

**Association of Dimethylguanidino Valeric Acid With Partial Resistance  
to Metabolic Health Benefits of Regular Exercise**

**IMPORTANCE:**

Metabolic responses to exercise training are variable. Metabolite profiling may aid in the clinical assessment of an individual's responsiveness to exercise interventions.

**OBJECTIVE:**

To investigate the association between a novel circulating biomarker of hepatic fat, dimethylguanidino valeric acid (DMGV), and metabolic health traits before and after 20 weeks of endurance exercise training.

**DESIGN, SETTING, AND PARTICIPANTS:**

This study involved cross-sectional and longitudinal analyses of the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study, a 20-week, single-arm endurance exercise clinical trial performed in multiple centers between 1993 and 1997. White participants with sedentary lifestyles who were free of cardiometabolic disease were included. Metabolomic tests were performed using a liquid chromatography, tandem mass spectrometry method on plasma samples collected before and after exercise training in the HERITAGE study. Metabolomics and data analysis were performed from August 2017 to May 2018.

**EXPOSURES:**

Plasma DMGV levels.

**MAIN OUTCOME AND MEASURES:**

The association between DMGV levels and measures of body composition, plasma lipids, insulin, and glucose homeostasis before and after exercise training.

**RESULTS:**

Among the 439 participants included in analyses from HERITAGE, the mean (SD) age was 36 (15) years, 228 (51.9%) were female, and the median (interquartile range) body mass index was 25 (22-28). Baseline levels of DMGV were positively associated with body fat percentage, abdominal visceral fat, very low-density lipoprotein cholesterol, and triglycerides, and inversely associated with insulin sensitivity, low-density lipoprotein cholesterol, high-density lipoprotein size, and high-density lipoprotein cholesterol (range of  $\beta$  coefficients, 0.17-0.46 [SEs, 0.026-0.050]; all  $P < .001$ , after adjusting for age and sex). After adjusting for age, sex, and baseline traits, baseline DMGV levels were positively associated with changes in small high-density lipoprotein particles ( $\beta$ , 0.14 [95% CI, 0.05-0.23]) and inversely associated with changes in medium and total high-density lipoprotein particles ( $\beta$ , -0.15 [95% CI, -0.24 to -0.05] and -0.19 [95% CI, -0.28 to -0.10], respectively), apolipoprotein A1 ( $\beta$ , -0.14 [95% CI, -0.23 to -0.05]), and insulin sensitivity ( $\beta$ , -0.13;  $P = 3.0 \times 10^{-3}$ ) after exercise training.

**CONCLUSIONS AND RELEVANCE:**

Dimethylguanidino valeric acid is an early marker of cardiometabolic dysfunction that is associated with attenuated improvements in lipid traits and insulin sensitivity after exercise training. Levels of DMGV may identify individuals who require additional therapies beyond guideline-directed exercise to improve their metabolic health.