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COMMENTARY

WILEY

Genetically determined lean mass and dietary response

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Abstract

Weight loss attenuates many obesity-related co-morbidities, but is difficult to sustain with dietary change. Dietary adherence, not macronutrient composition, is a better predictor of weight loss. Weight loss-induced endocrine changes promote food intake and increase energy efficiency, contributing to the difficulty with dietary adherence and weight regain. Macronutrient preference is partly genetically determined, suggesting that personalized dietary interventions might be more successful. In this issue, Li et al. report that a genetic risk score comprising the cumulative weighted effects of variants previously associated with increased lean mass is associated with increased satiety and weight loss 6 months after initiating a low- but not a high-fat diet. The effects were attenuated by 2 years. These findings suggest that genetic variants may influence response to specific diet. Further studies are necessary to assess whether genetically determined lean mass is causally associated with dietary response. Significant progress has recently been made in identifying additional genetic determinants of lean mass, which will enable such investigations and potentially inform future nutritional studies.

KEYWORDS

genetic risk score, lean mass, weight loss

Obesity is a major public health concern.[1] A number of diets with varying macronutrient composition effectively initiate short-term weight loss, but weight regain over time is common,[2] partly because of adaptive endocrine changes that promote food intake and increase energy efficiency.[3–5] Adherence, rather than the macronutrient composition of a diet, is a better predictor of long-term weight loss.[6]

Can dietary interventions be personalized to increase adherence and maintain weight loss? Obesity is heritable (estimated heritability of 40%-70% based on family and twin studies), as is its response to interventions such as bariatric surgery.[7,8] Loss of function variants in *MC4R*, the commonest monogenic cause for childhood obesity, are associated with a preference for high fat but not high sucrose foods.[9] Other data also show that genetic factors are associated with nutritional preferences.[10]

Skeletal muscle is a major determinant of energy expenditure and can thus influence body weight, appetite and response to dietary intervention.[11] Dual-energy x-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA) can be used to measure appendicular lean mass (a measure of skeletal muscle mass) and total lean mass (a measure of skeletal, smooth and cardiac muscle).[12] In this issue of the journal, Li et al. assess the effects of a genetic risk score (GRS) based on five single nucleotide polymorphisms (SNPs)[13] on appetite and weight loss in the Preventing Overweight Using Novel Dietary Strategies (POUNDS) lost trial.[14] These SNPs have previously been shown in a genome-wide association study (GWAS) to be associated with DEXA-derived lean mass (after adjustment for sex, age, height and fat mass) and cumulatively explain less than 1% of the heritability of lean mass (estimated to be ~65% in sibling studies).[13,15] The POUNDS lost trial is a multi-ethnic study (84% Caucasian, 61% female) that comprised four dietary interventions, including two low-fat and two high-fat diets.[14] All diets were low in saturated fat. The authors reported that a low GRS (predicted to increase lean mass based on a prior GWAS)[13] was associated with reduced appetite (as assessed by visual analogue scale) along with reduced waist circumference and weight after 6 months on a low-fat diet, but was not associated with these variables on a high-fat diet.[14] Dietary intake was assessed in a random sample of 50% of participants, by review of the 5-day diet record at baseline, and by 24-hour recall during a

telephone interview on 3 non-consecutive days at 6 months and 2 years. Two biomarkers of adherence (urinary nitrogen and respiratory quotient) were also assessed. By the end of the trial, 2 years after randomization, the weight-loss effects were attenuated in the low-fat group.[14] This study shows that genetic variants can potentially predict response to dietary intervention in a randomized clinical trial, in addition to influencing macronutrient preference.

These intriguing findings should encourage further studies to assess whether there is a causal relationship between skeletal muscle mass and response to low-fat diet. The GRS deployed by Li et al. explains less than 1% of the heritability of lean mass and did not correlate with lean mass in POUNDS lost study participants.[13,14] A more recent study identified 1059 SNPs at 799 loci, associated with BIA-measured appendicular lean mass in both sexes, adjusted for covariates including appendicular fat mass and age.[12] Together, these explain ~15.5% of the heritability of appendicular lean mass (which correlates with total lean mass).[12] These variants can potentially be used to investigate whether genetically determined appendicular lean mass and/or skeletal muscle mass is causally associated with response to low-fat diet through Mendelian randomization (MR) analyses. MR utilizes genetic variants as instruments to assess causal associations between phenotypes, which can inform future clinical studies. For example, genetic variants that increase the risk of type 2 diabetes also increase the risk of cardiovascular disease,[16] suggesting that type 2 diabetes increases the risk of cardiovascular disease. Loss of function mutations in *PCSK9* causally associate with very low density lipoprotein (LDL) and protect from coronary artery disease, consistent with low LDL being protective for heart disease.[17] PCSK9 inhibitors have been shown to lower LDL and prevent coronary artery disease.[18]

Although MR can be informative, variants that have pleiotropic effects on other traits are potential confounders and will need to be adjusted for in any analysis (horizontal pleiotropy).[19,20] For example, in the POUNDS lost trial, rs2943656, near *IRS1* (encoding insulin receptor substrate 1) was most significantly associated with appetite and weight loss at 6 months in the low-fat group.[14] rs2943656 is in linkage disequilibrium (1000 genomes phase 3 European super-population, r^2 = 0.87) with rs2943650,[13] which associates with reduced IRS1 expression in adipose tissue, reduced adiposity and insulin resistance.[21] IRS1 is an integral component of the insulin signalling pathway,[21] which in the central nervous system can potentially regulate appetite and food choice.[22] Thus, rs2943656 may potentially mediate the response to a low-fat diet via altered lean mass, adipose mass and/or central nervous system insulin action.

Most GRSs have largely been developed in people of recent European ancestry and may not perform as well in other ancestries.[23] The genetic variants associated with lean mass have been found in predominantly Caucasian cohorts.[12,13] Importantly, Li et al. reported concordant findings between Caucasian participants and the overall group.[14] Genetic studies of lean mass as well as intervention studies in non-Caucasian diverse populations will be informative, as shown recently in a multi-ancestry study of type 2 diabetes.[24]

In summary, Li et al. have identified genetic variants associated with increased satiety and weight loss in response to a low-fat diet, adding to their prior work that suggests genetic variants can influence response to dietary macronutrient composition[25] and previous work showing that genetic variants predict macronutrient preference.[9,10] MR analysis based on recent advances in genetic determinants of appendicular lean mass[12] can potentially determine whether there are causal associations between skeletal muscle mass and response to specific dietary interventions. This knowledge may inform future clinical studies assessing more individualized dietary interventions.

CONFLICT OF INTEREST

SD has received speaker fees and consultancy fees from Eli Lilly and NovoNordisk. ADP has no conflict of interests.

AUTHOR CONTRIBUTIONS

SD and ADP wrote and edited the manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13-27.
2. Johnston BC, Kanters S, Bandayrel K, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA*. 2014;312(9):923-933.
3. Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. *J Clin Invest*. 2008;118(7):2583-2591.
4. Rosenbaum M, Goldsmith R, Bloomfield D, et al. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. *J Clin Invest*. 2005;115(12):3579-3586.
5. Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med*. 2011;365(17):1597-1604.
6. Del Corral P, Bryan DR, Garvey WT, Gower BA, Hunter GR. Dietary adherence during weight loss predicts weight regain. *Obesity*. 2011;19(6):1177-1181.
7. Hatoum IJ, Greenawalt DM, Cotsapas C, Reitman ML, Daly MJ, Kaplan LM. Heritability of the weight loss response to gastric bypass surgery. *J Clin Endocrinol Metab*. 2011;96(10):E1630-E1633.
8. O'Rahilly S, Farooqi IS. Human obesity: a heritable neurobehavioral disorder that is highly sensitive to environmental conditions. *Diabetes*. 2008;57(11):2905-2910.
9. van der Klaauw AA, Keogh JM, Henning E, et al. Divergent effects of central melanocortin signalling on fat and sucrose preference in humans. *Nat Commun*. 2016;7:13055. Epub May 11.

10. Meddens SFW, de Vlaming R, Bowers P, et al. Genomic analysis of diet composition finds novel loci and associations with health and lifestyle. *Mol Psychiatry*. 2020. Epub May 11.
11. Deriaz O, Fournier G, Tremblay A, Despres JP, Bouchard C. Lean-body-mass composition and resting energy expenditure before and after long-term overfeeding. *Am J Clin Nutr*. 1992;56(5):840-847.
12. Pei YF, Liu YZ, Yang XL, et al. The genetic architecture of appendicular lean mass characterized by association analysis in the UK biobank study. *Commun Biol*. 2020;3(1):608.
13. Zillikens MC, Demissie S, Hsu YH, et al. Large meta-analysis of genome-wide association studies identifies five loci for lean body mass. *Nat Commun*. 2017;8(1):80.
14. Li X, Zhou T, Ma H, et al. Genetic variation of lean body mass, changes of appetite, and weight loss in response to diet interventions: the POUNDS lost trial. *Diabetes Obes Metab*. 2020;22(12):2305-2315.
15. Hsu FC, Lenchik L, Nicklas BJ, et al. Heritability of body composition measured by DXA in the diabetes heart study. *Obes Res*. 2005;13(2):312-319.
16. Ahmad OS, Morris JA, Mujammami M, et al. A Mendelian randomization study of the effect of type-2 diabetes on coronary heart disease. *Nat Commun*. 2015;6:7060.
17. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354(12):1264-1272.
18. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722.
19. Bowden J, Hemani G, Davey Smith G. Invited commentary: detecting individual and global horizontal pleiotropy in Mendelian randomization-a job for the humble heterogeneity statistic? *Am J Epidemiol*. 2018;187(12):2681-2685.
20. Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. *Hum Mol Genet*. 2018;27(R2):R195-R208.
21. Kilpelainen TO, Zillikens MC, Stancakova A, et al. Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. *Nat Genet*. 2011;43(8):753-760.
22. Hallschmid M, Higgs S, Thienel M, Ott V, Lehnert H. Postprandial administration of intranasal insulin intensifies satiety and reduces intake of palatable snacks in women. *Diabetes*. 2012;61(4):782-789.
23. Duncan L, Shen H, Gelaye B, et al. Analysis of polygenic risk score usage and performance in diverse human populations. *Nat Commun*. 2019;10(1):3328.
24. Vujkovic M, Keaton JM, Lynch JA, et al. Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis. *Nat Genet*. 2020;52(7):680-691.
25. Huang T, Qi Q, Li Y, et al. FTO genotype, dietary protein, and change in appetite: the preventing overweight using novel dietary strategies trial. *Am J Clin Nutr*. 2014;99(5):1126-1130.

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