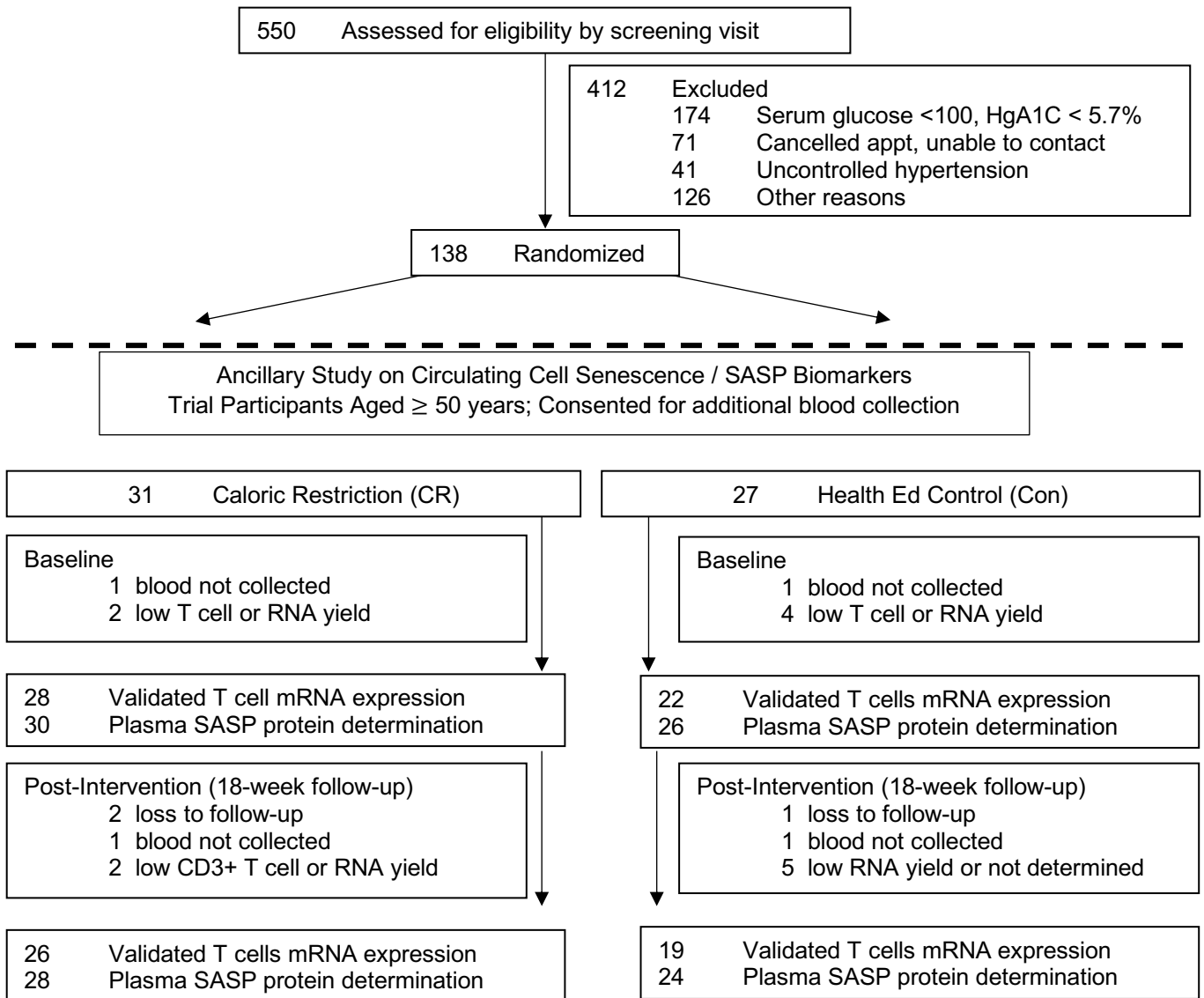
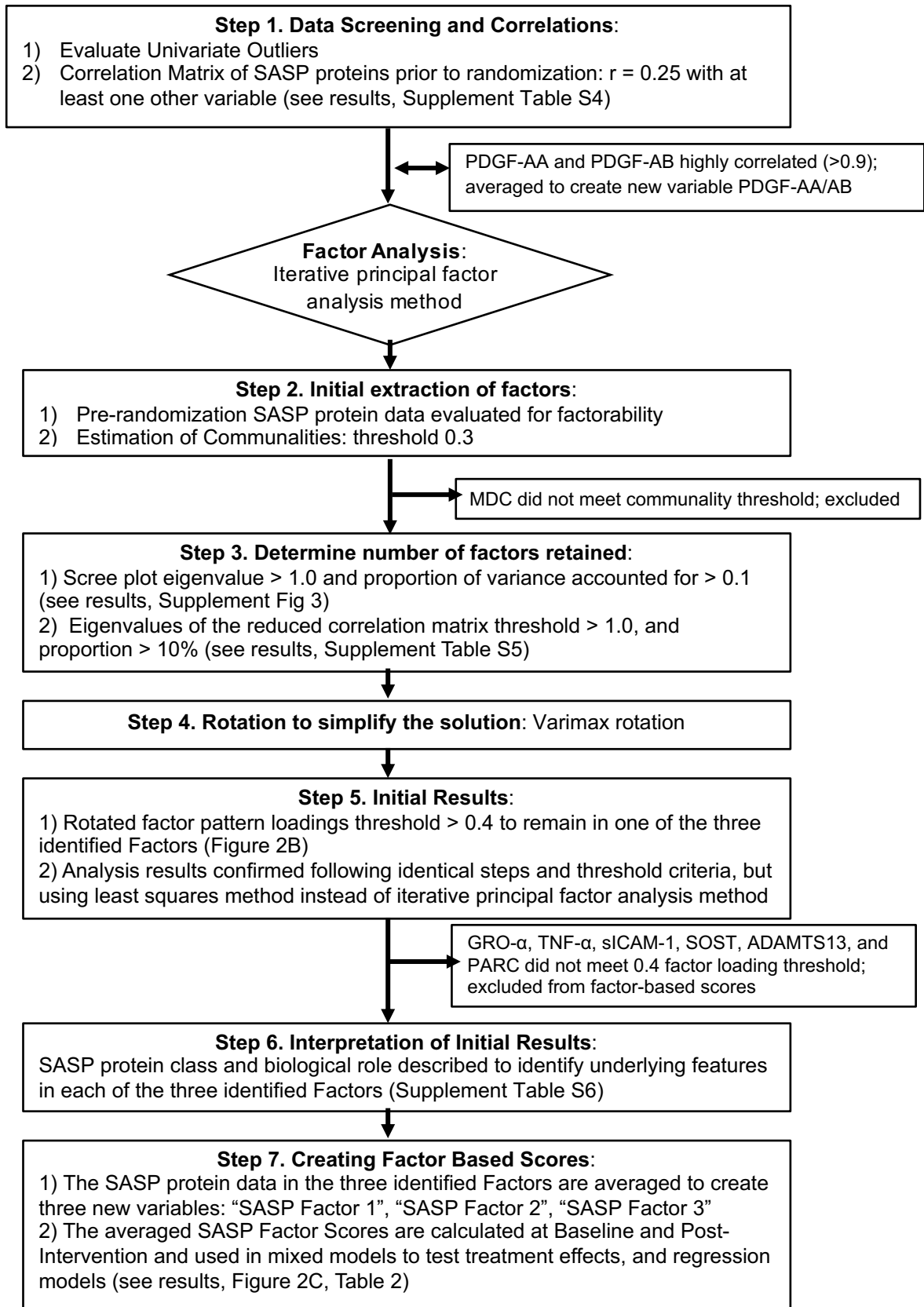


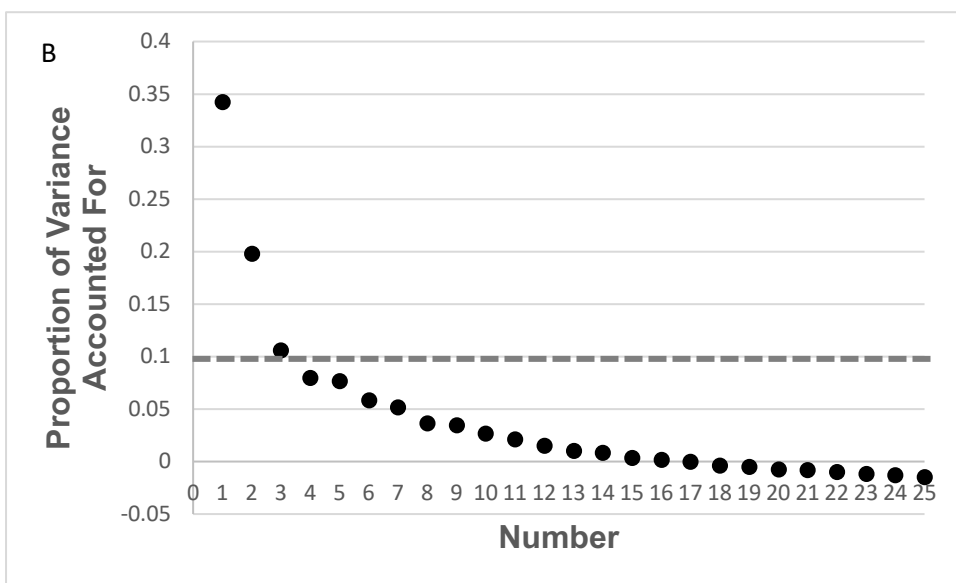
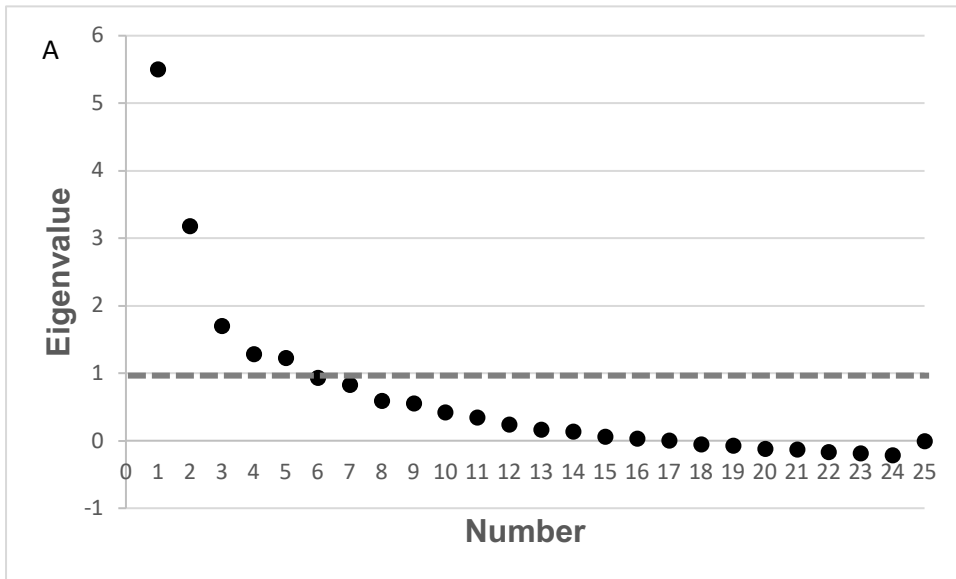
Supplemental Figure 1. Flow of Participants through NCT02869659 and SASP Biomarker Ancillary.



Supplemental Figure 2. Factor Analysis Flow Chart



Supplemental Figure 3. Scree plot of preliminary eigenvalues (A) and proportion of the variance accounted for (B) for inclusion in exploratory factor analysis with threshold for factor retention marked by dashed line on plot. Based on threshold criteria eigenvalue >1 and proportion of variance >0.1 criteria three factors are retained.



SUPPLEMENTAL TABLES

Table S1. Intervention effect on metabolic function and physical performance in the cell senescence/ SASP ancillary to VEGGIE at baseline and 18 weeks post-intervention of caloric restriction (CR) or health education control (Con).

| | Intervention Group (unadjusted) | | | Intervention Effect (adjusted) |
|----------------------------------|---------------------------------|--------------------|----------------------|--------------------------------|
| | CR | Control | Unadjusted | Adjusted |
| | est. mean \pm SE | est. mean \pm SE | p-value ¹ | p-value ² |
| Body weight (kg) | | | | p<0.001* |
| Baseline | 101.1 \pm 2.5 | 105.6 \pm 2.8 | 0.24 | |
| Post-intervention | 90.3 \pm 2.5 | 106.1 \pm 2.8 | <0.001* | |
| Change | -10.8 \pm 0.9 | +0.5 \pm 0.9 | <0.001* | |
| BMI (kg/m²) | | | | p<0.001* |
| Baseline | 36.20 \pm 0.95 | 37.91 \pm 1.04 | 0.23 | |
| Post-intervention | 32.23 \pm 0.95 | 37.88 \pm 1.04 | <0.001* | |
| Change | -3.97 \pm 0.32 | -0.03 \pm 0.35 | <0.001* | |
| Waist Circumference (cm) | | | | p<0.001* |
| Baseline | 110.8 \pm 1.8 | 113.7 \pm 2.1 | 0.30 | |
| Post-intervention | 100.35 \pm 1.9 | 114.6 \pm 2.1 | <.0001* | |
| Change | -10.4 \pm 0.90 | +1.0 \pm 0.95 | <0.001* | |
| Fasting insulin (mIU/L) | | | | p=0.03* |
| Baseline | 14.56 \pm 2.26 | 21.87 \pm 2.37 | 0.03* | |
| Post-intervention | 9.56 \pm 2.23 | 25.31 \pm 2.45 | <0.001* | |
| Change | -5.00 \pm 2.57 | +3.44 \pm 2.73 | 0.03* | |
| HbA1c (%) | | | | p<0.001* |
| Baseline | 5.74 \pm 0.06 | 5.75 \pm 0.07 | 0.93 | |
| Post-intervention | 5.54 \pm 0.06 | 5.75 \pm 0.07 | 0.04* | |
| Change | -0.20 \pm 0.03 | -0.01 \pm 0.04 | 0.0002* | |
| HOMA-IR (index) | | | | p =0.03* |
| Baseline | 3.87 \pm 0.61 | 5.88 \pm 0.65 | 0.03* | |
| Post-intervention | 2.53 \pm 0.61 | 6.80 \pm 0.67 | <0.001* | |
| Change | -1.33 \pm 0.68 | +0.93 \pm 0.73 | 0.03* | |
| Creatinine (mg/dL) | | | | p 0=.41 |
| Baseline | 0.857 \pm 0.03 | 0.837 \pm 0.03 | 0.65 | |
| Post-intervention | 0.849 \pm 0.03 | 0.804 \pm 0.03 | 0.33 | |
| Change | -0.008 \pm 0.02 | -0.033 \pm 0.02 | 0.39 | |
| LDL Cholesterol (mg/dL) | | | | p =1.0 |
| Baseline | 114.7 \pm 5.3 | 111.4 \pm 5.8 | 0.68 | |
| Post-intervention | 109.4 \pm 5.4 | 106.0 \pm 5.9 | 0.67 | |
| Change | -5.3 \pm 4.0 | -5.4 \pm 4.4 | 0.98 | |
| Total Cholesterol (mg/dL) | | | | p =0.58 |
| Baseline | 189.6 \pm 6.4 | 185.8 \pm 7.0 | 0.69 | |
| Post-intervention | 177.8 \pm 6.4 | 177.5 \pm 7.0 | 0.98 | |
| Change | -11.8 \pm 4.5 | -8.2 \pm 4.9 | 0.59 | |
| Systolic BP (mmHg) | | | | p =0.21 |
| Baseline | 130.3 \pm 2.7 | 128.8 \pm 2.9 | 0.71 | |
| Post-intervention | 122.1 \pm 2.7 | 125.9 \pm 3.0 | 0.35 | |

| | | | | |
|----------------------------|------------|------------|-------------|----------------|
| Change | -8.2 ± 2.8 | -2.9 ± 3.1 | 0.21 | |
| Diastolic BP (mmHg) | | | | p =0.03 |
| Baseline | 75.3 ± 1.5 | 72.6 ± 1.6 | 0.22 | |
| Post-intervention | 70.7 ± 1.5 | 73.6 ± 1.7 | 0.20 | |
| Change | -4.6 ± 1.8 | +1.1 ± 1.9 | 0.03 | |

1 Unadjusted comparison

2 Models were adjusted for age, gender, and race

Table S2. Intervention effect on circulating CD3+ T Cell expression of biomarkers related to cell senescence (p16^{INK4a}, p21^{CIP1/WAF1}) and cell death/ apoptosis (BCL2L, BAK1) at baseline and 18 weeks post-intervention in cell senescence/ SASP biomarker ancillary to VEGGIE, in unadjusted and age, sex, race adjusted models. Data are estimated means and standard error and change as difference of least squares means; intervention effect as mixed model Type 3 tests of fixed effects F-statistic and p-value. Simple linear regression was used to test if change in T cell gene expression significantly predicted % change in weight with intervention (R², p-value shown).

| | Intervention Group (unadjusted) | | | Intervention Effect (adjusted) | Regression, Δ Exp with % Change Weight |
|--------------------------------|---------------------------------|---------------|----------------------|--------------------------------|--|
| | CR | Control | Unadjusted | Adjusted | |
| | est. mean ±SE | est. mean ±SE | p-value ¹ | p-value ² | R ² F-, p-values |
| p16^{INK4a} | | | | p =0.451 | R ² = 0.001 |
| Baseline | 10.35 ± 0.15 | 10.15 ± 0.18 | 0.394 | | p = 0.87 |
| Post-intervention | 10.40 ± 0.16 | 10.35 ± 0.18 | 0.828 | | |
| Change | +0.049 ± 0.14 | +0.20 ± 0.15 | 0.467 | | |
| p21^{CIP1/WAF1} | | | | p =0.693 | R ² = 0.022 |
| Baseline | 12.32 ± 0.20 | 12.02 ± 0.22 | 0.317 | | p = 0.38 |
| Post-intervention | 12.51 ± 0.20 | 12.32 ± 0.22 | 0.547 | | |
| Change | +0.18 ± 0.23 | +0.30 ± 0.25 | 0.738 | | |
| BCL2L | | | | p =0.884 | R ² = 0.005 |
| Baseline | 16.47 ± 0.07 | 16.39 ± 0.089 | 0.490 | | p = 0.69 |
| Post-intervention | 16.45 ± 0.09 | 16.35 ± 0.10 | 0.486 | | |
| Change | -0.02 ± 0.12 | -0.037 ± 0.13 | 0.934 | | |
| BAK1 | | | | p =0.198 | R ² = 0.002 |
| Baseline | 15.03 ± 0.26 | 15.38 ± 0.30 | 0.386 | | p = 0.82 |
| Post-intervention | 14.88 ± 0.32 | 14.53 ± 0.34 | 0.468 | | |
| Change | -0.15 ± 0.39 | -0.85 ± 0.43 | 0.240 | | |

1 Unadjusted comparison

2 Models were adjusted for age, gender, and race

Table S3. Intervention effect and bivariate correlations (Spearman rank) on log-transformed plasma SASP biomarkers at baseline and 18 weeks post-intervention in cell senescence/ SASP biomarker ancillary to VEGGIE study. Data are estimated means and standard error and change as difference of least squares means; intervention effect as mixed model Type 3 tests of fixed effects p-value. Simple linear regression was used to test if change in SASP protein significantly predicted % change in weight with intervention (R^2 , p-value). * $p \leq 0.05$.

| | CR | Control | Adjusted mixed model | Regression, Δ Exp with % Change Weight |
|--------------------------------|-------------------------------------|-------------------------------------|----------------------|---|
| | est. mean \pm SE | est. mean \pm SE | p-value | R^2 p-values |
| Activin A | | | p<.0001* | $R^2 = 0.384$ |
| Baseline | 5.43 \pm 0.06 | 5.42 \pm 0.07 | p = 0.937 | p<0.001* |
| Post-intervention | 5.18 \pm 0.06 | 5.40 \pm 0.07 | p = 0.018 | |
| Change | -0.24 \pm 0.03* | -0.02 \pm 0.04 | | |
| ADAMTS13 | | | p=0.021* | $R^2 = 0.130$ |
| Baseline | 13.78 \pm 0.07 | 13.80 \pm 0.08 | p = 0.887 | p = 0.010* |
| Post-intervention | 13.79 \pm 0.07 | 13.69 \pm 0.08 | p = 0.345 | |
| Change | +0.01 \pm 0.03 | -0.11 \pm 0.04* | | |
| Eotaxin | | | p=0.831 | $R^2 = 0.010$ |
| Baseline | 4.53 \pm 0.09 | 4.52 \pm 0.09 | p = 0.965 | p = 0.46 |
| Post-intervention | 4.50 \pm 0.09 | 4.52 \pm 0.10 | p = 0.922 | |
| Change | -0.02 \pm 0.06 | -0.003 \pm 0.06 | | |
| Fas | | | p=0.031* | $R^2 = 0.049$ |
| Baseline | 8.57 \pm 0.08 | 8.87 \pm 0.08 | p = 0.013 | p = 0.12 |
| Post-intervention | 8.47 \pm 0.08 | 8.83 \pm 0.08 | p = 0.002 | |
| Change | -0.10 \pm 0.03* | -0.03 \pm 0.03 | | |
| GDF15 | | | p=0.216 | $R^2 = 0.056$ |
| Baseline | 6.16 \pm 0.07 | 6.35 \pm 0.07 | p = 0.060 | p = 0.09 |
| Post-intervention | 6.14 \pm 0.07 | 6.37 \pm 0.07 | p = 0.019* | |
| Change | -0.02 \pm 0.03 | +0.03 \pm 0.03 | | |
| Gro-α | | | p= 0.103 | $R^2 = 0.072$ |
| Baseline | 4.41 \pm 0.052 | 4.48 \pm 0.06 | p = 0.356 | p = 0.06 |
| Post-intervention | 4.35 \pm 0.053 | 4.50 \pm 0.06 | p = 0.066 | |
| Change | -0.06 \pm 0.031 | +0.02 \pm 0.03 | | |
| sICAM-1 | | | p= 0.002* | $R^2 = 0.307$ |
| Baseline | 12.31 \pm 0.15 | 12.21 \pm 0.17 | 0.640 | p<0.001* |
| Post-intervention | 12.23 \pm 0.15 | 12.22 \pm 0.17 | 0.976 | |
| Change | -0.08 \pm 0.02* | +0.02 \pm 0.02 | | |
| MCP-1 | | | p= 0.301 | $R^2 = 0.034$ |
| Baseline | 4.83 \pm 0.08 | 4.84 \pm 0.08 | p = 0.959 | p = 0.20 |
| Post-intervention | 4.80 \pm 0.08 | 4.89 \pm 0.08 | p = 0.430 | |

| | | | | |
|-----------------------|----------------------|--------------|-------------------|------------------------------|
| Change | -0.04 ± 0.05 | +0.05 ± 0.06 | | |
| MMP1 | | | p = 0.084 | R² = 0.084 |
| Baseline | 4.66 ± 0.10 | 4.74 ± 0.12 | p = 0.588 | p = 0.039* |
| Post-intervention | 4.49 ± 0.11 | 4.70 ± 0.12 | p = 0.036 | |
| Change | -0.16 ± 0.08* | -0.05 ± 0.08 | | |
| MMP2 | | | p = 0.300 | R ² = 0.008 |
| Baseline | 12.62 ± 0.05 | 12.62 ± 0.05 | p = 0.978 | p = 0.532 |
| Post-intervention | 12.61 ± 0.05 | 12.68 ± 0.05 | p = 0.301 | |
| Change | -0.01 ± 0.05 | +0.07 ± 0.05 | | |
| MMP7 | | | p = 0.562 | R ² = 0.001 |
| Baseline | 7.72 ± 0.09 | 7.76 ± 0.10 | p = 0.784 | p = 0.790 |
| Post-intervention | 7.66 ± 0.09 | 7.65 ± 0.10 | p = 0.936 | |
| Change | -0.06 ± 0.05 | -0.11 ± 0.06 | | |
| MMP9 | | | p = 0.361 | R ² = 0.001 |
| Baseline | 11.27 ± 0.09 | 11.19 ± 0.10 | p = 0.513 | p = 0.852 |
| Post-intervention | 11.40 ± 0.09 | 11.19 ± 0.10 | p = 0.116 | |
| Change | +0.13 ± 0.09 | +0.21 ± 0.13 | | |
| MPO | | | p = 0.855 | R ² = 0.028 |
| Baseline | 10.43 ± 0.06 | 10.44 ± 0.06 | p = 0.993 | p = 0.238 |
| Post-intervention | 10.46 ± 0.06 | 10.47 ± 0.06 | p = 0.881 | |
| Change | +0.02 ± 0.04 | +0.04 ± 0.05 | | |
| OPN | | | p = 0.6196 | R ² = 0.019 |
| Baseline | 10.29 ± 0.07 | 10.40 ± 0.08 | p = 0.275 | p = 0.339 |
| Post-intervention | 10.31 ± 0.07 | 10.39 ± 0.08 | p = 0.450 | |
| Change | +0.02 ± 0.05 | -0.01 ± 0.05 | | |
| PAI-1 / Serpin | | | p = 0.054* | R² = 0.125 |
| Baseline | 10.35 ± 0.12 | 10.49 ± 0.13 | p = 0.393 | p = 0.011 |
| Post-intervention | 9.97 ± 0.12 | 10.41 ± 0.13 | p = 0.017 | |
| Change | -0.36 ± 0.11* | -0.08 ± 0.12 | | |
| PARC | | | p = 0.556 | R ² = 0.053 |
| Baseline | 10.99 ± 0.08 | 10.87 ± 0.09 | p = 0.326 | p = 0.103 |
| Post-intervention | 11.02 ± 0.08 | 10.86 ± 0.09 | p = 0.196 | |
| Change | +0.03 ± 0.05 | -0.01 ± 0.05 | | |
| PDGF-AA | | | p = 0.888 | R ² = 0.026 |
| Baseline | 7.19 ± 0.19 | 7.23 ± 0.20 | p = 0.876 | p = 0.257 |
| Post-intervention | 7.12 ± 0.19 | 7.13 ± 0.21 | p = 0.955 | |
| Change | -0.07 ± 0.13 | -0.01 ± 0.14 | | |
| PDGF-AB | | | p = 0.758 | R ² = 0.018 |
| Baseline | 5.95 ± 0.20 | 6.00 ± 0.21 | p = 0.864 | p = 0.342 |
| Post-intervention | 5.90 ± 0.20 | 5.89 ± 0.22 | p = 0.967 | |
| Change | -0.05 ± 0.14 | -0.12 ± 0.15 | | |
| RAGE | | | p = 0.378 | R ² = 0.006 |
| Baseline | 7.10 ± 0.08 | 7.22 ± 0.09 | p = 0.305 | p = 0.599 |
| Post-intervention | 7.05 ± 0.08 | 7.22 ± 0.09 | p = 0.159 | |

| | | | | |
|-------------------|----------------------|---------------|--------------------|------------------------------|
| Change | -0.05 ± 0.04 | -0.17 ± 0.12 | | |
| RANTES | | | p=0.147 | R ² = 0.017 |
| Baseline | 9.38 ± 0.19 | 9.02 ± 0.21 | p =0.214 | p = 0.355 |
| Post-intervention | 9.40 ± 0.20 | 8.73 ± 0.21 | p =0.026 | |
| Change | +0.01 ± 0.14 | -0.67 ± 0.29 | | |
| SOST | | | p=0.112 | R ² = 0.057 |
| Baseline | 6.39 ± 0.12 | 6.56 ± 0.13 | p =0.343 | p = 0.090 |
| Post-intervention | 6.45 ± 0.12 | 6.50 ± 0.13 | p =0.751 | |
| Change | +0.06 ± 0.05 | -0.06 ± 0.18 | | |
| TNFR1 | | | p<0.001* | R² = 0.387 |
| Baseline | 6.71 ± 0.05 | 6.78 ± 0.05 | p =0.347 | p<0.001* |
| Post-intervention | 6.61 ± 0.05 | 6.78 ± 0.05 | p = 0.017 | |
| Change | -0.11 ± 0.02* | +0.001 ± 0.02 | | |
| TNFR2 | | | p = 0.017* | R² = 0.107 |
| Baseline | 7.82 ± 0.06 | 7.92 ± 0.06 | p =0.250 | p = 0.019* |
| Post-intervention | 7.75 ± 0.06 | 7.96 ± 0.06 | p = 0.020 | |
| Change | -0.07 ± 0.03* | +0.04 ± 0.03 | | |
| TNF-Alpha | | | p = 0.086 | R² = 0.087 |
| Baseline | 0.98 ± 0.09 | 1.11 ± 0.09 | p =0.291 | p = 0.036* |
| Post-intervention | 0.95 ± 0.09 | 1.18 ± 0.09 | p =0.069 | |
| Change | -0.03 ± 0.04 | +0.07 ± 0.04 | | |
| uPAR | | | p = 0.071 | R² = 0.105 |
| Baseline | 5.93 ± 0.07 | 6.03 ± 0.07 | p =0.286 | p = 0.020* |
| Post-intervention | 5.84 ± 0.07 | 6.04 ± 0.07 | p = 0.050 | |
| Change | -0.08 ± 0.03* | +0.01 ± 0.03 | | |
| VEGF | | | p = 0.087 | R² = 0.110 |
| Baseline | 3.42 ± 0.12 | 3.49 ± 0.13 | p =0.714 | p = 0.018* |
| Post-intervention | 3.27 ± 0.12 | 3.43 ± 0.13 | p =0.078 | |
| Change | -0.25 ± 0.08* | -0.06 ± 0.09 | | |

Table S4. Correlation Matrix (absolute value of Pearson r) between log transformed SASP factors. Color to reflect strength of association as criteria for inclusion in exploratory factor analysis.

| | Activin A | ADAMTS13 | Eotaxin | Fas | GDF15 | GroAlpha | ICAM1 | MCP1 | MMP1 | MMP2 | MMP7 | MMP9 | MPO | OPN | PAI1 | PARC | PDGF AA/AB | RAGE | RANTES | SOST | TNFa | TNFR1 | TNFR2 | uPAR | |
|------------|-----------|----------|---------|------|-------|----------|-------|------|------|------|------|------|------|------|------|------|------------|------|--------|------|------|-------|-------|------|--|
| ADAMTS13 | 0.10 | | | | | | | | | | | | | | | | | | | | | | | | |
| Eotaxin | 0.15 | 0.22 | | | | | | | | | | | | | | | | | | | | | | | |
| Fas | 0.20 | 0.02 | 0.03 | | | | | | | | | | | | | | | | | | | | | | |
| GDF15 | 0.41 | 0.00 | 0.03 | 0.34 | | | | | | | | | | | | | | | | | | | | | |
| GRO-a | 0.04 | 0.06 | 0.24 | 0.27 | 0.21 | | | | | | | | | | | | | | | | | | | | |
| ICAM1 | 0.11 | 0.01 | 0.16 | 0.04 | 0.01 | 0.21 | | | | | | | | | | | | | | | | | | | |
| MCP1 | 0.20 | 0.25 | 0.55 | 0.07 | 0.07 | 0.15 | 0.12 | | | | | | | | | | | | | | | | | | |
| MMP1 | 0.28 | 0.05 | 0.03 | 0.20 | 0.27 | 0.39 | 0.24 | 0.23 | | | | | | | | | | | | | | | | | |
| MMP2 | 0.50 | 0.08 | 0.29 | 0.03 | 0.16 | 0.25 | 0.36 | 0.23 | 0.39 | | | | | | | | | | | | | | | | |
| MMP7 | 0.43 | 0.11 | 0.10 | 0.07 | 0.20 | 0.17 | 0.07 | 0.19 | 0.32 | 0.35 | | | | | | | | | | | | | | | |
| MMP9 | 0.12 | 0.01 | 0.48 | 0.15 | 0.15 | 0.26 | 0.21 | 0.13 | 0.11 | 0.10 | 0.21 | | | | | | | | | | | | | | |
| MPO | 0.30 | 0.12 | 0.15 | 0.05 | 0.35 | 0.15 | 0.20 | 0.24 | 0.04 | 0.19 | 0.21 | 0.29 | | | | | | | | | | | | | |
| OPN | 0.23 | 0.04 | 0.26 | 0.30 | 0.20 | 0.26 | 0.29 | 0.25 | 0.33 | 0.32 | 0.05 | 0.13 | 0.13 | | | | | | | | | | | | |
| PAI1 | 0.29 | 0.22 | 0.69 | 0.07 | 0.10 | 0.25 | 0.16 | 0.40 | 0.15 | 0.25 | 0.03 | 0.35 | 0.13 | 0.18 | | | | | | | | | | | |
| PARC | 0.01 | 0.18 | 0.09 | 0.16 | 0.17 | 0.15 | 0.03 | 0.00 | 0.00 | 0.10 | 0.07 | 0.09 | 0.37 | 0.09 | 0.14 | | | | | | | | | | |
| PDGF AA/AB | 0.19 | 0.25 | 0.78 | 0.04 | 0.13 | 0.38 | 0.15 | 0.33 | 0.21 | 0.17 | 0.04 | 0.45 | 0.02 | 0.14 | 0.77 | 0.14 | | | | | | | | | |
| RAGE | 0.26 | 0.13 | 0.04 | 0.02 | 0.20 | 0.01 | 0.03 | 0.42 | 0.23 | 0.25 | 0.26 | 0.22 | 0.22 | 0.05 | 0.13 | 0.13 | 0.09 | | | | | | | | |
| RANTES | 0.15 | 0.18 | 0.48 | 0.16 | 0.01 | 0.25 | 0.02 | 0.09 | 0.05 | 0.03 | 0.13 | 0.27 | 0.05 | 0.02 | 0.59 | 0.05 | 0.75 | 0.44 | | | | | | | |
| SOST | 0.24 | 0.12 | 0.23 | 0.05 | 0.03 | 0.09 | 0.03 | 0.15 | 0.07 | 0.22 | 0.08 | 0.05 | 0.09 | 0.11 | 0.22 | 0.17 | 0.12 | 0.12 | 0.03 | | | | | | |
| TNF-a | 0.11 | 0.20 | 0.16 | 0.11 | 0.03 | 0.20 | 0.33 | 0.29 | 0.23 | 0.23 | 0.03 | 0.13 | 0.21 | 0.23 | 0.26 | 0.14 | 0.11 | 0.20 | 0.16 | 0.08 | | | | | |
| TNFR1 | 0.29 | 0.24 | 0.05 | 0.28 | 0.33 | 0.17 | 0.22 | 0.37 | 0.48 | 0.24 | 0.17 | 0.03 | 0.36 | 0.37 | 0.03 | 0.11 | 0.10 | 0.56 | 0.22 | 0.12 | 0.31 | | | | |
| TNFR2 | 0.21 | 0.21 | 0.06 | 0.24 | 0.37 | 0.27 | 0.28 | 0.27 | 0.47 | 0.28 | 0.01 | 0.08 | 0.27 | 0.34 | 0.19 | 0.14 | 0.09 | 0.24 | 0.12 | 0.10 | 0.31 | 0.65 | | | |
| uPAR | 0.25 | 0.08 | 0.39 | 0.34 | 0.41 | 0.40 | 0.26 | 0.29 | 0.49 | 0.28 | 0.20 | 0.35 | 0.36 | 0.39 | 0.27 | 0.19 | 0.44 | 0.19 | 0.20 | 0.03 | 0.17 | 0.40 | 0.19 | | |
| VEGF | 0.15 | 0.18 | 0.57 | 0.05 | 0.31 | 0.26 | 0.10 | 0.38 | 0.28 | 0.15 | 0.01 | 0.42 | 0.10 | 0.14 | 0.55 | 0.05 | 0.77 | 0.16 | 0.48 | 0.08 | 0.10 | 0.29 | 0.12 | 0.44 | |

Table S5. Eigenvalues of the reduced correlation matrix; Total 9.70, Average 0.39.

| | Eigenvalue | Proportion | Cumulative |
|-----------|-------------------|-------------------|-------------------|
| 1 | 5.29 | 0.55 | 0.55 |
| 2 | 2.99 | 0.31 | 0.85 |
| 3 | 1.43 | 0.15 | 1.00 |
| 4 | 0.98 | 0.10 | 1.10 |
| 5 | 0.93 | 0.10 | 1.20 |
| 6 | 0.66 | 0.07 | 1.26 |
| 7 | 0.57 | 0.06 | 1.32 |
| 8 | 0.34 | 0.04 | 1.36 |
| 9 | 0.24 | 0.03 | 1.38 |
| 10 | 0.15 | 0.02 | 1.40 |
| 11 | 0.06 | 0.01 | 1.41 |
| 12 | -0.01 | 0.00 | 1.41 |
| 13 | -0.04 | 0.00 | 1.40 |
| 14 | -0.10 | -0.01 | 1.39 |
| 15 | -0.15 | -0.02 | 1.38 |
| 16 | -0.16 | -0.02 | 1.36 |
| 17 | -0.20 | -0.02 | 1.34 |
| 18 | -0.26 | -0.03 | 1.31 |
| 19 | -0.31 | -0.03 | 1.28 |
| 20 | -0.36 | -0.04 | 1.24 |
| 21 | -0.40 | -0.04 | 1.20 |
| 22 | -0.42 | -0.04 | 1.16 |
| 23 | -0.48 | -0.05 | 1.11 |
| 24 | -0.49 | -0.05 | 1.06 |
| 25 | -0.58 | -0.06 | 1.00 |

Table S6. SASP factors presented according to factor loading. SASP measures can be classed generally as soluble signaling factors (cytokines, chemokines, and growth factors), soluble receptors or ligands, and proteases and regulators (MMP's and other enzymes), with further subclass or type, and biological role.

| | Variable | Name | Class | Subclass / Type | Role |
|----------|---------------------------------------|---|--------------------------|----------------------------------|--|
| Factor 1 | PDGF AA/AB | Platelet-Derived Growth Factor | Signaling factors | Growth factor | Proliferation; Chemoattractant; Mitogen |
| | Eotaxin / CCL11 | CC motif chemokine ligand, CCL11 | Signaling factors | CC Chemokine | Chemoattractant (eosinophils) |
| | PAI1 | Plasminogen Activator Inhibitor-1 | Proteases and regulators | Plasminogen activator system | Serine protease inhibitor (SERPIN) family; Regulate fibrinolytic system |
| | RANTES | Regulated upon Activation, Normal T Cell Expressed and Secreted | Signaling factors | CC Chemokine | Proinflammatory; Chemoattractant (T cells) |
| | VEGF | Vascular endothelial growth factor | Signaling factors | Growth factor | Vasculogenesis; Angiogenesis; PDGF subfamily |
| | MMP9 | Matrix Metalloproteinase-9 | Proteases and regulators | Enzyme (Matrixin) | Degradation of the extracellular matrix; Gelatinase |
| Factor 2 | TNFR1 | Tumor Necrosis Factor Receptor I | Receptors or ligands | TNF Superfamily | Immune cell regulation; Mediate apoptosis |
| | uPAR | Urokinase-type plasminogen activator receptor | Receptors or ligands | Plasminogen activator system | Wound healing; Proteolysis; Inflammation; Plasminogen activation system |
| | TNFR2 | Tumor Necrosis Factor Receptor II | Receptors or ligands | TNF Superfamily | Wound healing; Immune cell regulation |
| | MMP1 | Matrix Metalloproteinase-1 | Proteases and regulators | Enzyme (Matrixin) | Degradation of extracellular matrix; Collagenase |
| | GDF15 | Growth differentiating factor-15 | Signaling factors | TGF β Superfamily | Regulation of inflammatory pathways; Apoptosis; cell repair, and cell growth |
| | OPN | Osteopontin | Signaling factors | Extracellular structural protein | Apoptosis; Bone remodeling; Chemoattractant (neutrophils; macrophage) |
| | Fas | Fas Ligand | Receptors or ligands | TNF Superfamily | Mediate apoptosis |
| | MPO | Myeloperoxidase | Proteases and regulators | Leukocyte-derived enzyme | Catalyzes the formation of a number of reactive oxidant species |
| | GROα / CXCL1 | Growth-regulated protein alpha | Signaling factors | CXC Chemokine | Chemoattractant (neutrophils); Regulation of immune/inflammatory response |
| | TNFα | Tumor Necrosis Factor-alpha | Signaling factors | TNF Superfamily | Regulation of immune / inflammatory responses; Adipokine |
| | ICAM1 | Intercellular adhesion molecule-1 | Receptors or ligands | Immunoglobulin Superfamily | T-cell activation; Regulation of immune /inflammatory responses |
| Factor 3 | ActivinA | Activin A | Signaling factors | TGF β Superfamily | Regulation of proinflammatory responses; Differentiation |
| | RAGE | Receptor for advanced glycation end products | Receptors or ligands | Immunoglobulin Superfamily | Bind glycoproteins; Pro-inflammatory activation |
| | MMP7 | Matrix Metalloproteinase-7 | Proteases and regulators | Enzyme (Matrixin) | Degradation of the extracellular matrix; Wound healing |
| | MCP1 | Monocyte chemoattractant protein | Signaling factors | CC Chemokine / Cytokine | Chemoattractant (monocytes, basophils); Bone degradation |
| | MMP2 | Matrix Metalloproteinase-2 | Proteases and regulators | Enzyme (Matrixin) | Degradation of the extracellular matrix; Gelatinase |
| | SOST | Sclerostin precursor | Signaling factors | Secreted Glycoprotein | Wnt pathway inhibitor; Inhibit bone formation; |
| | ADAMTS13 | A disintegrin and metalloprotease with thrombospondin type motifs | Proteases and regulators | Enzyme (Matrixin) | Cleaves von Willebrand factor (vWf); Blood clotting |
| | PARC | Parkin-like ubiquitin ligase | Proteases and regulators | E3-ubiquitin ligase; RBR Family | Cytoplasmic anchor in p53-associated protein complexes |

Table S7. Intervention effect on circulating SASP factors presented according to factor loading at baseline and 18 weeks post-intervention of CR or health education control. Data are estimated means and standard error and change as difference of least squares means; intervention effect as mixed model Type 3 tests of fixed effects F-statistic and p-value. Simple linear regression was used to test if change in composite SASP Factor scores significantly predicted % change in weight with intervention (R^2 , F-statistic, p-value). * $p \leq 0.05$.

| | Intervention Group (unadjusted) | | | Intervention Effect (adjusted) | Regression, Δ Exp with % Change Weight |
|----------------------|--------------------------------------|--------------------|----------------------|--------------------------------|--|
| | CR | Control | Unadjusted | Adjusted | |
| | est. mean \pm SE | est. mean \pm SE | p-value ¹ | p-value ³ | R^2 p-values |
| SASP Factor 1 | | | | p=0.928 | $R^2 = 0.027$ p = 0.248 |
| Baseline | 7.59 \pm 0.11 | 7.55 \pm 0.12 | 0.840 | | |
| Post-intervention | 7.51 \pm 0.11 | 7.46 \pm 0.12 | 0.780 | | |
| Change | -0.077 \pm 0.09 | -0.091 \pm 0.093 | 0.916 | | |
| SASP Factor 2 | | | | p 0.046* | $R^2 = 0.123$ p = 0.011* |
| Baseline | 7.57 \pm 0.04 | 7.69 \pm 0.05 | 0.065 | | |
| Post-intervention | 7.51 \pm 0.04 | 7.69 \pm 0.05 | 0.005* | | |
| Change | -0.062 \pm 0.02* | 0.002 \pm 0.02 | 0.048* | | |
| SASP Factor 3 | | | | p 0.072 | $R^2 = 0.067$ p = 0.068 |
| Baseline | 7.54 \pm 0.04 | 7.57 \pm 0.05 | 0.644 | | |
| Post-intervention | 7.46 \pm 0.05 | 7.57 \pm 0.05 | 0.108 | | |
| Change | -0.082 \pm 0.03* | 0.003 \pm 0.03 | 0.072 | | |

1 Unadjusted comparison

2 Models were adjusted for age, sex and race

3 Age, sex, and race adjusted comparison to detect intervention effect. F-value and p correspond to Type III fixed effect model for adjusted time \times intervention group interaction in model adjusted for age, sex, and race