TO THE EDITOR: Kelly et al. (April 2 issue) compared liraglutide with placebo for weight reduction in 251 adolescents. Gastrointestinal adverse events were more common with liraglutide (81 of 125 participants [65%]) than with placebo (46 of 126 participants [37%]). Gastrointestinal problems are known to be associated with malabsorption. Nutrient replacement is recommended after gastric bypass, and whether it may also be needed in adolescents receiving glucagon-like peptide 1 (GLP-1) receptor agonists such as liraglutide should be studied, particularly in the context of the development of clinically significant gastrointestinal adverse events in adolescents receiving GLP-1 receptor agonists. We therefore ask the authors whether any data on the levels of ferritin and vitamin B12 and development of anemia with liraglutide treatment are available.

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**TO THE EDITOR:** Kelly et al. found that liraglutide is useful for weight management in adolescents with obesity. Roughly a quarter of the participants had dysglycemia, which the authors defined as “type 2 diabetes or prediabetes.” The authors excluded adolescents who received metformin for weight loss but not those who received metformin for diabetes control. The authors did not report the number of participants receiving metformin, which is associated with weight loss in adolescents. We believe these data are important to share to assess the validity of the authors’ main conclusion. Srinivasan et al. performed a randomized, controlled trial and found that metformin (at a dose of 1 g twice daily for 6 months) had a greater treatment effect than placebo with respect to weight and body-mass index (BMI) in children and adolescents with obesity.1 Similarly, Kay et al. found that adolescents with obesity who received metformin (at a dose of 850 mg twice daily for 8 weeks) and maintained a low-calorie diet had greater weight loss and less body fat than those who received placebo and maintained a low-calorie diet.2

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**TO THE EDITOR:** Kelly et al. tried to elucidate the probable beneficial effect of liraglutide in adolescents with obesity. We would like to question some aspects of this study.

First, energy intake and physical activity of the participants were not investigated, yet energy intake and physical activity are major factors affecting body weight, and data on these variables at baseline and at the end of the study were not reported. Also, whether liraglutide use can affect energy intake in adolescents was not discussed. Second, changes in body height as of the end of the study are not mentioned. Fifty-six weeks is a relatively long time, and adolescents can have substantial changes in height during that time. Differences between the groups may have occurred and should, in our view, have been reported. Third, the side effects of liraglutide, especially nausea and vomiting, may have caused the weight loss.

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**THE AUTHORS REPLY:** With regard to gastrointestinal adverse events and potential malabsorption, we observed no difference between the liraglutide group and the placebo group in the change in hemoglobin from baseline to 56 weeks (estimated treatment difference, 0.12 mmol per liter; 95% confidence interval [CI], −0.02 to 0.26; P=0.10). We did not measure levels of ferritin or vitamin B12, but no adverse events related to malabsorption, malnutrition, anemia, vitamin B12, or ferritin were reported by participants.

Regarding the potential effect of metformin on the primary outcome, a relatively low proportion of the enrolled participants (33 of 251) were concurrently treated with metformin (13 of 125 assigned to liraglutide and 20 of 126 assigned to placebo); all but 2 were receiving metformin at the time they began the trial. We performed a sensitivity analysis using data from the 218 participants who were not receiving concurrent metformin treatment. The estimated treatment difference in BMI standard-deviation scores with liraglutide as compared with placebo at week 56 was −0.25 (95% CI, −0.41 to −0.10; P=0.001). Therefore, we feel that any potential effect of metformin on the efficacy results is negligible. We did not measure energy intake or physical activity in the current trial. However, evidence from trials of liraglutide in adults suggests that weight loss is mediated primarily by reduced appetite and energy intake.3 In our current trial, we reported the standard-deviation score for height — which, in our opinion, is the most appropri-
ate height-related end point because it accounts for age and sex differences\(^2\) — at baseline, week 56, and week 82. The mean change in absolute height from baseline to 56 weeks was 0.01 m (5th to 95th percentile range, 0.00 to 0.06) in the liraglutide group and 0.02 m (5th to 95th percentile range, 0.00 to 0.07) in the placebo group. Many participants at baseline were near or at their final height, as determined by assessment of bone age, which could account for the minor changes in height observed in both groups over the duration of the trial.

A post hoc subgroup analysis of changes in BMI standard-deviation scores in participants with one or more gastrointestinal adverse events as compared with participants with no gastrointestinal adverse events during the 56-week treatment period showed that the effect of liraglutide in reducing BMI standard-deviation scores was independent of gastrointestinal adverse events (\(P = 0.82\)), a finding consistent with results from trials of liraglutide in adults.\(^3\)

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Since publication of their article, the authors report no further potential conflict of interest.

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