Resveratrol and exercise to treat functional limitations in late life (RESTORES): A pilot randomized controlled trial

The pilot RCT indicated that exercise and 1,000 mg/d dose of resveratrol may have benefits for physical function and mitochondrial function

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INTRODUCTION

- It is critical for older adults to maintain physical function during the aging process, to ward off disability and maintain independence.
- Few therapeutic strategies exist that are shown to improve physical function.
- One potential strategy is exercise (EX) + resveratrol

METHODS

- Multi-site, three-arm pilot randomized controlled trial (RCT)
- Who: older adults with functional limitations
- What: participants were randomized to receive either:
  (1) EX + placebo
  (2) EX + 500 mg/d resveratrol (low dose)
  (3) EX + 1,000 mg/d resveratrol (high dose)
- Where: UAB in AL and UF in FL
- Why: resveratrol has anti-oxidant, anti-inflammation, and metabolic benefits. These beneficial effects may manifest when resveratrol is combined with exercise
- Design: 12 week intervention
- Outcomes: clinical and biochemistry outcomes at weeks 0 and 12

DISCUSSION

- Therapies designed to optimize the efficacy of exercise could ultimately have a positive impact on reducing functional limitations in older adults.
- Relative change in 6 min walk for high dose resveratrol group was in a clinically-meaningful range.
- Our results suggest that a fully powered RCT is feasible and safe.
- Mitochondrial and physical function outcomes suggest EX + 1,000 mg/d resveratrol may have beneficial effects.

	EX+ placebo (n=20)	EX+ LR (n=20)	EX+HR (n=20)
Age, years	73.3 ± 7.8	72.0 ± 5.1	70.3 ± 5.8
Sex, Female	14 (70%)	13 (65%)	18 (90%)
Race, White	14 (70%)	13 (68)%	16 (80%)
Ethnicity, Hispanic	1 (5%)	1 (5%)	1 (5%)
Education – professional/graduate degree	5 (25%)	8 (40%)	10 (50%)
Height, cm	163.0 ± 9.5	166.1 ± 8.3	162.4 ± 6.6
Weight, kg	83.4 ± 19.8	86.1 ± 24.5	84.4 ±19.3
Body Mass Index, kg/m²	31.1 ± 5.5	31.3 ± 7.6	32.0 ± 6.9
Waist Circumference, cm	98.4 ± 26.1	105.0 ± 20.3	103.0 ±17.1
Systolic blood pressure, mm Hg	140 ±13.7	145 ± 15.1	133 ± 9.6
Diastolic blood pressure, mm Hg	79.3 ±11.8	82.4 ± 9.5	78.2 ± 8.2
MMSE, points	28.2 ±1.4	27.4 ± 2.0	28.7 ±1.5
CHAMPS questionnaire	53.0 ± 51.8	36.6 ± 45	30.2 ± 43.3
Chronic Pain Scale, score	1.2 ± 0.8	1.2 ± 0.8	0.9 ± 0.5
400 m walk gait speed, m/s	1.2 ± 0.2	1.12 ± 0.1	1.2 ± 0.1
Total number of prescription medications, n	6.0 ± 3.4	5.3 ± 3.3	6.1 ± 4.3
Total number of supplements, n	3.0 ± 3.3	3.9 ± 2.9	2.3 ± 2.6
History of hypertension, n	15 (79%)	12 (60%)	11 (55%)
History of diabetes, n	6 (32%)	5 (42%)	3 (15%)
History of lower-limb osteoarthritis, n	2 (10%)	3 (15%)	2 (10%)

Table 1: Participant baseline demographics and characteristics. Values are presented as unadjusted mean ± SD, or n (percentage). Abbreviations: EX: Exercise, LR: low dose resveratrol (500 mg/day), HR: high dose resveratrol (1,000 mg/day), MMSE: Mini-Mental State Examination, CHAMPS: Community Health Activities Program for Seniors, SPPB: Short Physical Performance Battery. All missing data is assumed missing at random.

group	safety	supplement adherence	exercise adherence
EX + Placebo	8 AE	84.00%	74.13%
EX + Low dose	12 AE		
EX + High dose	7 AE		

Table 2: Safety and adherence. The pilot study observed 27 post-randomized adverse events (AE) that were related, or possibly related to the pilot RCT. The most common adverse event was gastrointestinal issues (n= 9). Of those participants, two were in the high dose (1,000 mg/day) resveratrol group, and five were in the low dose (500 mg/day) resveratrol group. 84% of participants had ≥75% for supplement adherence while 74% of participants attended ≥75% of 24 exercise sessions.

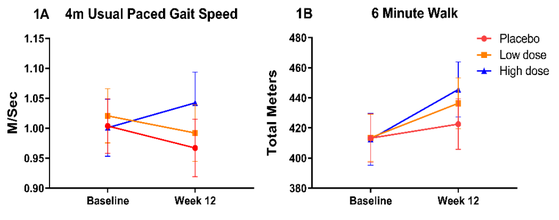

Figure 1: Functional status. Indices of physical function are key predictors of cardiovascular risk, health, and survival. Data are presented as the intent-to-treat analysis for 4 meter usual paced gait speed (1A) and 6 minute walk test (1B). For 4 m gait speed, the EX + placebo groups had a -0.04 m/sec (-0.1, 0.03) change while the EX + low dose group had -0.03 m/sec (-0.09, 0.04), and the EX + high dose group had 0.04 m/sec (-0.02, 0.11) week 12 relative to week 0. During the 6 min walk test, the EX + placebo group had a 9.45 m (-9.02, 27.7) change while the EX + low dose group had a 22.9 m (4.18, 41.6) and EX + high dose had 33.1 m (13.8, 52.4) relative change. Values indicate estimated marginal mean ± 95% confidence intervals.

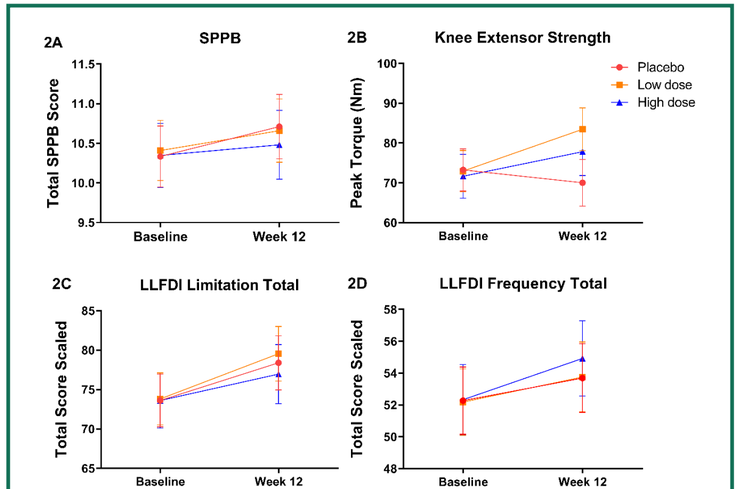

Figure 2: Additional clinical outcome measures. Indices of physical function are presented as the intent-to-treat within group changes for SPPB (2A), mean composite knee extensor peak torque across three speeds of movement (60, 90, 120°/s) (2B), LLFDI limitation total (2C), and LLFDI frequency total (2D) among older adults following 12-weeks of a multimodal exercise and supplementation. The EX + low dose group had a 10.5 Nm (4.28, 16.7) relative change for mean composite peak torque. Moreover, both the EX + placebo group 4.77 (0.06, 9.49) and the EX + low dose group 5.72 (0.93, 10.5) had relative increases in late life function and disability limitation total. Values indicate estimated marginal mean ± 95% confidence intervals. Abbreviations: SPPB: Short Physical Performance Battery; LLFDI: Late Life Function and Disability Instrument.

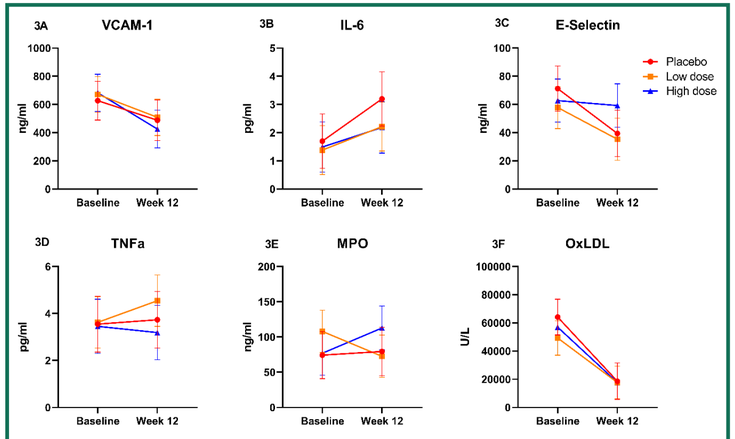

Figure 3: Markers of vascular systematic inflammation and oxidative stress. Enzyme-linked immunosorbent assays analyzed vascular cellular adhesion molecule 1 (VCAM-1), interleukin-6 (IL-6), E-selectin, tumor necrosis factor α (TNF-α), markers of systematic inflammation. Markers of CVD-related oxidative stress included myeloperoxidase (MPO) and oxidized low density lipoprotein (OXLDL). VCAM-1: EX + placebo -139 ng/ml (-267, -11), EX + low dose -162 ng/ml (-275, -49), EX + high dose -257 ng/ml (-374, -140). IL-6: EX + placebo 1.5 pg/ml (0.69, 2.31), EX + low dose 0.83 pg/ml (0.15, 1.52). E-selectin: EX + placebo -32 ng/ml (-43, -21), EX + low dose -22 ng/ml (-32, -12). TNF-α: EX + low dose 0.92 pg/ml (0.25, 1.59). MPO: EX + low dose -35 ng/ml (-57, -14), EX + high dose 36 ng/ml (14, 58). OxLDL: EX + placebo -45456 mU/L (-56206, -34707), EX + low dose -31552 mU/L (-41817, -21289), EX + high dose -35330 mU/L (-44780, -25860). Values indicate the estimated marginal mean ± SE.

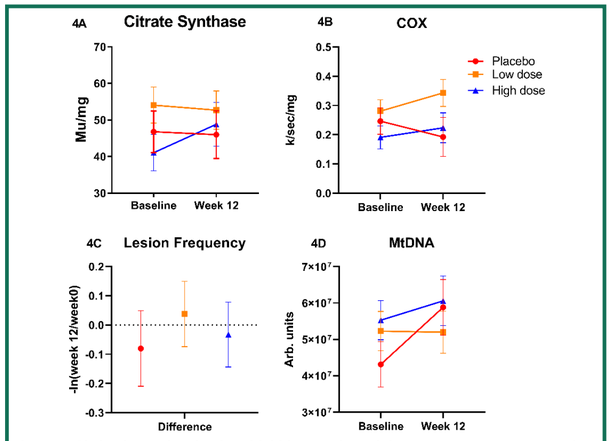

Figure 4: Skeletal muscle mitochondrial biogenesis and damage measures. Presented as the unadjusted within group changes, 12-week changes for citrate synthase included -0.80 Mu/mg (-15.45, 13.84) for placebo, for -1.38 Mu/mg (-12.16, 9.39) low dose, and for 7.75 Mu/mg (-4.68, 20.18) high dose resveratrol group (4A). Cytochrome c oxidase (COX) activity, which represents the rate limiting step in mitochondrial complex 4, showed similar mean changes including -0.05 k/sec/mg (-0.22, 0.11), 0.06 k/sec/mg (-0.06, 0.19), and 0.03 k/sec/mg (-0.10, 0.16) in Figure 4B, respectively. Lesion frequency was used to assess mtDNA damage across groups (4C). The relative change in MtDNA is presented in 4D. Values indicate unadjusted mean ± SE.

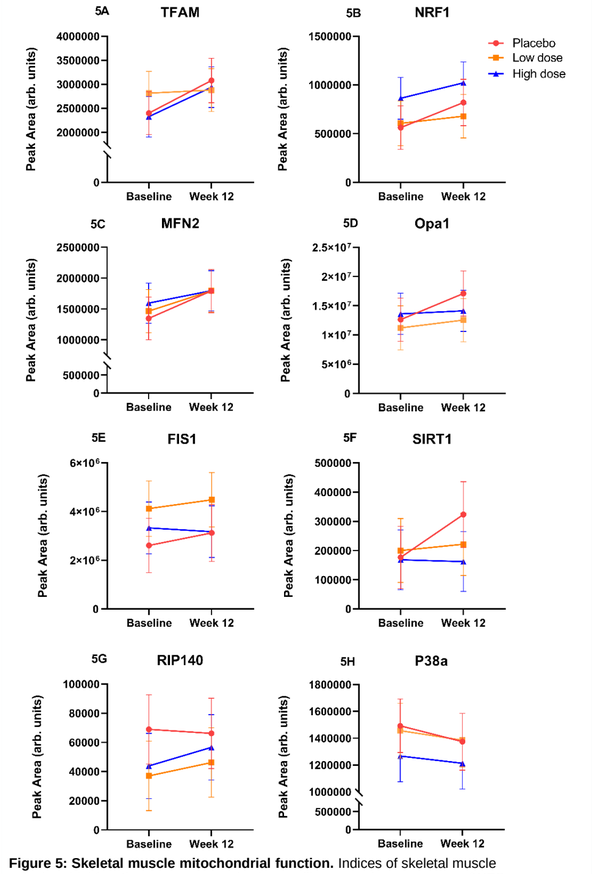

Figure 5: Skeletal muscle mitochondrial function. Indices of skeletal muscle mitochondrial function were assessed using capillary nano-immunoassays (WES, ProteinSimple, CA, USA). Data are presented week 12 relative to week 0 changes normalized for total protein area including TFAM, NRF1, RIP140, SIRT1 (transcriptional regulators); MFN2, Opa1, FIS1 (regulatory fission and fusion proteins) and P38a (cell signaling). Values indicate estimated marginal mean ± SE. Abbreviations: TFAM: Mitochondrial transcription factor A; NRF1: nuclear respiratory factor 1; RIP140: receptor-interacting protein 140; SIRT1: Sirtuin; MFN2: Mitofusin-2; Opa1: mitochondrial dynaminlike GTPase; FIS1: Mitochondrial fission 1 protein; P38α: p38-mitogen activated protein kinase α.

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