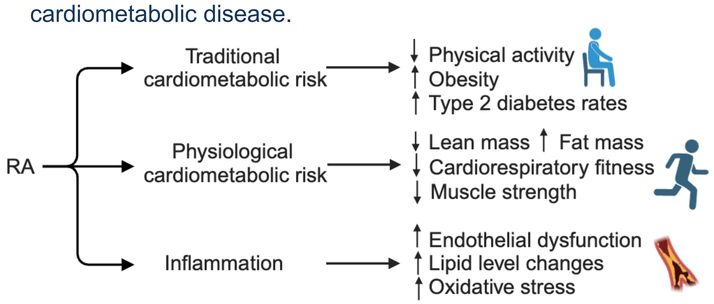
RELATIONSHIPS BETWEEN LIPOPROTEIN AND METABOLITE MEASURES WITH CARDIOMETABOLIC RISK FACTORS AND CLINICAL OUTCOMES IN RHEUMATOID ARTHRITIS

Grace Kim, Leanna M. Ross, Alyssa M. Sudnick, Johanna L. Johnson, Margery A. Connelly, William E. Kraus, Brian J. Andonian, and Kim M. Huffman

Duke University School of Medicine, Durham, NC

BACKGROUND

- Persons with rheumatoid arthritis (RA) have increased risk of cardiometabolic disease.



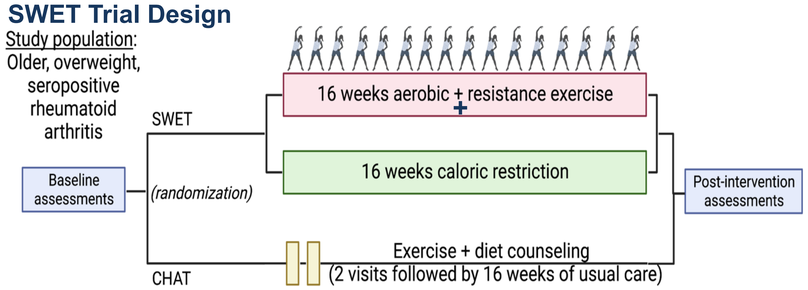
- Though weight loss and exercise may help target traditional, physiological, and inflammatory risks for cardiometabolic disease in RA, the optimal lifestyle regimen is still poorly defined.
- The Supervised Weight loss and Exercise Training (SWET) trial was the first to illustrate a remote, combined lifestyle intervention improves cardiometabolic health and RA clinical outcomes, including RA disease activity and patient-reported outcomes, for older persons with overweight/obesity and RA.
- Mass spectroscopy-based metabolites can help provide insight into physiological and pathological mechanisms.
- Nuclear magnetic resonance (NMR) spectroscopy, which measures lipoprotein sub-classes and small metabolites, can improve cardiometabolic risk assessments.

PURPOSE

To investigate the underlying effects of weight loss and exercise on RA cardiometabolic risk and clinical outcomes by assessing relationships for baseline and changes in clinical parameters with mass spectroscopy and NMR-based metabolites and lipoproteins.

METHODS

SWET Trial Design



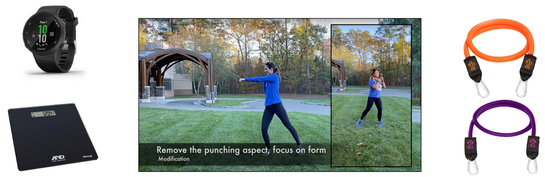
SWET Group Components

➔ **7% weight loss**

➔ **Aerobic exercise**
150 min/week of moderate-to-vigorous intensity; average 6,000 steps/day

➔ **Resistance exercise**
2x/week of 8-10 upper and lower body exercise for 3 sets and 10-15 repetitions of each

METHODS (continued)



Traditional Cardiometabolic Risk Factors

➔ Metabolic syndrome z-score (MSSc)

$$MSSc\ z-score = \frac{(40\ or\ 50*) - HDLc}{16.5} + \left(\frac{triglycerides-150}{38.5}\right) + \frac{fasting\ plasma\ glucose-100}{11.8} + \frac{waist\ circumference-88}{8.0} + \frac{mean\ arterial\ pressure-100}{9.1}$$

*(40-HDLc) for male participants; (50-HDLc) for female participants

➔ Fasting insulin

Physiological Cardiometabolic Risk Factors

➔ Body composition: fat mass & lean mass
➔ Cardiorespiratory fitness: absolute & relative VO_2 max (aVO_2, rVO_2)
➔ Strength: grip strength, peak & average knee extension torque

RA Clinical Outcomes

➔ RA disease activity
➔ Patient-reported outcomes

- All baseline measures underwent [log10 (measure + 1)].

Metabolite Measures

- "Change" scores = post-intervention – pre-intervention variable
- Principal components analysis reduced baseline measures and change scores into baseline and change factors.

Lipoprotein and Metabolite Measures

- "Change" scores = [(post-intervention variable minus pre-intervention variable)/pre-intervention variable × 100]
- Spearman's rank correlations assessed baseline and change associations between mass spectroscopy metabolite factors and NMR measures with cardiometabolic risk factors and clinical outcomes. Baseline associations were controlled for sex and prednisone use.

RESULTS

Table 1. Baseline Characteristics

Variables	SWET (n=10)	CHAT (n=10)
Age, mean (SD), y	65.6 (5.4)	67.7 (5.4)
Sex, female n (%)	9 (90)	7 (70)
Race, white n (%)	4 (40)	9 (90)
Weight, mean (SD), kg	86.3 (11.3)	83.0 (7.1)
DAS-28-CRP (SD)	3.1 (1.0)	2.9 (1.2)
Disease remission (<2.6), n (%)	3 (30)	5 (50)
Low disease activity (2.6–3.2), n (%)	4 (40)	1 (10)
Moderate disease activity (>3.2–5.1), n (%)	3 (30)	4 (40)

Table 2. Metabolite Factors

Baseline Factors	
Factor 1	Medium-chain acylcarnitines (ACs), C4OH
Factor 2	Large neutral amino acids
Factor 3	Non-esterified fatty acids, long-chain ACs, C2
Factor 4	Amino acids

Change Factors	
Factor 1	Short and medium-chain ACs
Factor 2	Branched-chain amino acids (BCAA), long-chain ACs
Factor 3	Medium-chain ACs
Factor 4	Amino acids

RESULTS (continued)

Table 3. Metabolite Baseline Factor Correlations

Variable	TGs (mg/dl)	Fasting glucose (mg/dL)	Fasting insulin (pg/mL)	Peak knee extension torque (Nm)	Average knee extension torque (Nm)	Right grip strength (kg)	Left grip strength (kg)
Factor 1	**-0.50***	0.22	-0.04	0.13	0.19	0.11	0.32
Factor 2	0.29	0.20	**0.53***	**0.57***	**0.50***	**0.52****	**0.56***
Factor 3	0.17	**0.57***	**0.55***	-0.22	-0.21	0.18	0.24
Factor 4	0.22	0.09	0.20	-0.03	-0.08	0.30	0.09

Table 4. Metabolite Change Factor Correlations

Variable	TGs (mg/dl)	Fasting insulin (pg/mL)	Right grip strength (kg)	Patient-reported cognitive function	Patient-reported fatigue
Factor 1	**-0.69*****	0.01	0.33	0.21	**-0.50***
Factor 2	-0.12	**0.49***	0.20	**-0.48***	-0.07
Factor 3	-0.23	-0.43	**-0.53***	0.34	0.08
Factor 4	-0.24	0.22	-0.02	0.02	0.13

Table 5. Lipoprotein and Metabolite Change Score Correlations

Variable	MSSc	Fat mass (kg)	aVO2 peak (mL/min)	rVO2 peak (mL/min/kg)	Patient-reported physical health	Patient-reported fatigue
Total HDL particles (μmol/L)	0.21	**0.49***	0.04	-0.13	-0.36	0.31
Very small TG-rich lipoproteins (nmol/L)	-0.21	-0.02	**-0.50***	**-0.49***	-0.30	-0.30
Apo A-I (mg/dL)	0.18	**0.53***	0.08	-0.11	-0.47*	0.33
Ketone bodies (μmol/L)	**-0.45***	-0.23	0.11	0.01	-0.03	-0.31
Total BCAAs (μM)	-0.31	-0.20	0.27	0.28	0.06	**-0.46***

For Tables 3-5, values are Spearman's rank correlation coefficients. *, **, and *** indicate P<0.05, P<0.01, and P<0.001, respectively, and are all bolded.

CONCLUSIONS

- Exercise may help mitigate fatigue through enhanced whole-body metabolism and β-oxidation.
- Caloric restriction induces ketone body production, which may improve lipid handling.
- Decreased HDL may be a favorable outcome affected by dietary composition.
- BCAAs need to be further investigated in specific contexts.
- Lifestyle interventions may have the potential to target metabolic pathways and enhance cardiometabolic and overall health for persons with RA.

ACKNOWLEDGEMENTS

The trial reported was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the NIH (R21-AR-076663).
Travel funds were supported by the ACSM Lisa S. Krivickas Award and Duke University School of Medicine's Third Year Dean's Award.
The authors would like to thank LabCorp for their NMR analyses, the Duke Center for Living research staff, and all study participants.

Contact Information: gk125@duke.edu