 2A, p = 0.0063). Similarly, flavanol intake reduced LAVI by ~12.6 ± 3.5% (SEM) (32.1 ± 7.2 ml m^{-2} at baseline *versus* 28.1 ± 8.9 ml m^{-2} at follow-up, Fig. 2B, p = 0.0067). The control regiment did not affect LA_{max} (69 ± 23.7 ml at baseline *versus* 69.3 ± 25.5 ml at follow-up, Fig. 2A, p = 0.99) or LAVI (34.8 ± 11.3 ml m^{-2} at baseline *versus* 35.1 ± 12.5 ml m^{-2} at follow-up, Fig. 2B, p = 0.97). In line with atrial changes, participants from the flavanol group had a lower LV_{EDV} by ~4.4 ± 1.9% (SEM) after intervention (147.8 ± 29 ml at baseline *versus* 141 ± 29.5 ml at follow-up, Fig. 2C, p = 0.0499) and LVI_{EDV} by ~4.4 ± 1.9%

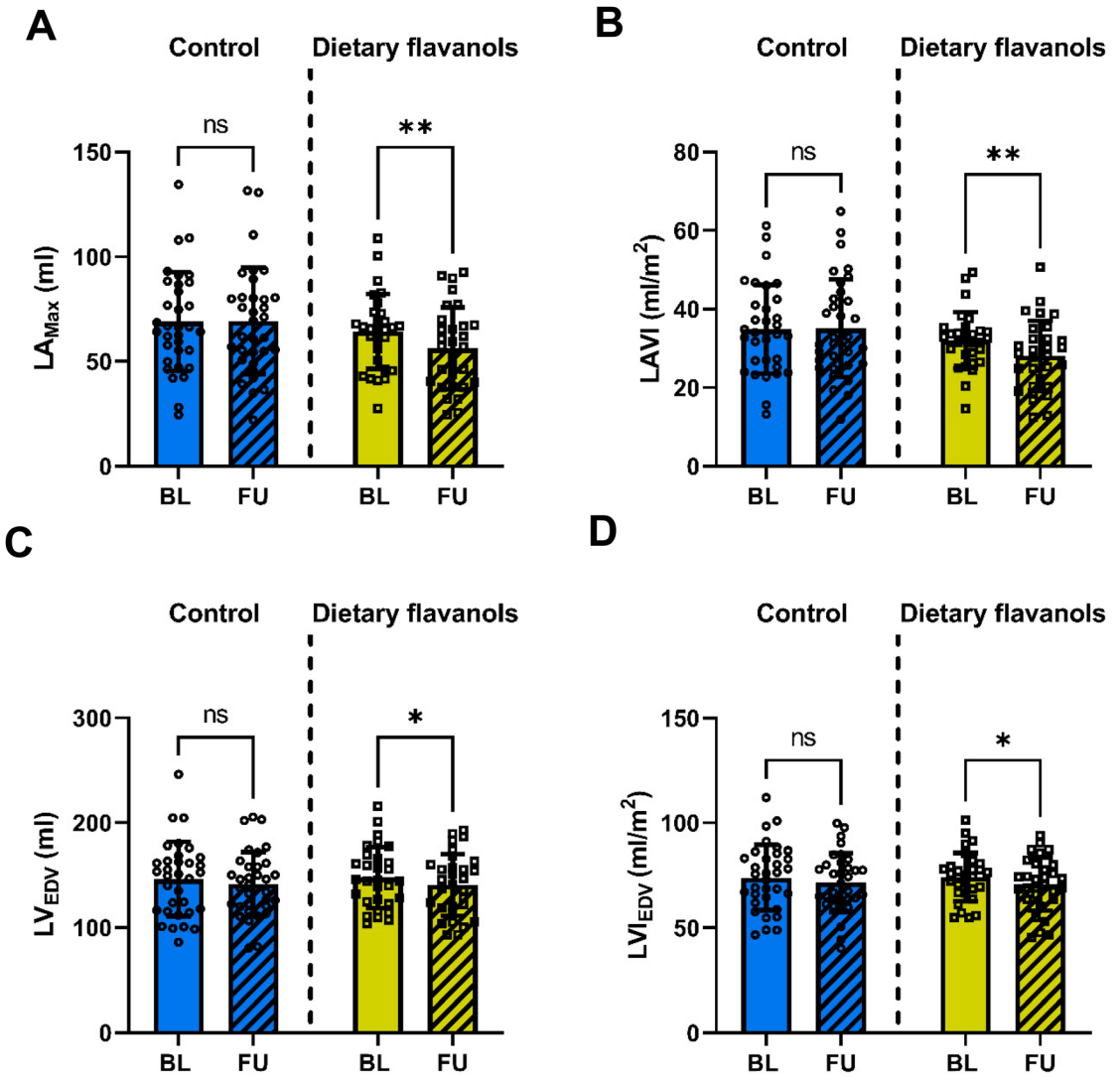

Fig. 2 Cocoa flavanols reduce maximal left-atrial volume, its index, and end-diastolic left-ventricular volume as well as its index. (A) and (B): Change in maximal left-atrial volume and index after 30 days of flavanol (1000 mg, containing 160 mg of (−)-epicatechin) intake compared to baseline. No changes were observed in the control group. (C) and (D): Significant decrease in maximal end-diastolic left-ventricular volume and its index by flavanol intake. No changes were observed in the control group. * $p < 0.05$, ** $p < 0.01$; repeated measurements two-way ANOVA with Bonferroni's *post hoc* test. $n_{Control} = 33$, $n_{CF} = 30$; BL = baseline; FU = follow-up.

(SEM) (74.2 ± 11.5 ml at baseline *versus* 70.9 ± 15.6 ml at follow-up, Fig. 2D, $p = 0.0413$). The control regiment did not affect these parameters (LV_{EDV}: 146.4 ± 35.6 at baseline *versus* 141.5 ± 30.9 ml at follow-up, Fig. 2C, $p = 0.17$; LVI_{EDV}:74 ± 15.6 ml m^{-2} at baseline *versus* 71.7 ± 14 ml m^{-2} at follow-up, Fig. 2D, $p = 0.17$). Neither of the groups showed changes in longitudinal and circumferential SRe or SRa (Table 2).

Cocoa flavanol intake did not affect LV systolic function. This was evidenced by EF (65.2 ± 7.1% at baseline *versus* 65.0 ± 5.2% at follow-up, Table 2, $p = 0.98$) and SV (95.5 ± 17.6 ml at baseline *versus* 91.1 ± 18.3 ml at follow-up, Table 2, $p = 0.18$).

Cocoa flavanols improve blood pressure

One month of flavanol administration led to a significant decrease in both systolic and diastolic blood pressure (Fig. 3): systolic blood pressure was reduced by 4.7 ± 1.9% (137.9 ± 15.3 mmHg at baseline *versus* 131.4 ± 13.5 mmHg at follow-up, $p = 0.034$) and diastolic blood pressure by 3.4 ± 1.6% (80.2 ± 8.1 mmHg at baseline *versus* 77.5 ± 8.1 mmHg at follow-up, $p = 0.02$).

Gender, age and baseline blood pressure are not associated with positive LA remodeling

Neither elevated systolic blood pressure at baseline >130 mmHg (OR 2.6, 95% CI 0.49–20.6, $p = 0.29$), nor the absolute differences in blood pressure evoked by cocoa flavanols (OR per % reduction: 1.02, 95% CI 0.94–1.1, $p = 0.62$) were associated with positive LA remodeling. Similarly, gender, age, or body mass index were not associated with a higher degree of LA remodeling in a logistic regression model (OR for

Table 2 Baseline and follow-up echocardiographic and CMR parameters (N = 63). Values represent mean ± SD. Δ represents the absolute difference between the respective groups. p for pre-post comparison by repeated measurements two-way ANOVA. Absolute differences between the groups were compared by Student's t-test. (SBP = systolic blood pressure, DBP = diastolic blood pressure, EF = ejection fraction, SV(I) = stroke volume (index), LA(VI) = left-atrial (volume index), GLS = global longitudinal strain, GLSRe/a = early and late longitudinal diastolic strain rate)

	Control (n = 33)				Cocoa flavanols (n = 30)				
	Baseline	+30 d	p	Δ [95% CI]	Baseline	+30 d	p	Δ [95% CI]	$p(\Delta)$
SBP, mmHg	138.6 ± 16.0	133.0 ± 16.8	0.06	−5.6 [−10.1; −1.1]	137.9 ± 15.3	131.4 ± 13.5	0.04	−6.5 [−12.6; −0.42]	0.74
DBP, mmHg	80.7 ± 9.7	78.5 ± 7.2	0.19	−2.1 [−5.0; 0.8]	80.6 ± 8.0	77.2 ± 8.1	0.03	−3.4 [−5.8; −1.1]	0.49
NT-proBNP, pg ml^{-1}	84.4 ± 65.7	97.1 ± 96.3	0.14	13.7 [−5.0; 32.4]	69.4 ± 54.5	68.8 ± 58.0	0.89	0.9 [−12.0; 13.8]	0.26
CMR									
EF, %	65.0 ± 6.6	62.4 ± 5.3	0.02	−2.5 [−4.6; 0.5]	65.2 ± 7.1	65.0 ± 5.2	0.98	−0.2 [−2.2; 1.8]	0.09
SV, ml	94.7 ± 23.7	88.2 ± 19.9	0.02	−6.5 [−11.0; 2.0]	95.5 ± 17.6	91.1 ± 18.3	0.18	−4.4 [−10.0; 1.3]	0.55
SVI, ml m^{-2} BSA	47.8 ± 10.1	44.6 ± 8.9	0.02	−3.2 [−5.4; 0.9]	48.0 ± 6.98	45.9 ± 8.0	0.16	−2.1 [−4.7; 0.5]	0.54
LA Max Volume, ml	69.0 ± 23.7	69.3 ± 25.5	0.99	0.34 [−4.95; 5.64]	64.3 ± 17.9	56.2 ± 19.5	0.0063	−8.01 [−13.16; −2.86]	**0.03**
LAVI, ml m^{-2} BSA	34.8 ± 11.3	35.1 ± 12.5	0.97	0.25 [−2.42; 2.91]	32.1 ± 7.2	28.1 ± 8.9	0.0067	−3.93 [−6.35; −1.51]	**0.02**
GLS, %	−15.7 ± 2.1	−15.0 ± 2.3	0.07	0.77 [−0.04; 1.58]	−15.0 ± 1.9	−14.7 ± 2.2	0.75	0.26 [−0.44; 0.96]	0.34
GLSRe, 1 s^{-1}	0.71 ± 0.20	0.65 ± 0.23	0.22	−0.06 [−0.14; 0.02]	0.67 ± 0.19	0.67 ± 0.22	0.97	−0.006 [−0.08; 0.06]	0.33
GLSRa, 1 s^{-1}	0.72 ± 0.21	0.66 ± 0.23	0.29	−0.05 [−0.13; 0.02]	0.70 ± 0.19	0.66 ± 0.16	0.40	−0.05 [−0.12; 0.03]	0.92

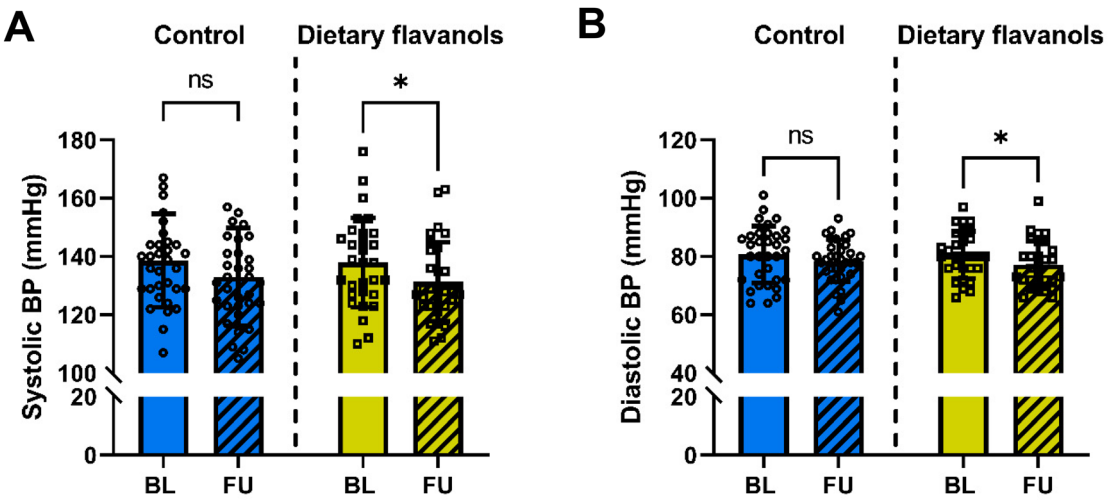

Fig. 3 Cocoa flavanols decrease systolic blood and diastolic blood pressure (BP). (A) Change in systolic blood pressure after 30 days of flavanol (1000 mg, containing 160 mg of (−)-epicatechin) intake compared to baseline. No changes were observed in the control group. (B) Significant decrease in diastolic blood pressure by supplementation with flavanol or in the control group. * $p < 0.05$; repeated measurements two-way ANOVA with Bonferroni's *post hoc* test. $n_{Control}$ = 33, n_{CF} = 30; BL = baseline; FU = follow-up.

male participants: 0.52, 95% CI 0.31–2.45, p = 0.42; OR for age [per year]: 1.04, 95% CI 0.87–1.25, p = 0.66; OR for BMI [per unit]: 1.14, 95% CI 0.91–1.46, p = 0.26, SI Table S2).

Discussion

Over a 30-day period, daily intake of 1000 mg of cocoa flavanol extract, containing 160 mg (−)-epicatechin, promoted cardiovascular health by reversing left atrial and left ventricular enlargement in healthy older individuals. The LA volume, whose enlargement was previously recognized as an age-related, subclinical manifestation of diastolic dysfunction, was reduced. Our present study is the first to provide a non-pharmacological, non-operative approach mediating beneficial changes in ventricular volumetry in healthy individuals. These outcomes were corroborated through high-resolution cine steady-state free precession CMR imaging, regarded as the gold standard for cardiac volumetry.[15]

In a previous study, we demonstrated that the same cocoa flavanol intake regimen led to improvements in cardiorespiratory fitness in healthy older adults, particularly through increases in peak oxygen consumption and maximum exercise capacity.[14] Given that diastolic dysfunction has been previously associated with reduced exercise capacity – including lower peak VO_2 and tidal volume,[27,28] the present findings may offer a mechanistic explanation for the previously observed functional benefits. However, further research is required to confirm and better understand this potential link. Consistent with our prior studies[29,30] cocoa flavanol intake induced favor-

able changes in the systemic circulation, leading to reductions in systolic and diastolic blood pressure, which may have interacted with the observed cardiac alterations. However, there were no independent associations between baseline systolic blood pressure or its dynamics and the positive left atrial remodeling. Improvement in endothelial function, as measured by FMD, has been documented after both acute and chronic flavanol intake, summarized in detail,[31] including in our previous trial using the same regimen.[14] Notably, lower FMD has been associated with increased left-heart volumes.[32] Endothelial dysfunction may theoretically contribute to increased cardiac afterload and pressure or volume overload, thereby promoting left atrial and ventricular remodeling. Taken together, these findings suggest that cocoa flavanol intake can potentially reverse early signs of diastolic dysfunction. Although speculative, it is possible that progression towards symptomatic diastolic dysfunction or the manifestation of heart failure with preserved ejection fraction could be delayed. The flavanol effects were independent of gender or systemic blood pressure at baseline.

The COSMOS trial, as the first large-scale, randomized-controlled trial to investigate flavanol intake in relation to cardiovascular disease and cardiovascular mortality,[33] showed a reduction in cardiovascular death by ~27%.[9] The test material used in COSMOS consisted of a cocoa extract providing 500 mg of cocoa flavanols, including 80 mg of (–)-epicatechin, which is the same to the intervention used in the present study. The underlying mechanisms in terms of mortality reduction observed in COSMOS remain unknown. However, COSMOS recorded cardiovascular diseases with high mortality and morbidity, such as acute myocardial infarction, stroke, and the need for revascularizations of various arteries.[9] Our current study might augment knowledge by providing insight into the cardiovascular benefits cocoa flavanol intake in age-related incipient dysfunctions.

Beyond the diastolic component, LA enlargement has been shown to be an independent long-term predictor of cardiovascular events in the general population.[34] In our study cohort, the average LAVI of 34.8 ± 11.3 ml m^{-2} in the control and 32.1 ± 7.2 ml m^{-2} in the flavanol group was well situated within the standard physiological ranges of 17–59 in men and 17–61 ml m^{-2} in women.[35] LA enlargement is often observed in individuals with cardiovascular diseases[5,36,37] and its reduction to date has been proven so far only by drug intake,[38,39] medical interventions[40,41] or surgery[42] but not by dietary interventions. We found a LA volume reduction achieved over one month of flavanol intake of ~13%, uncovering the first dietary intervention to reduce LA volumes in healthy older individuals.

The daily intake of 1000 mg flavanol in our study exceeded the recommended intake range outlined by the Academy of Nutrition and Dietetics (400–600 mg daily)[10] and the amount employed in the COSMOS trial (500 mg daily, containing 80 mg (–)-epicatechin).[33] At the same time, whilst the COSMOS trial investigated long-term effects of flavanols intake from cocoa extract, mirrored by the median follow-up time of 3.6 years,[9] we tested specific effects in a shorter timeframe, thus opting for a higher intake amount. This amount was selected based on a preliminary study from our laboratory, which indicated a dose-dependent effect on FMD, with the highest FMD response observed at approximately 820 mg of cocoa flavanols.[21] Thus, it is possible that lower intake amounts of cocoa flavanols but consumed for much longer periods could result in similar beneficial health effects as reported here and thus, help to provide mechanistic insights behind the long-term cardiovascular effects of flavanols as shown in COSMOS and supported by the Academy of Nutrition and Dietetics recommendations.[10] In our study, all test materials were well tolerated. This is in line with previously reported safety margins for flavanol consumption.[22]

No changes in LV systolic parameters, GLS or diastolic strain rate parameters were visible by flavanol intake. In an earlier clinical study, consuming 1 g of flavanols daily ameliorated chronic heart failure in patients with reduced EF, reflected by a reduction in NT-proBNP levels.[43] Since our participants all showed normal LV systolic function at baseline, the effect of LV function improvement might be only in reduced systolic function before starting flavanol intake, however, further research is needed to confirm or deny this hypothesis.

Vascular effects evoked by flavanol were recorded as secondary endpoints of the present study. In the intervention group, systolic blood pressure was decreased by ~6.5 mmHg. A recent meta-analysis summarized the effects of flavanols on blood pressure and found a slight but significant reduction in preponderantly healthy subjects, especially if the analyzed collective were prehypertensive or hypertensive.[44] Our data align with this finding, whereas the higher amount of administered flavanol might explain the larger effect size. The potential for blood pressure reduction observed in our healthy cohort is similar to that achieved with commonly used antihypertensive medications, although flavanols cannot be considered a pharmacological agent.

Several limitations must be addressed. Most importantly, our study's first objective was to assess flavanol-mediated changes to diastolic function in healthy older individuals with normal systolic function. Data on CMR-derived strain analysis, especially diastolic strain rate, is rare. Effect sizes can only be estimated, and we could not define any cut-off criteria for pre-clinical diastolic dysfunction. In addition, due to our purely descriptive analysis, we could only show a reduction in LA volumes without establishing the physiological and biochemical mechanisms behind it. Furthermore, since this study represents one of the first successful interventions to reduce LA volume. Its effects on future CV events need further investigation for validation. Lastly, several participants included in the current analysis were part of our previously published RCT addressing the effects of flavanols on exercise capacity.[14] As all participants were older than 55 and of Western-European descent, generalizability of our findings to younger people or other ethnic groups needs to be further investigated.

In an aging population worldwide, preventing cardiovascular disease and delaying disease onset improves health span and quality of life. Therefore, any intervention to preserve cardiovascular health is warranted. Healthy older individuals who consumed 1000 mg of cocoa flavanols over one month showed benefits in surrogate parameters for cardiac relaxation and peripheral blood pressure intake. Our data add to better understand the contributing mechanisms behind the growing evidence of flavanol's beneficial cardiovascular effects. Further investigations will be needed to determine if these changes take place when smaller amounts of flavanols or those containing lower amounts of (–)-epicatechin are consumed in longer time periods.

Conclusion

We provide evidence that 30-day flavanol intake of 1000 mg day^{-1}, containing 160 mg of (–)-epicatechin, mitigates early changes of diastolic dysfunction by reversing left atrial and left ventricular remodeling in older, healthy individuals. These findings suggest a potential protective effect of flavanols against age-related cardiac changes and open the field for future research in flavanol and cardiac interactions.

Author contributions

D. A. D.: data curation, writing – original draft; M. G.: data curation, funding acquisition, validation, writing – review & editing; N. O., N. K. & He. S.: investigation; J. O. & Ha. S.: methodology, resources; methodology, resources; C. Q., F. B., C. H. & R. S.: data curation; C. J. & M. K.: conceptualization, funding acquisition, project administration, supervision, writing – review & editing; R. E.: conceptualization, funding acquisition, methodology, project administration, writing – review & editing.

Abbreviations

BMI	Body mass index
BSA	Body surface area
CI	Cardiac index
CMR	Cardiac magnetic resonance
COSMOS	COcoa Supplement and Multivitamin Outcomes Study
EF	Ejection fraction
eNOS	Endothelial NO synthase
FMD	Flow-mediated vasodilation
GCSRe	Early circumferential diastolic strain rate
GCSRa	Late circumferential diastolic strain rate
GLS	Global longitudinal strain
GLSRe	Early longitudinal diastolic strain rate
GLSRa	Late longitudinal diastolic strain rate
HFpEF	Heart failure with persistent ejection fraction
LA	Left-atrial
LA_{max} volume	Maximum left-atrial volume
LAVI	Left-atrial volume index
LV	Left ventricle
LV_{EDV}	End-distolic left-ventricular volume
LVI_{EDV}	End-diastolic left-ventricular volume index
PWV	Pulse wave velocity
SD	Standard deviation
SEM	Standard error of the mean
SR	Strain rate
SV(I)	Stroke volume (index)

Conflicts of interest

H. S. and J. O. are employees of Mars Edge (a segment of Mars, Incorporated). Mars Edge is dedicated to human health through nutrition, including flavanol research and flavanol-related activities. All other authors declare no conflicts of interest.

Data availability

All data supporting the findings of this study are presented in the figures and tables. The raw data are not publicly available due to confidentiality restrictions but may be provided by the corresponding author upon reasonable request.

Supplementary information (SI) is available. See DOI: https://doi.org/10.1039/d5fo02589c.

Acknowledgements

This study initiated by M. K., M. G. and R. E. was partially funded by an investigator-initiated grant from Mars Edge. Mars Edge is a segment of Mars Incorporated, dedicated to nutrition research and products. Mars Edge had no influence on study design, data collection, and analysis. The graphical abstract was created in BioRender (biorender.com).

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