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Impact of BMI and comorbidities on efficacy of once-weekly semaglutide: Post hoc analyses of the STEP 1 randomized trial

Barbara M. McGowan[1] | Azadeh Houshmand-Oeregaard[2] | Peter Nørkjær Laursen[2] | Niels Zeuthen[2] | James Baker-Knight[2]

[1]Department of Diabetes and Endocrinology, Guy's and St. Thomas' NHS Foundation Trust, London, UK

[2]Novo Nordisk A/S, Søborg, Denmark

Correspondence
Barbara M. McGowan, Department of Diabetes and Endocrinology, Guy's and St. Thomas' NHS Foundation Trust, Westminster Bridge Rd., London, SE1 7EH, UK.
Email: barbara.mcgowan@gstt.nhs.uk

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Abstract

Objective: This study assessed the effects of semaglutide on body weight, cardiometabolic risk factors, and glycemic status in individuals categorized by baseline BMI with or without additional obesity-related comorbidities, including prediabetes and high risk of cardiovascular disease (CVD).

Methods: This was a post hoc exploratory subgroup analysis of the Semaglutide Treatment Effect in People with Obesity (STEP) 1 trial (NCT03548935), in which participants without diabetes and BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with ≥1 weight-related comorbidity, were randomized to once-weekly subcutaneous semaglutide 2.4 mg or placebo for 68 weeks. For this analysis, individuals were categorized into subgroups based on baseline BMI <35 versus ≥35 kg/m^2 (with no additional criteria, with ≥1 comorbidity, with prediabetes, and with prediabetes and high risk of CVD).

Results: Mean changes in body weight from baseline to week 68 with semaglutide were −16.2% and −14.0% in the subgroups with baseline BMI <35 and ≥35 kg/m^2, respectively (both $p < 0.0001$ vs. placebo). Similar changes were observed in individuals with comorbidities, with prediabetes, and with prediabetes plus high CVD risk. The beneficial effects of semaglutide on cardiometabolic risk factors were consistent across all subgroups.

Conclusions: This subgroup analysis confirms that semaglutide is effective in individuals with baseline BMI <35 and ≥35 kg/m^2, including in those with comorbidities.

INTRODUCTION

The glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide is approved for weight management on the basis of four clinical trials that were part of the global phase 3 Semaglutide Treatment Effect in People with Obesity (STEP) program [1–4]. In Europe and the United States, semaglutide is approved in people with obesity (body mass index [BMI] ≥30 kg/m^2) or those with overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity. This is the same population for which the GLP-1 receptor agonist liraglutide 3.0 mg (Saxenda) is indicated. Approval of liraglutide 3.0 mg was based, in part, on a 56-week phase 3 clinical trial in people with BMI ≥30 kg/m^2, or BMI ≥27 kg/m^2 with dyslipidemia or hypertension, in which treatment resulted in significantly greater weight loss compared with placebo (8.0% vs. 2.6%) [5].

However, experience with liraglutide 3.0 mg has shown that, at a national and/or regional level, cost pressures can result in public reimbursement authorities recommending its use be restricted to more limited populations than the approved label. For example, reimbursement of liraglutide 3.0 mg for weight management is recommended

only for people with BMI ≥35 kg/m^2 in Scotland and the Netherlands; for people with BMI ≥35 kg/m^2, prediabetes, and a high risk of cardiovascular disease (CVD) in England, Wales, and Finland; or for people with BMI ≥35 kg/m^2 and at least one comorbidity in Norway. As a result, some patients who could benefit from weight management pharmacotherapy may be denied access to treatment.

It has previously been reported that semaglutide 2.4 mg is effective across a broad population of patients with overweight or obesity, including in those who do not meet these reimbursement criteria. In the STEP 1 trial of 1961 people with BMI ≥30 kg/m^2 (or ≥27 with ≥1 weight-related comorbidity) without diabetes, once-weekly subcutaneous (s.c.) semaglutide 2.4 mg was associated with a mean change in body weight from baseline to week 68 of −14.9%, compared with −2.4% for placebo [1]. A post hoc analysis of STEP 1 revealed substantial weight loss in all subgroups of participants stratified by baseline age (≤65, 65 to <75, or ≥75 years), race (White, Asian, Black or African American, or other), ethnicity (Hispanic or Latino, not Hispanic or Latino, or not reported), and renal function (normal, mild impairment, or moderate impairment) [6, 7]. Weight loss with semaglutide 2.4 mg was significantly greater in female participants than male (female: 18.4% at week 68 with semaglutide vs. 2.1% with placebo; male: 12.9% vs. 3.5%). Substantial weight loss was seen in individuals with normoglycemia at baseline as well as in those with baseline prediabetes. While an interaction was observed between baseline body weight and weight loss, marked weight loss of at least 13.9% occurred in all body weight subgroups. Similarly, baseline BMI had no significant effect on weight loss, with all subgroups (including BMI <30) showing weight loss of at least 15.5% [6, 7]. This suggests that, if the reimbursement thresholds commonly applied in Europe for liraglutide were also adopted for semaglutide 2.4 mg, many patients who could benefit from semaglutide would be denied access to it. This is particularly concerning given that, in STEP 1, beneficial effects were also seen with semaglutide versus placebo on cardiometabolic risk factors, including glycated hemoglobin (HbA_{1c}), blood pressure, waist circumference, and lipid levels [1].

Similar patterns of efficacy, regardless of baseline characteristics, have been observed in individuals with overweight or obesity and type 2 diabetes (T2D). In a subgroup analysis of Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN)-1 to -5, s.c. semaglutide (0.5 or 1 mg) was associated with greater reductions in body weight versus comparators, irrespective of baseline BMI [8, 9]. Similarly, in a subgroup analysis of Peptide Innovation for Early Diabetes Treatment (PIONEER) 1 to 5, 7, and 8, greater reductions in HbA_{1c} and body weight were seen with oral semaglutide (7 or 14 mg) versus comparators in most subgroups examined, including in individuals stratified by baseline BMI [10]. Lastly, in a pooled analysis of four observational Semaglutide Real-world Evidence (SURE) studies of real-world semaglutide use, once-weekly semaglutide was associated with improvements in HbA_{1c} and body weight in people with T2D, again irrespective of baseline BMI [11]. A pooled analysis of the cardiovascular outcome trials SUSTAIN-6 and PIONEER 6 revealed beneficial effects of semaglutide versus comparators on major adverse cardiovascular events (MACE) in patients with T2D and varying cardiovascular risk [12–14].

Study Importance

What is already known?

- Once-weekly subcutaneous (s.c.) semaglutide 2.4 mg is approved for weight management in people with obesity (BMI ≥30 kg/m^2) or with overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity.
- However, experience with liraglutide 3.0 mg has shown that cost pressures can result in public reimbursement authorities restricting the use of weight management therapies to more limited populations than the approved label, e.g., BMI ≥35 kg/m^2, with or without comorbidities.

What does this study add?

- In these post hoc subgroup analyses of the Semaglutide Treatment Effect in People with Obesity (STEP) 1 trial, once-weekly s.c. semaglutide 2.4 mg provided effective weight loss in individuals with baseline BMI <35 and ≥35 kg/m^2, including in those with ≥1 comorbidity, those with prediabetes, and those with prediabetes and high risk of CVD.
- The beneficial effects of semaglutide on cardiometabolic risk factors (waist circumference, systolic blood pressure, glycated hemoglobin) were consistent across all subgroups.

How might these results change the direction of research or the focus of clinical practice?

- By showing that semaglutide 2.4 mg has beneficial effects in a broad population of individuals with obesity, including those at increased risk of poor outcomes, irrespective of whether their baseline BMI was <35 or ≥35 kg/m^2, our results suggest that many individuals who could benefit from semaglutide may be denied access to it based on current European reimbursement thresholds for weight management therapies.
- Lowering reimbursement thresholds to values consistent with the evidence base from clinical trials would enable more individuals with overweight or obesity to benefit from the improvements in cardiometabolic risk factors associated with the use of semaglutide 2.4 mg.

Given these reports of beneficial effects of semaglutide in individuals with diverse baseline characteristics, we wished to investigate the effects of semaglutide 2.4 mg on body weight, glycemic status, and cardiometabolic risk factors in individuals categorized by baseline BMI and obesity-related comorbidities according to the reimbursement thresholds commonly used for weight management pharmacotherapy (liraglutide) in Europe. We therefore performed a post hoc subgroup

analysis of the STEP 1 trial to examine the effects of semaglutide in participants with baseline BMI <35 versus ≥35 kg/m^2 and in those with ≥1 weight-related comorbidity (including prediabetes), prediabetes only, or prediabetes and high risk of CVD.

METHODS

Study design

STEP 1 was a randomized, double-blind, placebo-controlled trial conducted at 129 sites in 16 countries. The full methodology of the STEP 1 trial has been reported previously [1]. Key inclusion criteria were as follows: age ≥18 years, BMI ≥30 kg/m^2 (or ≥27 kg/m^2 with one or more weight-related comorbidities, i.e., hypertension, dyslipidemia, obstructive sleep apnea, or CVD), and a history of one or more self-reported unsuccessful dietary attempts to lose weight. Key exclusion criteria were history of type 1 diabetes or T2D, HbA_{1c} ≥6.5% (≥48 mmol/mol), previous surgical treatment for obesity, and use of antiobesity medications within 180 days prior to enrollment.

Participants were randomly assigned 2:1 to receive once-weekly s.c. semaglutide 2.4 mg for 68 weeks or matching placebo, in addition to lifestyle intervention. Semaglutide was initiated at a dose of 0.25 mg once weekly for the first 4 weeks, with the dose increased every 4 weeks to reach the maintenance dose of 2.4 mg weekly by week 16. The co-primary end points in STEP 1 were the percentage change in body weight from baseline to week 68 and achievement of a reduction in body weight of ≥5% from baseline to week 68. Confirmatory secondary end points in STEP 1 were the achievement of a reduction in body weight of ≥10% and ≥15% by week 68 and changes from baseline to week 68 in waist circumference, systolic blood pressure (SBP), Physical Functioning score on the 36-item Short Form Health Survey v2, and Physical Function score on the Impact of Weight on Quality of Life-Lite Clinical Trials Version questionnaire. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by an independent ethics committee or institutional review board at each study site.

Subgroup analyses

The current post hoc subgroup analyses were exploratory and were not prespecified in the trial protocol. Subgroups were selected based on populations for whom weight management drug therapy (liraglutide 3.0 mg) is recommended by public health authorities. Individuals who were randomized to receive either semaglutide 2.4 mg or placebo in the STEP 1 trial were stratified into two subgroups based on baseline BMI (<35 vs. ≥35 kg/m^2); these two groups were further categorized into people with ≥1 weight-related comorbidity (including prediabetes), those with prediabetes only, and those with prediabetes and high risk of CVD.

The weight-related comorbidities defined at baseline that were included were dyslipidemia, hypertension, coronary artery disease, cerebrovascular disease, obstructive sleep apnea, prediabetes, reproductive system disorder (menstrual disorder, polycystic ovary syndrome, or involuntary impaired fertility/infertility), liver disease (nonalcoholic fatty liver disease or nonalcoholic steatohepatitis), kidney disease, osteoarthritis of the knee or hip, gout or hyperuricemia, and asthma or chronic obstructive pulmonary disease. Prediabetes was defined as fasting plasma glucose 5.5 to 6.9 mmol/L or HbA_{1c} 6.0% to 6.4%. A high risk of CVD was defined as having total cholesterol >5.0 mmol/L, high-density lipoprotein (HDL) cholesterol <1.0 mmol/L (men) or <1.3 mmol/L (women), or SBP >140 mmHg. These definitions are based on those used by the UK National Institute for Health and Care Excellence (NICE) [15–17].

Statistical analyses

Two estimands were used to assess treatment efficacy: the treatment policy estimand (all randomized participants, regardless of premature discontinuation of randomized treatment or rescue intervention, i.e., antiobesity medication or bariatric surgery) and the trial product estimand (all randomized participants, assuming they remained on randomized treatment for the entire study duration and without rescue intervention). We anticipate that the treatment policy estimand is of more relevance to health care decision-makers; therefore, reported results are for the treatment policy estimand unless otherwise stated. For the treatment policy estimand, continuous efficacy end points were analyzed at weeks 20, 28, and 68, depending on the end point, using ANCOVA with treatment as factor and baseline value as covariate. Multiple imputations based on the McEvoy approach were used for missing data for participants on treatment at a specific visit ($n = 6$ for semaglutide 2.4 mg and $n = 3$ for placebo for the change in body weight from baseline for the overall population). For participants off treatment at a specific visit, single imputation was done using linear extrapolation based on off-treatment change estimates for each treatment arm ($n = 88$ for semaglutide 2.4 mg and $n = 75$ for placebo for the change in body weight from baseline for the overall population). For the trial product estimand, all responses prior to first discontinuation of treatment (or initiation of other antiobesity medication or bariatric surgery) are included in a mixed model for repeated measurements with randomized treatment as factor and baseline value as covariate, all nested within visit.

Efficacy data were reported as changes from baseline with semaglutide 2.4 mg or placebo in body weight (at weeks 28 and 68), HbA_{1c}, SBP, waist circumference, and ratio to baseline for HDL cholesterol and total cholesterol (all at weeks 20 and 68). For each comparison, estimated treatment differences (estimated treatment ratios for total and HDL cholesterol) and 95% confidence intervals (CI) were calculated. *P* values were not adjusted for multiplicity because these were exploratory post hoc analyses for which the original STEP 1 study was not powered (see Rothman [18], Feise [19], and Althouse [20] for further discussion of this issue).

Change in glycemic status over time was determined by comparing the percentage of participants with normoglycemia, prediabetes (fasting plasma glucose 5.5–6.9 mmol/L or HbA_{1c} 6.0%–6.4%), and T2D (fasting plasma glucose ≥7.0 mmol/L or HbA_{1c} ≥6.5%) at baseline and at weeks 20, 52, and 68.

TABLE 1 Demographics and baseline characteristics for participants in each subgroup

	BMI <35 kg/m^2	BMI ≥35 kg/m^2	BMI <35 kg/m^2 + ≥1 comorbidity	BMI ≥35 kg/m^2 + ≥1 comorbidity	BMI <35 kg/m^2 + prediabetes	BMI ≥35 kg/m^2 + prediabetes	BMI <35 kg/m^2 + prediabetes + high CVD risk	BMI ≥35 kg/m^2 + prediabetes + high CVD risk
N	760	1201	587	993	274	547	210	421
Age (y)	48 (18–86)	45 (18–81)	52 (21–86)	47 (18–81)	53 (26–86)	49 (19–81)	53 (26–82)	48 (19–81)
Female, *N* (%)	538 (70.8)	915 (76.2)	394 (67.1)	745 (75.0)	168 (61.3)	391 (71.5)	133 (63.3)	314 (74.6)
BMI (kg/m^2)	32.1 (26.5–35.0)	39.9 (35.0–83.0)	32.1 (26.5–35.0)	39.9 (35.0–83.0)	32.0 (26.5–35.0)	40.3 (35.0–83.0)	32.0 (26.5–34.9)	40.5 (35.0–83.0)
Waist circumference (cm)	104.0 (83.8–133.8)	120.0 (84.0–182.9)	104.0 (85.0–133.8)	120.7 (84.0–182.9)	104.0 (85.0–133.8)	122.0 (93.0–180.0)	104.0 (85.0–122.0)	122.0 (93.0–180.0)
HbA_{1c} at baseline (%)	5.7 (4.8–6.6)	5.7 (4.1–6.6)	5.7 (4.8–6.6)	5.8 (4.1–6.6)	5.9 (5.0–6.4)	6.0 (4.2–6.4)	5.9 (5.0–6.4)	6.0 (4.2–6.4)
Fasting plasma glucose (mmol/L)	5.2 (3.8–9.2)	5.3 (3.7–8.7)	5.3 (3.9–9.2)	5.4 (3.7–8.7)	5.7 (4.3–6.9)	5.6 (4.3–6.9)	5.7 (4.3–6.9)	5.6 (4.3–6.9)
HDL cholesterol (mg/dL)	52.5 (24.3–118.5)	47.5 (18.5–95.0)	52.1 (25.1–118.5)	47.9 (18.5–95.0)	51.0 (25.9–94.6)	47.3 (20.8–93.4)	48.8 (25.9–94.6)	45.6 (20.8–93.4)
Total cholesterol (mg/dL)	196.9 (102.7–393.4)	188.4 (70.7–373.0)	199.4 (103.1–393.4)	190.2 (97.7–373.0)	201.9 (119.7–339.4)	190.0 (97.7–373.0)	210.0 (129.3–339.4)	200.8 (97.7–373.0)
Triglycerides (mg/dL)	121.0 (38.3–1300.3)	122.8 (39.2–2610.4)	126.4 (40.1–1300.3)	126.4 (39.2–1279.8)	129.1 (43.6–588.3)	134.4 (42.7–1139.2)	140.6 (43.6–588.3)	146.0 (51.6–1139.2)
Smoking status, *N* (%)								
Current smoker	91 (12.0)	137 (11.4)	73 (12.4)	113 (11.4)	38 (13.9)	69 (12.6)	32 (15.2)	58 (13.8)
Previous smoker	184 (24.2)	312 (26.0)	158 (26.9)	273 (27.5)	74 (27.0)	151 (27.6)	59 (28.1)	114 (27.1)
Never smoked	485 (63.8)	752 (62.6)	356 (60.6)	607 (61.1)	162 (59.1)	327 (59.8)	119 (56.7)	249 (59.1)
SBP (mmHg)	124.0 (81.0–184.0)	127.0 (88.0–187.0)	126.0 (81.0–184.0)	128.0 (88.0–187.0)	127.0 (81.0–184.0)	128.0 (88.0–187.0)	128.0 (81.0–184.0)	130.0 (88.0–187.0)
Glycemic status, *N* (%)								
Normoglycemic	475 (62.5)	630 (52.5)	304 (51.8)	425 (42.8)	–	–	–	–
Prediabetes	274 (36.1)	547 (45.5)	274 (46.7)	547 (55.1)	274 (100)	547 (100)	210 (100)	421 (100)
T2D	11 (1.4)	24 (2.0)	9 (1.5)	21 (2.1)	–	–	–	–
On antihypertensive medication, *N* (%)	165 (21.7)	298 (24.9)	165 (28.1)	298 (30.0)	78 (28.5)	168 (30.7)	56 (26.7)	129 (30.6)
On lipid-lowering medication, *N* (%)	150 (19.7)	213 (17.7)	148 (25.2)	210 (21.1)	74 (27.0)	129 (23.6)	43 (20.5)	86 (20.4)

Note: All continuous data are medians (range).
Abbreviations: CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; SBP, systolic blood pressure; T2D, type 2 diabetes.

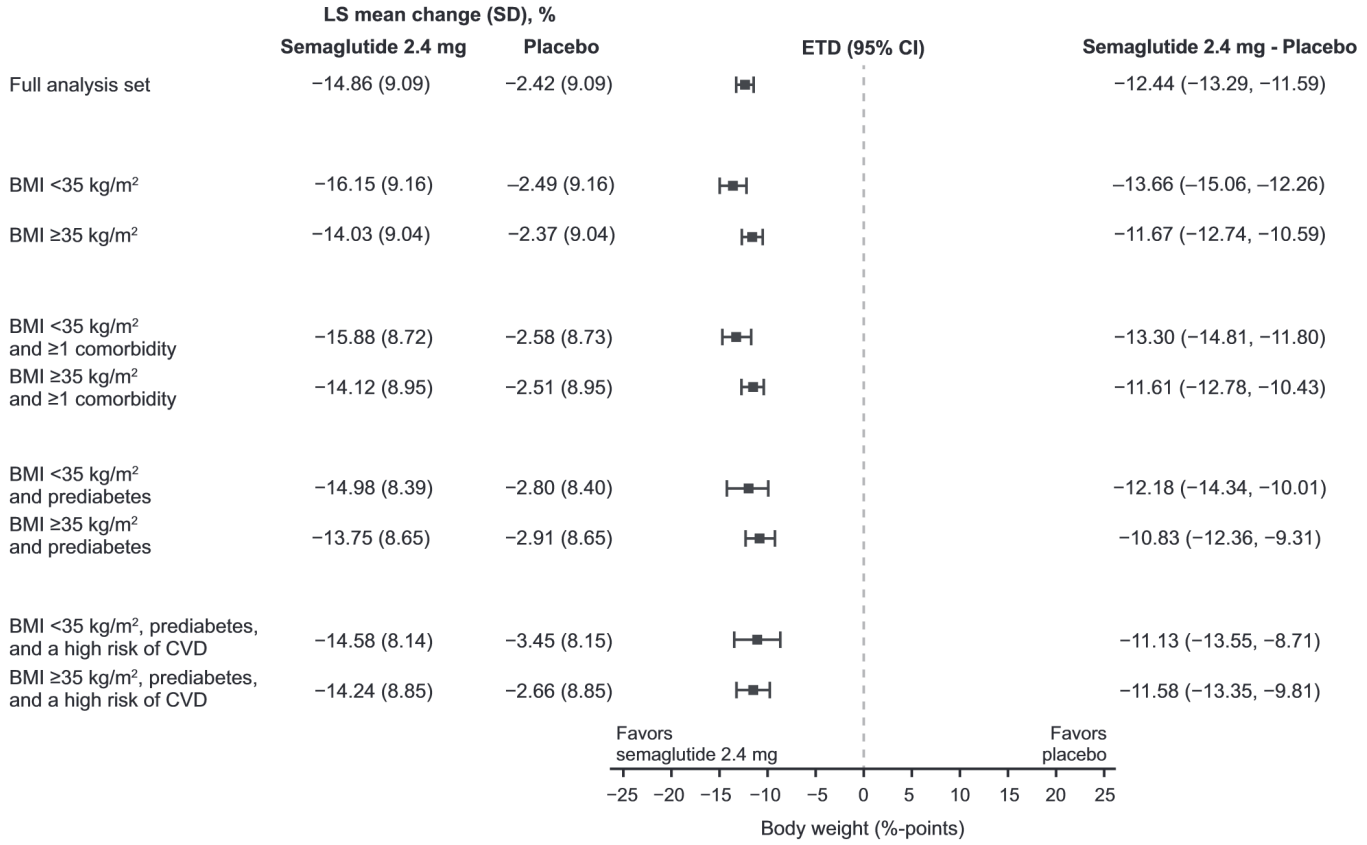

FIGURE 1 Percentage change from baseline to week 68 in body weight. Prediabetes defined as fasting plasma glucose 5.5–6.9 mmol/L or glycated hemoglobin 6.0%–6.4%. High risk of CVD was defined as total cholesterol >5.0 mmol/L, high-density lipoprotein cholesterol <1.0 mmol/L (men) or <1.3 mmol/L (women), or systolic blood pressure >140 mmHg. CVD, cardiovascular disease; ETD, estimated treatment difference; LS, least-squares

RESULTS

Participants

Demographics and baseline characteristics are summarized for all participants in each subgroup (Table 1) and separately for participants receiving semaglutide 2.4 mg or placebo within each subgroup (Supporting Information Tables S1–S4). Baseline characteristics were generally comparable across both treatment arms and subgroups, with the median age ranging from 45 to 53 years and approximately 70% of participants being female. Within each subgroup, females were slightly overrepresented among individuals with BMI ≥35 kg/m^2 (vs. BMI <35). Within each subgroup, participants with BMI ≥35 had lower median HDL cholesterol than participants with BMI <35; total cholesterol was also slightly lower among individuals with BMI ≥35.

Effects on body weight

In the overall population in STEP 1, once-weekly s.c. semaglutide 2.4 mg was associated with a mean change in body weight from baseline to week 68 of −14.9% compared with −2.4% for placebo, with an estimated treatment difference of −12.4 percentage points (95% CI: −13.4 to −11.5; $p < 0.001$) (Figure 1; trial product estimand shown in Supporting Information Figure S1) [1]. Treatment effects in the post hoc subgroup analyses are summarized in Figure 1 and Supporting Information Figure S1. Mean percentage change in body weight from baseline to week 68 with once-weekly s.c. semaglutide 2.4 mg was −16.2% in participants with baseline BMI <35 and −14.0% in participants with baseline BMI ≥35 (Figure 1; trial product estimand shown in Supporting Information Figure S1).

Similar mean percentage changes in body weight from baseline to week 68 with once-weekly s.c. semaglutide 2.4 mg were observed in individuals with comorbidities, with prediabetes, and with prediabetes plus high CVD risk (Figure 1). Within each subgroup, mean percentage change in body weight was also similar for individuals with baseline BMI <35 versus ≥35 (Figure 1).

Effects on cardiometabolic risk factors

In the overall population in STEP 1, once-weekly s.c. semaglutide 2.4 mg was associated with significantly larger improvements versus placebo in cardiometabolic risk factors including waist circumference and SBP [1]. Beneficial effects of semaglutide 2.4 mg versus placebo were also observed with respect to HbA_{1c} and fasting lipids [1].

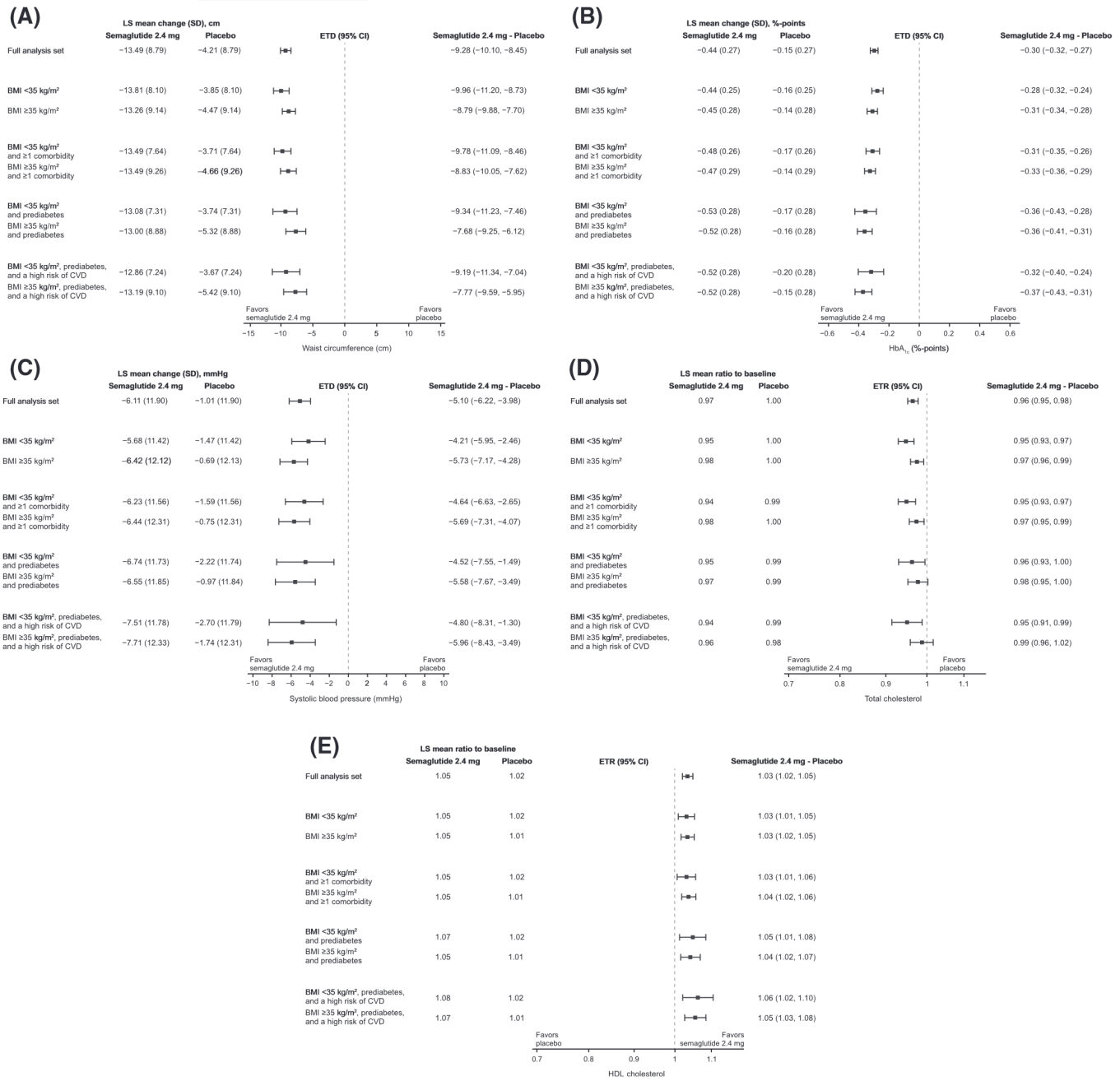

FIGURE 2 Changes from baseline to week 68 in (A) waist circumference, (B) HbA_{1c}, (C) SBP, (D) total cholesterol, and (E) HDL cholesterol. Prediabetes defined as fasting plasma glucose 5.5–6.9 mmol/L or HbA_{1c} 6.0–6.4%. High risk of CVD was defined as total cholesterol >5.0 mmol/L, HDL cholesterol <1.0 mmol/L (men) or <1.3 mmol/L (women), or SBP >140 mmHg. CVD, cardiovascular disease; ETD, estimated treatment difference; ETR, estimated treatment ratio; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; LS, least-squares; SBP, systolic blood pressure

In the post hoc subgroup analyses, the beneficial effects of semaglutide on waist circumference, HbA_{1c}, SBP, and total and HDL cholesterol were generally consistent across subgroups with comorbidities, with prediabetes, and with prediabetes plus high CVD risk (Figure 2; trial product estimand shown in Supporting Information Figure S2).

Change in glycemic status

Among participants who were normoglycemic at baseline, a lower proportion of those who received semaglutide 2.4 mg progressed to having either prediabetes or T2D at week 68 than among those who received placebo (Figure 3; trial product estimand shown in Supporting Information Figure S3). This was true for individuals with baseline BMI either <35 or ≥35, including for those with comorbidities. Among participants with prediabetes at baseline, a higher proportion achieved normoglycemia with semaglutide 2.4 mg than with placebo, irrespective of their baseline BMI (Figure 3).

The same pattern was seen among participants with prediabetes and high CVD risk at baseline, regardless of baseline BMI (Figure 3).

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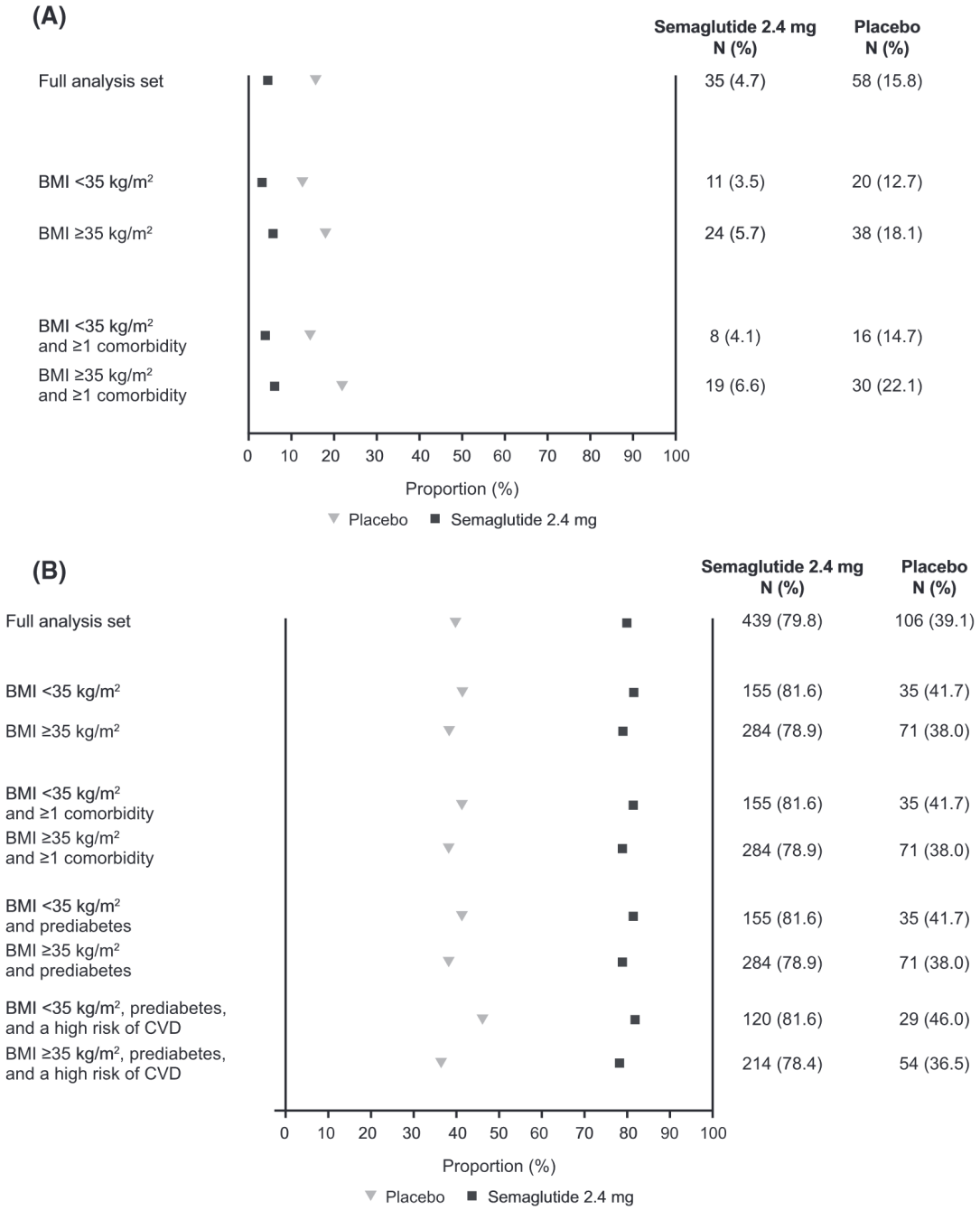

FIGURE 3 Change in glycemic status from baseline to week 68: (A) normoglycemic to prediabetes and (B) prediabetes to normoglycemic. Prediabetes defined as fasting plasma glucose 5.5–6.9 mmol/L or glycated hemoglobin 6.0%–6.4%. Three patients in the semaglutide group and eleven in the placebo group progressed from prediabetes to T2D at week 68; three patients in the placebo group (none in the semaglutide group) also progressed from normoglycemic to T2D. These data are not presented for subgroups because of small patient numbers. CVD, cardiovascular disease; T2D, type 2 diabetes

DISCUSSION

In the STEP 1 trial, once-weekly s.c. semaglutide 2.4 mg was associated with clinically meaningful weight loss versus placebo in people with obesity or in those with overweight and at least one weight-related comorbidity. Semaglutide 2.4 mg also had beneficial effects on multiple cardiometabolic risk factors. A previous subgroup analysis of STEP 1 found that the beneficial effects of semaglutide on weight loss compared with placebo were generally consistent across subgroups defined by baseline age, sex, race, ethnicity, body weight, BMI, renal function, and glycemic status [6]. Here, we show that the beneficial effects of semaglutide 2.4 mg on weight loss, glycemic status, and cardiometabolic risk factors are consistent across subgroups based on baseline BMI and the presence of comorbidities. Across all subgroups, the effects of semaglutide 2.4 mg versus placebo were consistent between those with baseline BMI <35 kg/m^2 and those with baseline

BMI ≥35 kg/m^2, including in those with comorbidities, prediabetes, or prediabetes and high CVD risk. This included the observation that more participants with prediabetes at baseline were normoglycemic at week 68 with semaglutide versus placebo, consistent with analysis across the STEP 1, 3, and 4 trials that reported significant improvements in glucose metabolism and a greater likelihood of achieving normoglycemia with semaglutide [21]. Thus, semaglutide 2.4 mg is effective in people with obesity with a BMI that may be below the threshold for reimbursement as well as in those with BMI ≥35, including those with comorbidities.

The costs of complications related to overweight and obesity are increasing worldwide. In 2019, the economic impact of overweight and obesity was already equivalent to 2.19% of global gross domestic product [22], and by 2025, annual health care costs for obesity-related complications are expected to reach approximately $1.2 trillion [23]. Reducing the increase in overweight and obesity prevalence by 5% compared with current projected trends could save more $420 billion annually [22].

In a study comparing the cost-effectiveness of GLP-1 receptor agonists for the treatment of obesity, semaglutide was found to be more cost-effective than liraglutide, dulaglutide, and exenatide in a US setting [24]. Semaglutide was also judged to be more effective than five other pharmacotherapies for weight management in people with BMI of 30 to <35 kg/m^2 over 3- and 5-year horizons, although it was not considered to be cost-effective [25]. Over a 30-year span in the United States, semaglutide 2.4 mg was deemed cost-effective for the treatment of obesity in individuals with BMI ≥30 or BMI ≥27 kg/m^2 plus ≥1 weight-related comorbidity, compared with diet and exercise alone and compared with other weight management medications [26]. Cost-effectiveness was also demonstrated in a Canadian study [27]. Studies in multiple countries have also variously found oral or s.c. formulations of semaglutide to be cost-effective compared with medications such as insulin, empagliflozin, liraglutide, and dulaglutide for the treatment of T2D [28–34].

Although BMI has long been the standard means of diagnosing and categorizing overweight and obesity, the limitations of the measure are increasingly being recognized (e.g., Nuttall [35]). Targeting markers of cardiometabolic risk can be clinically worthwhile, especially because these markers may be more strongly associated with mortality risk than obesity, per se [36]. As a class, GLP-1 receptor agonists reduce body weight, improve glycemia, and may have additional cardioprotective effects [37]. In exploratory post hoc analyses of STEP 1, 2, and 3, semaglutide 2.4 and 1.0 mg reduced levels of the inflammatory biomarker C-reactive protein, compared with placebo, in individuals with overweight or obesity, with or without T2D, irrespective of baseline BMI, body weight, or glycemic status [38]. Several GLP-1 receptor agonists have shown reductions in the risk of MACE in populations with T2D [39–41]. In two cardiovascular outcome trials in patients with T2D and high CVD risk, semaglutide, administered by s.c. injection or orally, was associated with a lower incidence of MACE compared with placebo (SUSTAIN-6: hazard ratio [HR] 0.74 [95% CI: 0.58 to 0.95], $p = 0.016$; PIONEER 6: HR 0.79 [95% CI: 0.57 to 1.11], $p = 0.017$) [12, 13]; however, the patient population and doses/formulations of semaglutide in SUSTAIN-6 and PIONEER 6 were different from those in STEP 1. In exploratory analyses of STEP 1 and 4, semaglutide 2.4 mg improved cardiometabolic risk factors (including waist circumference, SBP, fasting plasma glucose, fasting serum insulin, and lipids) versus placebo in individuals with overweight or obesity without T2D [42]. The ongoing Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity (SELECT) cardiovascular outcome trial is examining whether once-weekly s.c. semaglutide 2.4 mg added to standard of care is superior to placebo for preventing MACE in a cohort of patients with overweight or obesity, without T2D, and established CVD [37].

In both the overall population and in the current subgroup analyses of STEP 1, the effects of semaglutide 2.4 mg on cholesterol levels (total and HDL) were smaller than those seen with the other cardiometabolic markers of waist circumference, SBP, and HbA_{1c}, suggesting that GLP-1 receptor agonists may reduce CVD risk via an alternative mechanism to lipid-lowering therapies. Reduction in CVD risk may involve both indirect mechanisms via modification of risk factors, as well as direct effects via GLP-1 receptors in the cardiovascular system.

A strength of the current analyses is that they examined the effects of semaglutide on multiple cardiometabolic risk factors in addition to changes in body weight and glycemic status. However, the analyses were post hoc and were not specified in the STEP 1 protocol. Moreover, the stratification of participants into subgroups inevitably reduced the size of each group, and the subgroups were not mutually exclusive. Nevertheless, the smallest subgroup still contained >150 individuals. Another possible limitation is that participants were not analyzed by race or ethnicity. Although a lower BMI threshold than 30 kg/m^2 to indicate high risk (typically 27.5 kg/m^2) has been recommended for people of South Asian, Chinese, and Black African or Caribbean race and ethnicity, numbers of participants from these groups in this trial were insufficient for meaningful stratification into subgroups by baseline BMI with or without obesity-related comorbidities.

CONCLUSION

In summary, many studies of obesity have classified participants solely on the basis of their BMI. However, there has been increasing recognition that targeting cardiometabolic status may also be key to reducing obesity-related morbidity and mortality. These subgroup analyses of the STEP 1 trial confirm that once-weekly s.c. semaglutide 2.4 mg is efficacious in individuals at increased risk of poor outcomes, specifically in those with comorbidities, with prediabetes, or with prediabetes plus high CVD risk. Importantly, these benefits are seen irrespective of whether baseline BMI is <35 or ≥35 kg/m^2. Once-weekly s.c. semaglutide 2.4 mg can thus reduce body weight and improve cardiometabolic health and glycemic status across a broad population of individuals with obesity, including in those who may be denied access to treatment on the basis of current reimbursement thresholds.

AUTHOR CONTRIBUTIONS

Barbara M. McGowan contributed to the conduct of the trial; data collection, analysis, and interpretation; and manuscript development. James Baker-Knight, Azadeh Houshmand-Oeregaard, Peter Nørkjær Laursen, and Niels Zeuthen contributed to data analysis and interpretation, and manuscript development.

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CONFLICT OF INTEREST

Barbara M. McGowan reports receiving educational fees from Merck, lecture fees from Janssen Biotech, advisory board fees from Johnson & Johnson Health Care Systems and Lilly, grant support, paid to Guys and St. Thomas' Hospital, consulting fees, and educational fees from Novo Nordisk, and owning stock in Reset Health Clinics. James Baker-Knight, Azadeh Houshmand-Oeregaard, and Niels Zeuthen are employees of and own shares in Novo Nordisk. Peter Nørkjær Laursen is an employee of Novo Nordisk.

DATA AVAILABILITY STATEMENT

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. Data will be made available after research completion and approval of the product and product use in the European Union and the United States. Information about data access request proposals can be found at https://www.novonordisk-trials.com/

ORCID

Barbara M. McGowan https://orcid.org/0000-0003-2015-726X
Azadeh Houshmand-Oeregaard https://orcid.org/0000-0002-1595-5892
Peter Nørkjær Laursen https://orcid.org/0000-0002-3905-292X
James Baker-Knight https://orcid.org/0000-0002-7936-9593

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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