abdominal adiposity and circulating glutamate is causal, as well as the direction of this association, is unknown. Here, we aimed to determine whether obesity and abdominal obesity were causally associated with circulating glutamate levels. **Methods:** We used a two-sample bi-directional inverse-variance weighted Mendelian randomization study design (IVW-MR). We derived summary statistics for our exposures and outcomes from published genome-wide association studies from the GIANT consortium (n = 681 275) and blood metabolites (n = 7 804). We identified independent genetic variants ($r^2 < 0.1$) associated with body mass index (BMI) and waist-to-hip ratio adjusted for BMI (WHRadjBMI, $p < 5x10^{-8}$) as well as circulating glutamate ($p < 5x10^{-5}$). **Results:** We found no causal association between circulating glutamate levels and BMI (beta = 0.082, SE = 0.0413, p = 0.0471) or WHRadjBMI (beta = -0.00106, SE = 0.0401, p = 0.979). However, there was a positive effect of BMI (beta = 0.0608, SE = 0.0150, $p = 5.19x10^{-5}$) and WHRadjBMI (beta = 0.0701, SE = 0.0198, $p = 3.98x10^{-4}$) on circulating glutamate level. **Conclusion:** This Mendelian randomization analysis suggests that obesity and abdominal obesity are causally related to elevated circulating glutamate levels. Glutamate levels are not causally related to adiposity. Whether the downregulation of branched-chain amino acid catabolism in adipose tissue reported in obesity underlies this association should be explored.

Adipose Tissue, Appetite, and Obesity
INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

Once-weekly Subcutaneous Semaglutide 2.4 mg Reduces Body Weight in Adults with Overweight or Obesity Regardless of Baseline Characteristics (STEP 1)

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Background: Semaglutide is a long-acting, subcutaneous (s.c.), glucagon-like peptide-1 analogue that is currently being investigated for obesity management in adults with overweight or obesity in the phase 3 STEP clinical trial program. Varying degrees of weight loss were observed with once-weekly s.c. semaglutide 2.4 mg in STEP 1, and a post-hoc analysis was conducted to investigate weight loss in subgroups of participants based on their baseline characteristics.

Methods: STEP 1 was a randomized, double-blind, placebo-controlled, phase 3 trial (NCT03548935). Adults aged ≥18 years with either body mass index (BMI) ≥27 kg/m^2 with ≥1 weight-related comorbidity or BMI ≥30 kg/m^2, without type 2 diabetes, were randomized 2:1 to 68 weeks' treatment with once-weekly s.c. semaglutide 2.4 mg or placebo, as adjunct to lifestyle intervention. A descriptive evaluation of categorical weight loss with semaglutide from baseline to week 68 (≥20%, 15-<20%, 10-<15%, 5-<10%) by baseline characteristics (age, sex, race [White, Asian, Black or African American, other], body weight, BMI, waist circumference, and glycemic status [normo-glycemia, prediabetes]) was conducted. Mean percent weight loss with semaglutide from baseline to week 68 was analyzed separately by sex (male, female) and baseline body weight (≥115 kg, 100-<115 kg, 90-<100 kg, <90 kg) using a mixed model for repeated measurements analysis with treatment, subgroup (of sex or baseline body weight), and the interaction between treatment and subgroup as factors, and baseline body weight as a covariate, all nested within visit (based on the trial product estimand [treatment effect assuming treatment adherence and without use of rescue intervention] for the on-treatment period).

Results: STEP 1 included 1,961 randomized participants (mean age 46 years, body weight 105.3 kg, BMI 37.9 kg/m^2; 74.1% female). For categorical weight loss, the observed proportions of participants with ≥20%, 15-<20%, 10-<15%, and 5-<10% weight loss at week 68 were 34.8%, 19.9%, 20.0%, and 17.5% with semaglutide vs 2.0%, 3.0%, 6.8%, and 21.2% with placebo, respectively. The distribution of participants across weight loss groups did not appear to be affected by any baseline characteristics, except sex and baseline body weight. Mean percent weight loss at week 68 with semaglutide was greater among females than males, and in participants with lower vs higher baseline body weight. Sex and baseline body weight were independently associated with weight loss with semaglutide vs placebo at week 68 ($p<0.001$ for both tests for subgroup interactions).

Conclusion: In STEP 1, weight loss with once-weekly s.c. semaglutide 2.4 mg was seen in all subgroups evaluated, and was generally not influenced by baseline characteristics. The exception was sex and baseline body weight; female sex and a low baseline body weight were associated with a greater response to semaglutide.

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Prevalence of Childhood Obesity in the United States 1999 - 2018: A 20-Year Analysis

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