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Effect of Semaglutide on Insulin Sensitivity and Cardiometabolic Risk Factors in Adolescents With Obesity: The STEP TEENS Study

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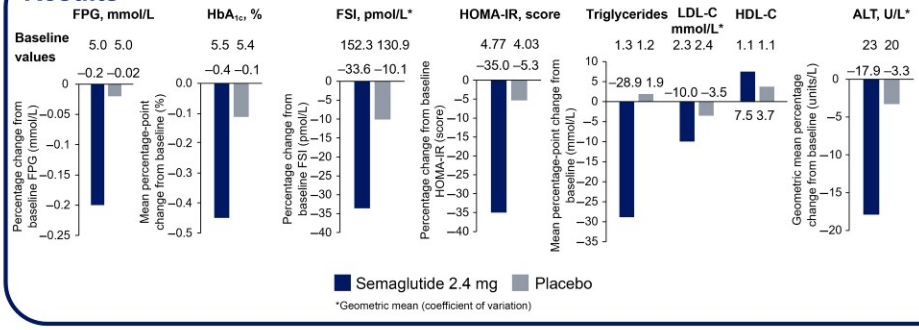
In this secondary analysis of the STEP TEENS trial, semaglutide 2.4 mg improved insulin sensitivity, glycemic measures, and cardiovascular risk factors in adolescents living with obesity

Background The STEP TEENS (NCT04102189) study in adolescents (aged 12 to <18 years) with obesity demonstrated that once-weekly subcutaneous semaglutide 2.4 mg provided a greater percentage reduction in BMI than placebo at week 68.

Aim This secondary analysis of STEP TEENS investigated the effect of semaglutide 2.4 mg versus placebo on insulin sensitivity, glycemic measures, and cardiovascular risk factors in adolescents with obesity and without type 2 diabetes.

Results



Participants treated with semaglutide had significantly **greater improvements in insulin sensitivity, glycemic measures, and cardiovascular risk factors** compared with placebo.

Semaglutide-treated participants achieving ≥20% body weight reduction had greater improvements in glycemic and cardiovascular risk parameters compared with those achieving <20%.

These data support that semaglutide 2.4 mg, besides providing efficacious weight reduction has the added advantage of improving health by reducing obesity-related cardiometabolic risk factors in adolescents with obesity.

ALT, alanine aminotransferase; FPG, fasting plasma glucose; FSI, fasting serum insulin; HbA_{1c}, glycated hemoglobin; HDL-C, HDL cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; LDL-C, LDL cholesterol; STEP TEENS, Semaglutide Treatment Effect in People with obesity (STEP) TEENS.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Semaglutide is an approved weight management treatment for adolescents with obesity. However, its effects on insulin sensitivity, glycemia, and cardiometabolic risk factors remain unknown and need elucidation.
- **What is the specific question(s) we wanted to answer?**
  How does once-weekly subcutaneous semaglutide 2.4 mg versus placebo affect insulin sensitivity, glycemic measures, and cardiometabolic risk factors in adolescents living with obesity?
- **What did we find?**
  Participants treated with semaglutide 2.4 mg had significantly greater improvements in insulin sensitivity, glycemic measures, and cardiometabolic risk factors compared with placebo.
- **What are the implications of our findings?**
  These novel data support that semaglutide 2.4 mg, in addition to providing efficacious weight reduction, improves health by reducing obesity-related cardiometabolic risk factors in adolescents with obesity.

Effect of Semaglutide on Insulin Sensitivity and Cardiometabolic Risk Factors in Adolescents With Obesity: The STEP TEENS Study

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OBJECTIVE

This secondary analysis of the Semaglutide Treatment Effect in People with obesity (STEP) TEENS (NCT04102189) study investigated the effect of semaglutide 2.4 mg versus placebo on insulin sensitivity and cardiometabolic risk factors.

RESEARCH DESIGN AND METHODS

The STEP TEENS phase 3a randomized study in adolescents (aged 12 to <18 years) with obesity demonstrated that once-weekly subcutaneous semaglutide 2.4 mg provided a significantly greater percentage reduction in BMI than placebo at week 68 (estimated difference −16.7 percentage points; $P = 0.0001$). This analysis investigated changes in insulin sensitivity and cardiometabolic risk factors from baseline to week 68.

RESULTS

Overall, 193 participants without type 2 diabetes were included in the analysis. Participants receiving semaglutide 2.4 mg ($n = 129$) compared with those receiving placebo ($n = 64$) had greater reductions from baseline in fasting serum insulin (−33.6% vs. −10.1%; $P = 0.0012$), homeostatic model assessment for insulin resistance (HOMA-IR) score (−35.0% vs. −5.3%; $P = 0.0002$), glycemic measures (glycated hemoglobin: $P < 0.0001$; fasting plasma glucose: $P = 0.0181$), alanine aminotransferase (ALT; −17.9% vs. −3.3%; $P = 0.0232$), waist-to-height ratio ($P < 0.0001$), triglycerides ($P < 0.0001$), LDL cholesterol ($P = 0.0105$), and total cholesterol ($P < 0.0001$). Moreover, greater improvements in insulin sensitivity, glycemic measures, and cardiometabolic risk factors were seen in semaglutide 2.4 mg recipients with BMI reductions of ≥20% versus <20%.

CONCLUSIONS

These novel data support semaglutide 2.4 mg as an efficacious obesity treatment in adolescents with obesity and advance its application by showing associated improvements in insulin sensitivity, glycemic measures, ALT, and other cardiometabolic risk factors.

Obesity in children and adolescents is defined as abnormal or excessive body fat accumulation that presents a risk to health (1). In 2020, globally, ∼430 million children and adolescents aged 5–19 years were estimated to have obesity, a figure which is projected to increase to 770 million by 2035 (2). Early childhood is a critical time in the development of obesity; once manifested, obesity tracks into adolescence and adulthood (3). Excessive body fat accumulation during childhood is

ORIGINAL ARTICLE

associated with the development of serious chronic diseases, such as type 2 diabetes, dyslipidemia, hypertension, metabolic dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnea, cardiovascular disease, and premature death (4–8).

Current evidence suggests that the increasing prevalence of youth-onset type 2 diabetes is driven by an increase in childhood obesity (9), and severe adolescent obesity substantially increases the risk of type 2 diabetes in early adulthood in both sexes (10), with the first signs of metabolic deterioration already present at a young age in children with obesity (11). Additionally, type 2 diabetes in adolescents exhibits an aggressive clinical course characterized by rapid deterioration in β-cell function, early onset and rapid progression of complications, and inferior treatment response compared with adult type 2 diabetes (12–14). Therefore, prevention of type 2 diabetes is of paramount importance.

Obesity and type 2 diabetes, whether in adults or adolescents, share insulin resistance as a common pathophysiological mechanism (15). However, insulin resistance in adolescents is worse than in adults. Adolescents with obesity and impaired glucose tolerance matched to adults for BMI, sex, and race had ∼53% lower hepatic insulin sensitivity, ∼42% lower peripheral insulin sensitivity, and twofold higher fasting serum insulin despite having a similar body fat percentage (15). Similar results were demonstrated by the RISE Consortium, which reported ∼46% lower clamp-measured peripheral insulin sensitivity and ∼50% lower 1/fasting serum insulin, a surrogate for insulin sensitivity (16,17). A substantial body of evidence has accumulated regarding the issue of obesity-related cardiovascular risk in childhood (18), notably the number of identified risk factors escalates in proportion to the severity of childhood obesity (19). Therefore, not only is the early treatment of childhood obesity of paramount importance (9,20,21), but alleviation of the characteristics of severe insulin resistance and reduction of cardiometabolic risk are essential in adolescents with obesity.

Between 2003 and 2022, five obesity pharmacotherapies were approved by the U.S. Food and Drug Administration for adolescents: liraglutide, semaglutide, orlistat, and phentermine/topiramate extended-release capsules (for those aged ≥12 years), and phentermine for short-term use (for those aged >16 years), two of which (liraglutide and semaglutide) are also approved by the European Medicines Agency (for those aged ≥12 years) (6,7,22–26). Setmelanotide is also approved by both agencies for use in people with rare monogenetic obesity (for those aged ≥2 years) (27,28).

Semaglutide 2.4 mg is a long-acting glucagon-like peptide 1 (GLP-1) analog approved for once-weekly subcutaneous injection for chronic weight management in adolescents (aged ≥12 years) with obesity (25,26). The Semaglutide Treatment Effect in People with obesity (STEP) TEENS study (ClinicalTrials.gov reg. no. NCT04102189) demonstrated that once-weekly semaglutide 2.4 mg was superior to placebo in terms of mean percentage reduction in BMI from baseline to week 68, with an estimated difference of −16.7 percentage points for the treatment policy estimand ($P < 0.0001$) (29). Furthermore, a secondary analysis of the STEP TEENS study demonstrated that treatment with semaglutide 2.4 mg resulted in 44.9% of participants achieving a BMI below the obesity threshold, compared with 12.1% of participants in the placebo group (30). To further probe the insulin-sensitizing and cardiometabolic benefits of once-weekly subcutaneous semaglutide 2.4 mg in adolescents with obesity, the present secondary analysis was conducted.

The objective of this secondary analysis was to evaluate insulin sensitivity, glucose metabolism, and cardiometabolic risk factors in participants with obesity from the STEP TEENS study. This analysis also evaluated cardiometabolic risk factors by BMI reduction from baseline to week 68.

RESEARCH DESIGN AND METHODS

Study Design and Participants

STEP TEENS was a 68-week, double-blind, randomized, placebo-controlled, phase 3a clinical study conducted at 37 sites across eight countries from October 2019 through March 2022; the full methodology has previously been published (29).

The study included adolescents aged 12 to <18 years, with a BMI ≥95th percentile or a BMI ≥85th percentile with ≥1 comorbidity who had at least one self-reported unsuccessful dietary effort to lose weight. Exclusion criteria were weight change >5 kg or obesity medication use ≤90 days before screening, prior bariatric surgery, uncontrolled thyroid disease, presence of secondary obesity causes, major depressive disorder ≤2 years before screening, personal or family history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma, history of type 1 diabetes, diagnosis of severe psychiatric disorder or bulimia nervosa, and history of suicide attempt. For the present analysis, participants with type 2 diabetes ($n = 8$) were excluded to ensure homogeneity among the participants included.

Efficacy Outcomes and Analyses

The primary end point of the STEP TEENS study was the percentage change in BMI from baseline (time of randomization) to week 68 (29). In this secondary analysis, the following prespecified supportive secondary and exploratory end points from the STEP TEENS study were assessed from baseline (week 0) to week 68: body weight (kg and percentage); waist circumference (cm); systolic and diastolic blood pressure (mmHg); glycated hemoglobin (HbA_{1c}) at screening only for participants without type 2 diabetes who are part of the present analysis; (percentage and mmol/mol); fasting plasma glucose (FPG; mmol/L and mg/dL); fasting serum insulin (pmol/L and mU/L); homeostatic model assessment for insulin resistance (HOMA-IR; score); liver enzyme alanine aminotransferase (ALT; U/L); and fasting lipids (mmol/L and mg/dL), which included total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides. Additional exploratory end points included changes from baseline (week 0) to week 68 in waist-to-height ratio and estimated glomerular filtration rate (eGFR), and the proportion of participants with prediabetes at baseline achieving normoglycemia at week 68. Additionally, the proportion of participants with cardiometabolic risk factors was assessed. Hypertriglyceridemia, low HDL, elevated systolic and diastolic blood pressure, FPG, and ALT at week 68 were assessed. Thresholds for risk were defined as follows: hypertriglyceridemia as serum triglyceride levels ≥1.7 mmol/L (≥150 mg/dL); low HDL cholesterol as ≤1.0 mmol/L (≤40 mg/dL); high systolic and diastolic blood pressure were ≥130 and ≥80 mmHg, respectively; high FPG ≥5.6 mmol/L; and elevated ALT >25.8 U/L and >22.1 U/L in male and female participants, respectively.

All end points were also assessed according to stratification of BMI reduction in participants receiving semaglutide 2.4 mg only (<5% [this group includes those whose BMI increased], ≥5% to <20%, and ≥20% BMI reduction). An analysis comparing semaglutide 2.4 mg versus placebo responder subgroups was not performed, because differences in their respective trajectories could not be explained as a result of unknown underlying differences in semaglutide 2.4 mg versus placebo recipients.

Laboratory testing was conducted centrally by ICON Laboratory Services, Inc. (all standard laboratory assessments for efficacy and safety) in STEP TEENS and all global phase 3a STEP studies. Assessments were reported with pediatric reference ranges (age- and sex-specific cutoffs) for the lower and upper limit of normal, specifically for assays and methods used.

Statistical Analyses

The analysis model for all end points was a linear regression model (ANCOVA) with randomized treatment and stratification factor (sex, Tanner stage [2–3 vs. 4–5], and their interaction) as factors and baseline value as covariates. A multiple imputation approach was used for missing data (31). The resulting estimated treatment differences (ETDs) were reported with 95% CIs and corresponding *P* values. These analyses addressed a treatment policy estimand, in which all data collected during the study were included for all randomized participants regardless of adherence to treatment or initiation of other antiobesity therapies (32). *P* values <0.05 were considered statistically significant. Statistical analyses were not adjusted for multiplicity. Statistical analyses were carried out for change from baseline to week 68 in HbA_{1c}, fasting serum insulin, HOMA-IR, cardiometabolic risk factors (including serum lipids and ALT), for semaglutide 2.4 mg versus placebo in the entire study population (excluding those with type 2 diabetes). For change from baseline to week 68 in various end points in the semaglutide 2.4 mg group by BMI reduction, descriptive statistics are presented. Statistical analyses were performed with the use of SAS software (version 9.4; SAS Institute).

Data and Resource Availability

Data will be shared with bona fide researchers who submit a research proposal approved by the independent review board. Individual participant data will be shared in data sets in a deidentified and anonymized format. Information about data access request proposals can be found at novonordisk-trials.com.

RESULTS

Participants and Treatment

In the STEP TEENS study, 201 participants were randomized to receive semaglutide 2.4 mg (*n* = 134) or placebo (*n* = 67). For the present secondary analysis, eight participants with type 2 diabetes at baseline were excluded, leaving 129 participants in the semaglutide 2.4 mg group and 64 in the placebo group. A total of 127 (98.4%) participants in the semaglutide 2.4 mg group and 61 (95.3%) in the placebo group completed the study (attended week 75 visit). At week 68, 116 (89.9%) participants were receiving semaglutide 2.4 mg and 57 (89.1%) participants were receiving placebo (Supplementary Fig. 1). The mean age of participants was 15.4 years, with a mean weight of 107.7 kg and a mean BMI of 37.1 kg/m^2 (Table 1). Baseline and clinical characteristics by treatment group and BMI reduction in the semaglutide 2.4 mg group are listed in Table 1 and Supplementary Table 1, respectively.

Changes in Insulin Sensitivity and Glycemic Measures

Semaglutide 2.4 mg, compared with placebo, was associated with significant improvements in insulin sensitivity and glycemic measures (Fig. 1). Specifically, from baseline to week 68, there were significantly greater reductions with semaglutide 2.4 mg compared with placebo in fasting serum insulin (−33.6 vs. −10.1 percentage points; ETD −26.2; 95% CI −38.6, −11.3; *P* = 0.0012) (Fig. 1*A*), HOMA-IR (−35.0 vs. −5.3 percentage points; ETD −31.4; 95% CI −43.9, −16.1; *P* = 0.0002) (Fig. 1*B*), FPG (−0.2 vs. −0.02 mmol/L; ETD −0.2; 95% CI −0.31, −0.03; *P* = 0.0181) (Fig. 1*C*), and HbA_{1c} (−0.4 vs. −0.1 percentage points; ETD −0.2; 95% CI −0.29, −0.14; *P* < 0.0001) (Fig. 1*D*). Among the 27 participants with prediabetes at baseline, the proportion achieving normoglycemia by week 68 was similar between groups (38.9% and 37.5% of participants in the semaglutide 2.4 mg and placebo groups, respectively) (Supplementary Fig. 2).

Changes in Liver Enzyme ALT

Semaglutide 2.4 mg was associated with significant improvements in ALT, compared with placebo. The estimated percentage reduction from baseline to week 68 was greater with semaglutide 2.4 mg (−17.9%) versus placebo (−3.3%; ETD −15.1 percentage points; 95% CI −26.3, −2.2; *P* = 0.0232) (Fig. 1*E*).

Changes in Cardiometabolic Risk Factors

For participants receiving semaglutide 2.4 mg versus placebo, significantly greater reductions from baseline to week 68 were observed in total cholesterol (ETD −7.3 percentage points; 95% CI −10.9, −3.7; *P* = 0.0001), LDL cholesterol (ETD −6.8 percentage points; 95% CI −11.6, −1.6; *P* = 0.0105), VLDL cholesterol (ETD −29.5 percentage points; 95% CI −37.5, −20.6; *P* < 0.0001), and triglycerides (ETD −30.2 percentage points; 95% CI −38.2, −21.3; *P* < 0.0001) (Fig. 2). A greater proportion of participants treated with semaglutide 2.4 mg experienced a change from hypertriglyceridemia to normal triglyceride levels from baseline to week 68, compared with the placebo group (19.4 – vs. 3.1– percentage-point reduction in the semaglutide 2.4 mg vs. placebo group, respectively) (Supplementary Fig. 3*A*). Moreover, participants treated with semaglutide 2.4 mg had significantly greater reductions from baseline to week 68 in waist-to-height ratio compared with those receiving placebo (ETD −0.07; 95% CI −0.09, −0.05; *P* < 0.0001) (Fig. 2). Proportions of participants achieving improvements in the remaining cardiometabolic risk factors, including blood pressure, were similar between groups (Supplementary Fig. 3). Supplementary Fig. 4 shows the associations between changes from baseline to week 68 in HOMA-IR and HbA_{1c} (semaglutide 2.4 mg: R^2 = 0.1811; placebo: R^2 = 0.1298), ALT (semaglutide 2.4 mg: R^2 = 0.0546; placebo: R^2 = 0.0085), and triglycerides (semaglutide 2.4 mg: R^2 = 0.1751; placebo: R^2 = 0.1187).

Table 1—Baseline demographics and clinical characteristics by treatment group (excluding participants with type 2 diabetes)

Characteristic	Semaglutide 2.4 mg (*n* = 129)	Placebo (*n* = 64)	Total (*N* = 193)
Sex, *n* (%)			
Male	49 (38.0)	25 (39.1)	74 (38.3)
Female	80 (62.0)	39 (60.9)	119 (61.7)
Age, years	15.5 (1.5)	15.3 (1.6)	15.4 (1.5)
Tanner stage, *n* (%)*			
2	3 (2.3)	5 (7.8)	8 (4.1)
3	10 (7.8)	3 (4.7)	13 (6.7)
4	39 (30.2)	14 (21.9)	53 (27.5)
5	77 (59.7)	42 (65.6)	119 (61.7)
Body weight, kg	110.2 (25.5)	102.7 (22.1)	107.7 (24.6)
BMI, kg/m^2	37.7 (6.7)	35.9 (5.4)	37.1 (6.3)
Waist circumference, cm	111.8 (17.0)	106.9 (13.1)	110.2 (16.0)
FPG, mmol/L	5.0 (0.5)	5.0 (0.6)	5.0 (0.5)
Proportion of participants with elevated FPG, *n* (%)	11 (8.5)	7 (10.9)	18 (9.3)
HOMA-IR, score	4.77 (57.3)	4.03 (71.9)	4.51 (62.9)
FSI, pmol/L, geometric mean (CV)	152.3 (52.2)	130.9 (65.8)	144.8 (57.3)
HbA_{1c}, %	5.5 (0.3)	5.4 (0.3)	5.4 (0.3)
Glycemic category, *n* (%)†			
Normoglycemia	110 (85.3)	56 (87.5)	166 (86.0)
Prediabetes	19 (14.7)	8 (12.5)	27 (14.0)
Type 2 diabetes	0	0	0
SBP, mmHg	120 (11)	120 (12)	120 (11)
Proportion of participants with elevated SBP, *n* (%)	28 (21.7)	16 (25.0)	44 (22.8)
DBP, mmHg	73 (9)	73 (9)	73 (9)
Proportion of participants with elevated DBP, *n* (%)	15 (11.6)	9 (14.1)	24 (12.4)
Lipids, mmol/L, geometric mean (CV)			
Total cholesterol	4.1 (19.3)	4.2 (18.9)	4.1 (19.1)
HDL cholesterol	1.1 (23.1)	1.1 (22.2)	1.1 (22.8)
Proportion of participants with low HDL cholesterol, *n* (%)	36 (27.9)	20 (31.3)	56 (29.0)
LDL cholesterol	2.3 (29.8)	2.4 (26.9)	2.3 (28.8)
VLDL cholesterol	0.6 (47.8)	0.6 (48.5)	0.6 (47.9)
Triglycerides	1.3 (47.5)	1.2 (48.7)	1.2 (47.8)
Proportion of participants with hypertriglyceridemia, *n* (%)	37 (28.7)	13 (20.3)	50 (25.9)
ALT, U/L, geometric mean (CV)	23 (69.9)	20 (70.8)	22 (70.7)
Proportion of participants with elevated ALT, *n* (%)	51 (39.5)	17 (26.6)	68 (35.2)

All data are given as mean (SD) unless otherwise stated. ALT, alanine aminotransferase; CV, coefficient of variation; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FSI, fasting serum insulin; HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostatic model for insulin resistance; SBP, systolic blood pressure; SD, standard deviation. *Tanner stages 2 and 3 indicate early puberty, stage 4 indicates late puberty, and stage 5 indicates adult-level maturity (29). †Glycemic category was determined from HbA_{1c} assessments per American Diabetes Association HbA_{1c} criteria. Normoglycemia was defined as HbA_{1c} <5.7% (39 mmol/mol), prediabetes as HbA_{1c} 5.7–6.4% (39–47 mmol/mol), and type 2 diabetes as HbA_{1c} ≥6.5% (48 mmol/mol) (46). Thresholds for risk were defined as follows: hypertriglyceridemia as serum triglyceride levels ≥1.7 mmol/L (≥150 mg/dL); low HDL as ≤1.0 mmol/L (≤40 mg/dL); elevated SBP and DBP as ≥130 and ≥80 mmHg, respectively; elevated FPG as ≥5.6 mmol/L; and elevated ALT as >25.8 U/L and >22.1 U/L in male and female participants, respectively.

Changes in Glycemic Measures, Insulin Sensitivity, and Cardiometabolic Risk Factors by BMI Reduction

In the semaglutide 2.4 mg group, changes in HbA^{1c}, FPG, fasting insulin, and HOMA-IR from baseline to week 68 were greater in participants with ≥20% BMI reduction compared with those with ≥5% to <20% or <5% BMI reduction (Fig. 3). Similarly, the mean percentage changes from baseline to week 68 in fasting lipids were also greater in participants with ≥20% BMI reduction compared with those with ≥5% to <20% or <5% BMI reduction (Fig. 3). Additionally, changes in waist circumference and systolic blood pressure were greater in participants with ≥20% BMI reduction compared with those with ≥5% to <20% or <5% BMI reduction (Supplementary Table 2).

CONCLUSIONS

Results from this secondary analysis of the STEP TEENS study showed that semaglutide 2.4 mg compared with placebo was associated with significantly greater

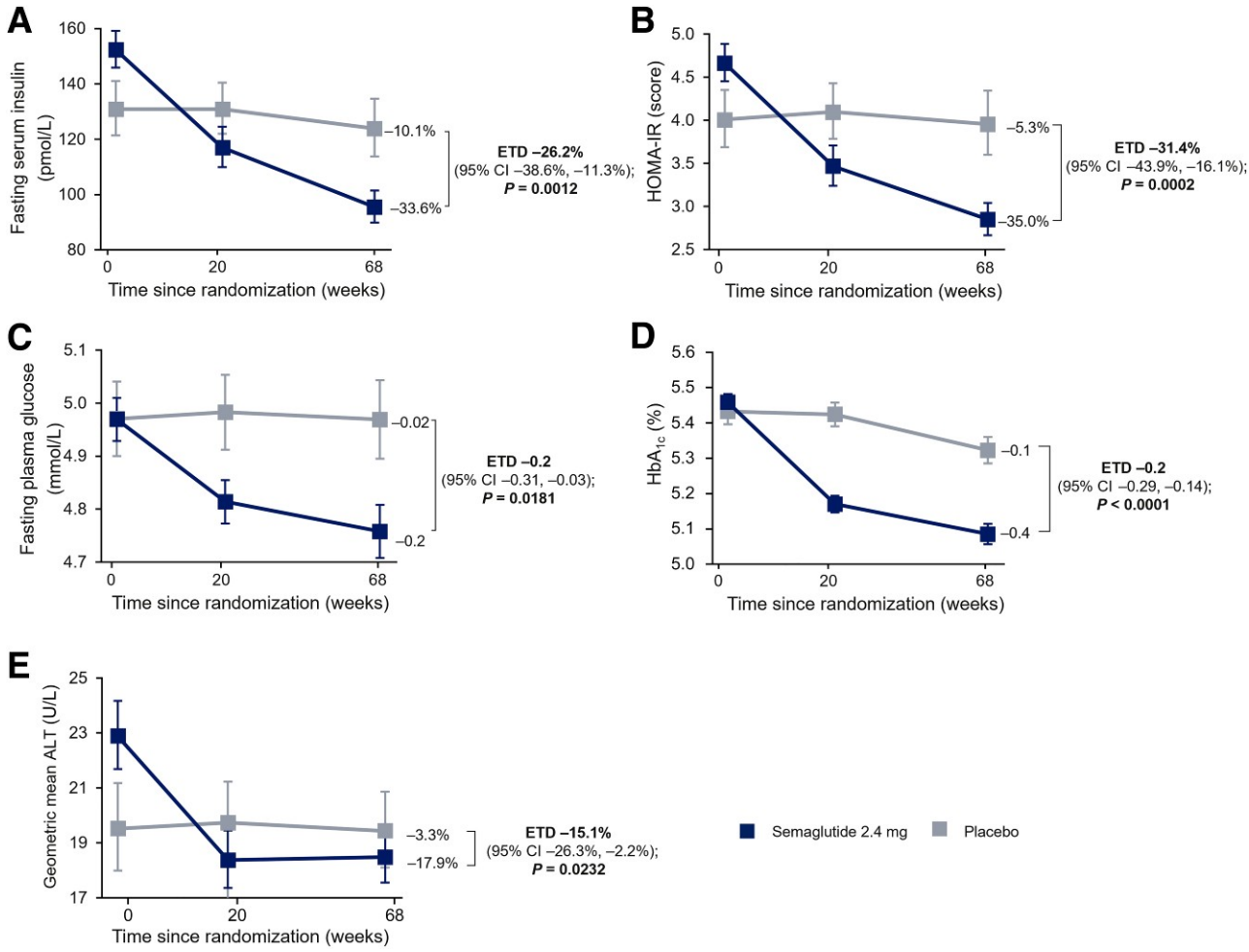

Figure 1—Mean changes from baseline in fasting serum insulin (*A*), HOMA-IR (*B*), fasting plasma glucose (*C*), HbA_{1c} (*D*), and ALT (*E*) for semaglutide 2.4 mg versus placebo. Observed mean change for participants in the full analysis set during the in-trial observation period over time (error bars indicate ±95% CI of the mean). ETDs are for the treatment policy estimand at week 68. Fasting serum insulin, HOMA-IR, and ALT were analyzed as ratio to baseline, with ETD in percentage change calculated as (ETR − 1) * 100. ALT, alanine aminotransferase; ETD, estimated treatment difference; ETR, estimated treatment ratio; HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance.

improvements from baseline to week 68 in insulin sensitivity, glycemic measures, HOMA-IR, and cardiometabolic risk factors (e.g., serum lipids and ALT) in adolescents with obesity. Additionally, greater improvements in insulin sensitivity, glycemic measures, and cardiometabolic risk factors were observed in semaglutide 2.4 mg recipients with ≥20% versus ≥5% to <20% or <5% BMI reduction. Data are not presented for the placebo group because of the low number of participants achieving these weight loss thresholds, as described in the STEP TEENS primary publication (29). Considering that obesity is a chronic disease associated with cardiometabolic complications, with insulin resistance being a major contributing factor that can lead to obesity-associated complications, including type 2 diabetes, metabolic syndrome, and cardiovascular disease (33), any therapeutic approach that can alleviate insulin resistance and its consequences will have wide-scale clinical applications. The present results not only corroborate the noteworthy weight-reducing benefits of once-weekly semaglutide 2.4 mg for adolescents living with obesity, but also advance its application by demonstrating significant improvements in insulin sensitivity and cardiometabolic complications in this population.

The reductions in selected glycemic measures from baseline to week 68 with semaglutide 2.4 mg were substantially greater than those reported in adolescents treated with other GLP-1 receptor agonists (34). In this secondary analysis of STEP TEENS, the placebo-corrected reductions in FPG and HbA_{1c} at week 68 were 0.20 mmol/L and 0.22%, compared with 0.10 mmol/L and 0.06% at week 56, respectively, in the phase 3 study of once-daily liraglutide 3.0 mg in adolescents (34). A 3-month randomized clinical study investigating the effects of the GLP-1 receptor agonist exenatide on BMI and cardiometabolic risk factors in adolescents with severe obesity reported a placebo-corrected reduction in HbA_{1c} of 0.11 percentage points (35).

Treatment with semaglutide 2.4 mg also resulted in a significantly greater mean reduction in HOMA-IR (placebo-corrected reduction of 31.4 percentage points), which was more pronounced in participants with ≥20% BMI reduction compared with those with <20% reduction, in addition to a reduction in fasting serum insulin (placebo-corrected reduction of 26.2%) at week 68. In contrast, a 56-week randomized study investigating

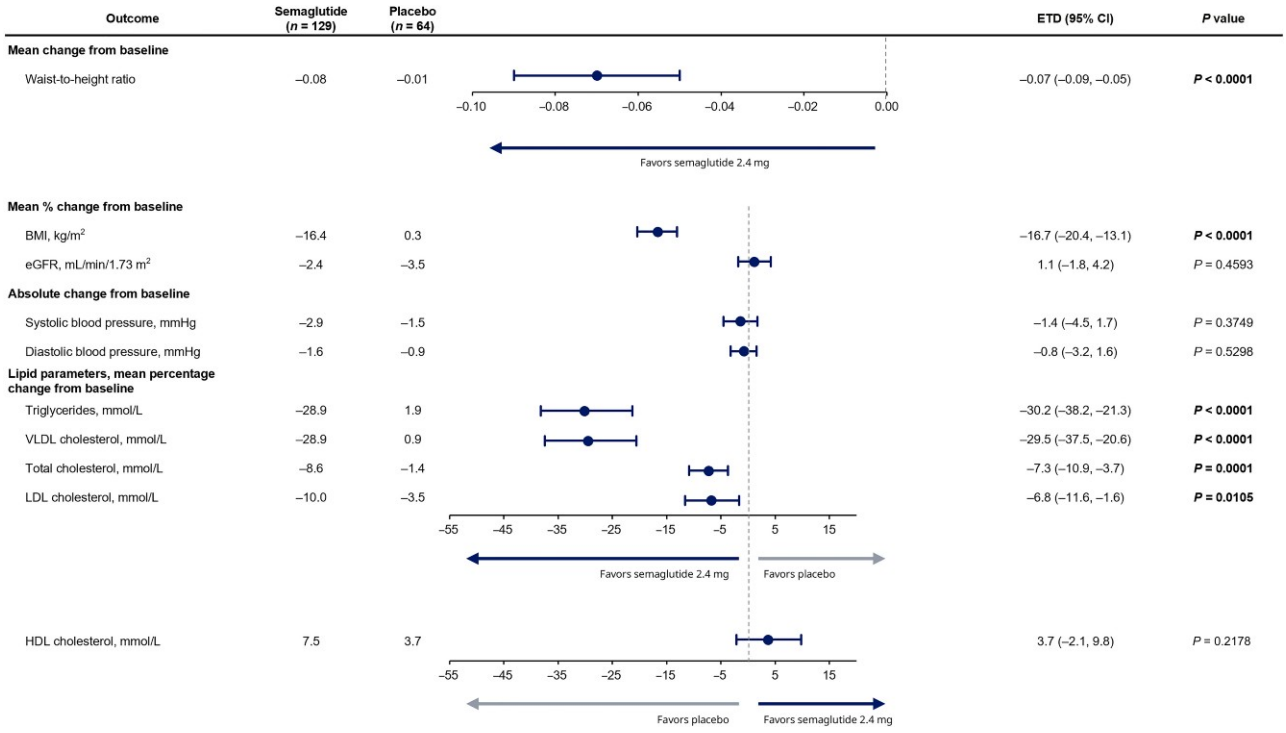

Figure 2—Changes in cardiometabolic risk factors from baseline to week 68 for the semaglutide 2.4 mg versus placebo groups. Data are mean change from baseline unless otherwise stated. Observed data are for the in-trial observation period. ETDs are for the treatment policy estimand at week 68. eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference.

phentermine/topiramate treatment for weight management in adolescents with obesity reported no significant difference between phentermine/topiramate and placebo in insulin sensitivity or glycemic measures (36). Additionally, a 54-week randomized study investigating the effect of orlistat on BMI and cardiometabolic risk factors in adolescents with obesity reported no significant difference between orlistat and placebo on insulin sensitivity or glycemic measures (37). To date, no obesity medication has proven similar weight reduction and health benefits to semaglutide 2.4 mg in adolescents. In the Teen-LABS (Teen-Longitudinal Assessment of Bariatric Surgery) study, which investigated the 3-year outcomes of various bariatric surgical methods (Roux-en-Y gastric bypass, vertical sleeve gastrectomy, or adjustable gastric banding) in adolescents, cardiovascular risk factors improved postsurgery, with increased weight loss predicting a higher probability of improvement of risk factors (38). These improvements were similar to those observed in the present analysis for the group with >20% BMI reduction (38), suggesting that some of the benefits observed in this study could be driven by the magnitude of body weight and BMI reduction achieved with semaglutide 2.4 mg treatment.

When considering the findings from these studies, it should be noted that these are not head-to-head comparisons; therefore, results must be interpreted with caution because of differences in participant populations and treatment durations and secular trends, such as the COVID-19 pandemic.

The magnitude of improvement in insulin sensitivity of ∼30% with semaglutide 2.4 mg has translational value, considering that despite having similar adiposity, insulin resistance is worse in adolescents than in adults. Insulin sensitivity is ∼50% lower in adolescents compared with adults with obesity and dysglycemia (15–17). Therefore, a 30% alleviation in insulin resistance early in the course of obesity in adolescents may help to delay the progression and worsening of insulin resistance consequent to sustained obesity and its effect on overall health.

Additionally, semaglutide 2.4 mg led to a significant reduction in ALT of −15.1 percentage points (95% CI −26.3, −2.2; P = 0.0232) compared with placebo. This finding is important in light of data showing that MASLD is not only a risk factor but also a predictor of deteriorating glucose metabolism (39). In contrast, another study investigating the effect of exenatide on BMI and liver parameters in adolescents with obesity reported that exenatide had no significant effect on liver parameters versus placebo (40). While this suggests that semaglutide 2.4 mg may be a beneficial treatment option for lowering ALT in adolescents with obesity, additional studies are needed, specifically testing the effect of semaglutide 2.4 mg on MASLD in the pediatric population.

Finally, greater reductions in cardiometabolic risk factors were observed with semaglutide 2.4 mg compared with placebo. The associations seen between changes in HOMA-IR and changes in any of the cardiometabolic risk factors were low. This may be partially explained by the low percentage of adolescents with elevated risk factors at baseline, because the study population consisted predominantly of non-Hispanic White adolescents who are at much lower risk of cardiometabolic consequences of obesity (41). Furthermore, the STEP TEENS study population had fewer participants compared with similar studies in adults.

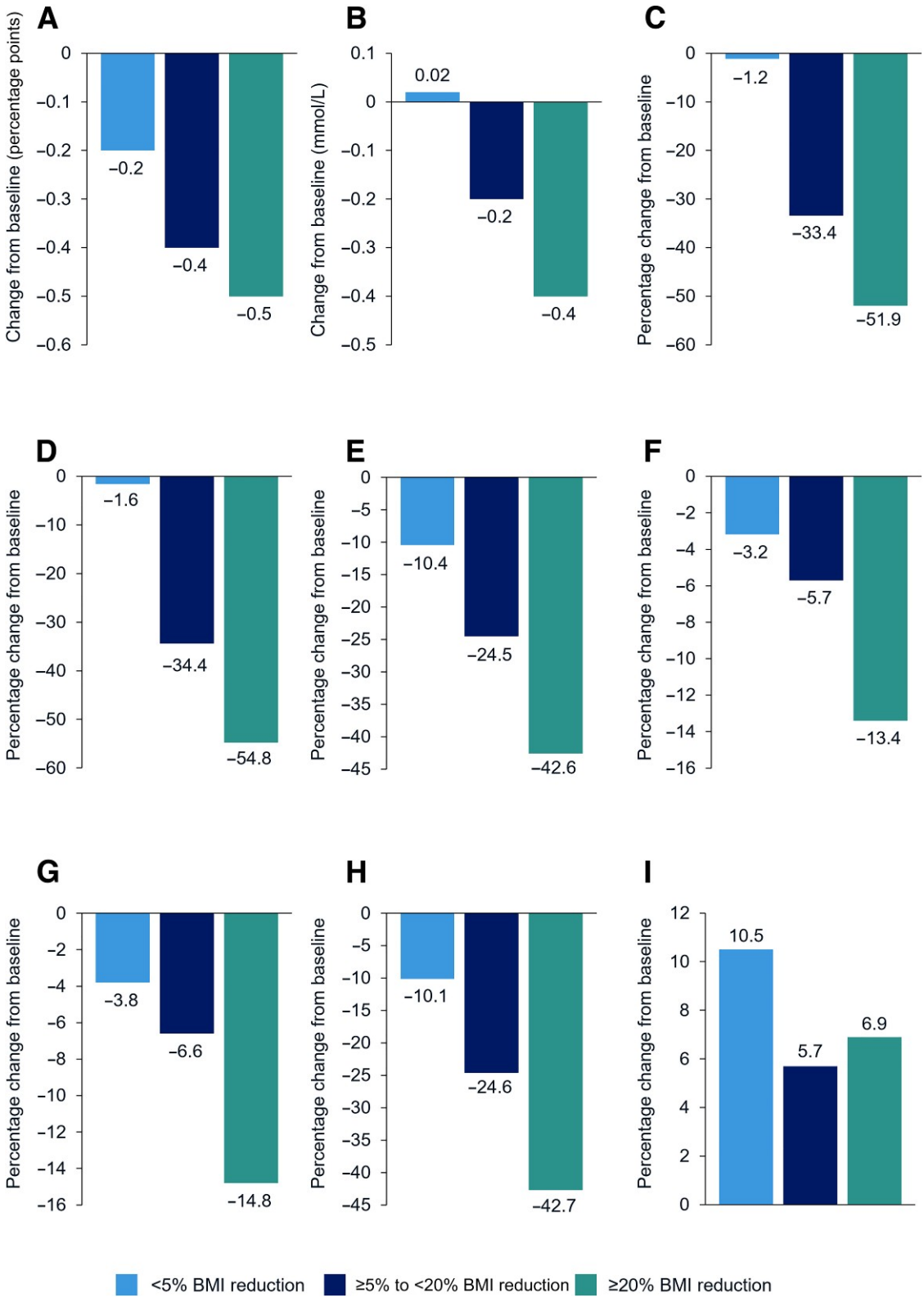

Figure 3—Changes in glucose metabolism parameters and serum lipids from baseline to week 68 by BMI reduction in the semaglutide 2.4 mg group: HbA_{1c} (*A*), FPG (*B*), FSI (*C*), HOMA-IR (*D*), triglycerides (*E*), total cholesterol (*F*), LDL cholesterol (*G*), VLDL cholesterol (*H*), and HDL cholesterol (*I*). Data are percentage change from baseline for participants in the full analysis set during the in-trial observation period. FPG, fasting plasma glucose; FSI, fasting serum insulin; HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance.

Additionally, besides body weight reduction, improvements in HOMA-IR may be in part mediated by other potential effects of GLP-1 receptor agonist treatment, such as improvement in β-cell function and suppression of glucagon (42,43). Therefore, changes in HOMA-IR may not be clearly associated with improvements in ALT and serum triglycerides.

Except for hypertriglyceridemia and ALT, the proportion of participants achieving reduction thresholds for cardiometabolic risk factors was similar between groups. Although greater improvements in those treated with semaglutide 2.4 mg with ≥20% BMI reduction versus ≥5% to <20% or <5% BMI reduction were observed, indicating that participants with a greater BMI reduction may experience greater cardiometabolic benefits with semaglutide 2.4 mg compared with those with less BMI reduction. However, BMI reduction may not be the sole contributor to cardiometabolic benefits, because participants with little to no BMI reduction still experienced some improvement in cardiometabolic risk factors. This suggests that the improvement in cardiometabolic risk factors may be partly independent of weight loss. In line with such a theory, the SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity) study, although in an adult population, found that glycemic benefits were still observed in participants receiving semaglutide 2.4 mg who experienced <2% body weight reduction or those with weight gain (42). It should be noted that the analyses by BMI reduction category in the present study were descriptive and therefore do not test a formal hypothesis and should be interpreted with caution. There was no significant improvement observed in blood pressure according to BMI reduction category, however, this is expected, because in the overall results of the STEP TEENS study (29), semaglutide 2.4 mg did not have an effect.

Numerical improvements in blood pressure were seen in the semaglutide 2.4 mg group, though these were not significant compared with placebo. In STEP TEENS, the mean baseline blood pressure in adolescents was lower than in the adults included in the STEP 1 study (29,43); this aligns with findings from a real-world study of adolescents and adult patients (44). Achieving such improvements may be more difficult if starting at a lower baseline blood pressure, and the present study was not powered to show any difference. However, a numerically greater reduction in blood pressure was observed in participants treated with semaglutide 2.4 mg with ≥20% versus <5% BMI reduction; this corresponds to findings that changes in blood pressure are often strongly related to changes in BMI (45).

A strength of this secondary analysis is that it provides novel data regarding the important health benefits of semaglutide 2.4 mg with regard to insulin sensitivity, glycemic measures, and cardiometabolic risk factors including liver ALT. However, the study was not designed to identify parameters related to treatment response, and any inferences should be treated with caution and viewed through a hypothesis-generating lens.

Semaglutide 2.4 mg compared with placebo provided not only provided important reductions in weight and BMI (29) but also resulted in significant and clinically relevant improvements in insulin sensitivity, glycemic measures, serum lipids, and liver parameters in adolescents with obesity. These data support semaglutide 2.4 mg as an efficacious weight management treatment for adolescents living with obesity with the added benefit of improvements in insulin sensitivity, glycemic measures, and cardiometabolic risk factors, all contributing to improved patient health within clinical practice.

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The study sponsor (Novo Nordisk A/S) undertook site monitoring, data collation, and analysis. Investigators were responsible for data collection.

Author Contributions. S.A., I.G., A.S.K., M.W., and D.W. were responsible for study investigations, participant enrollment, and collection and assembly of data. S.A., B.G., T.K., A.K., and N.M.H.-L. analyzed data. S.A., B.G., and N.M.H.-L. designed the study. S.A., B.G., T.K., and N.M.H.-L. prepared the manuscript. All authors contributed to data interpretation, manuscript review and revision, and approved the final version of the manuscript. S.A. and D.W. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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