



Changes in Glucose Metabolism and Glycemic Status With Once-Weekly Subcutaneous Semaglutide 2.4 mg Among Participants With Prediabetes in the STEP Program

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OBJECTIVE

This analysis of 3,375 adults with overweight/obesity across the Semaglutide Treatment Effect in People with obesity (STEP) 1, 3, and 4 trials evaluated whether more participants with prediabetes had normoglycemia after 68 weeks' treatment with once-weekly semaglutide 2.4 mg plus lifestyle intervention versus placebo and assessed changes in glucose metabolism in participants with prediabetes.

RESEARCH DESIGN AND METHODS

STEP 1, 3, and 4 were phase 3, 68-week, randomized, placebo-controlled, multinational trials; STEP 4 had a 20-week semaglutide run-in and 48-week randomized period. Analyses included changes (week 0–68; before the washout period) in glycemic status (prespecified: STEP 1 and 3; post hoc: STEP 4), and in HbA_{1c}, fasting plasma glucose (FPG), and HOMA insulin resistance (HOMA-IR) among participants with prediabetes (post hoc).

RESULTS

Significantly more participants with baseline (week 0) prediabetes ($n = 1,536$) had normoglycemia at week 68 with semaglutide versus placebo (STEP 1, 84.1% vs. 47.8%; STEP 3, 89.5% vs. 55.0%; STEP 4, 89.8% vs. 70.4%; all $P < 0.0001$). Fewer participants with baseline normoglycemia had prediabetes at week 68 with semaglutide versus placebo (STEP 1, 2.9% vs. 10.9%; STEP 3, 3.2% vs. 5.8%; STEP 4, 1.1% vs. 5.0%). Semaglutide resulted in greater improvements in HbA_{1c}, FPG, and HOMA-IR than placebo among participants with baseline prediabetes (all $P < 0.01$).

CONCLUSIONS

STEP 1, 3, and 4 collectively provide a robust assessment of the effects of semaglutide on glucose metabolism and prediabetes in a large cohort of adults with overweight/obesity while on treatment. Among participants with baseline prediabetes, 68 weeks' treatment with semaglutide versus placebo led to significant improvements in glucose metabolism and a higher likelihood of normoglycemia.

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Obesity is a risk factor for prediabetes and type 2 diabetes (1). In the U.S., 88 million adults were estimated to have prediabetes in 2018 (2). The Diabetes Prevention Program and other clinical trials testing intensive lifestyle modification and

antiobesity medication have demonstrated that weight loss can restore normoglycemia in those with prediabetes (3–7).

Prediabetes and type 2 diabetes are associated with an increased risk of cardiovascular disease and related adverse events (8,9). In individuals with prediabetes, weight loss and prevention of diabetes are accompanied by improvements in cardiometabolic risk factors (e.g., blood pressure, waist circumference, triglycerides, and HDL cholesterol) (6,10), and these improvements are maintained long-term (11).

Subcutaneous semaglutide is a glucagon-like peptide-1 analog approved for the treatment of type 2 diabetes at once-weekly doses of up to 1.0 mg (12). On the basis of data from the Semaglutide Treatment Effect in People with obesity (STEP) 1–4 trials (13–16), once-weekly subcutaneous semaglutide 2.4 mg was approved for weight management, as an adjunct to lifestyle intervention, in adults with obesity or overweight with one or more weight-related conditions (17,18).

Among participants with baseline prediabetes in STEP 1, 84.1% of participants receiving once-weekly semaglutide 2.4 mg versus 47.8% receiving placebo had normoglycemia at week 68, and semaglutide was associated with improvements in glycosylated hemoglobin (HbA_{1c}) levels at week 68 (13). However, data on changes in glycemic status and HbA_{1c} in participants with prediabetes have not been reported for STEP 3 and 4. Additionally, across all three trials, no data have been published for changes in fasting plasma glucose (FPG), HOMA of insulin resistance (HOMA-IR), and HOMA of β -cell function (HOMA-B) in participants with prediabetes or for change in percentage of body weight according to glycemic status at week 0.

The objective of this analysis was to evaluate whether a higher proportion of participants with prediabetes at week 0 had normoglycemia after 68 weeks' treatment with semaglutide 2.4 mg versus placebo and assess changes in glucose metabolism with semaglutide 2.4 mg versus placebo in participants with prediabetes at week 0, defined according to American Diabetes Association (ADA) criteria, across the STEP 1, 3, and 4 trials. As these trials included similar patient populations—adults with overweight/obesity, without type 2 diabetes—the collective

results provide a robust assessment of the effects of semaglutide on glycemic status and glucose metabolism in a large cohort of such patients.

RESEARCH DESIGN AND METHODS

Trial Design

STEP 1, 3, and 4 were phase 3, 68-week, double-blind, randomized, multicenter, multinational trials, the designs of which have been published previously (Supplementary Fig. 1) (13,15,16). In STEP 1 and 3, participants were randomized (2:1) to once-weekly subcutaneous semaglutide 2.4 mg or placebo, plus lifestyle intervention (STEP 1) or intensive behavioral therapy (IBT; STEP 3), for 68 weeks, with 7 weeks' follow-up. In STEP 4, participants received lifestyle intervention throughout the trial and initially received open-label subcutaneous semaglutide during a 20-week run-in period. Participants reaching the maintenance dose of 2.4 mg by week 16 and still receiving this at week 20 were randomized (2:1) to continue with semaglutide or switched to placebo from week 20 to 68, with 7 weeks' follow-up.

All trials included initial dose escalation, with semaglutide initiated at 0.25 mg once weekly for 4 weeks, then escalated every 4 weeks thereafter to 0.5 mg, 1.0 mg, 1.7 mg, and finally 2.4 mg at week 16. Matching placebo dose escalation was used.

Lifestyle interventions were identical for STEP 1 and 4, while participants in STEP 3 received IBT (Supplementary Table 1).

The trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Protocols were approved by independent ethics committees or institutional review boards at each study site and are available online with the full-text articles of the primary analyses (13,15,16).

Participants

Participants were aged ≥ 18 years, with one or more self-reported unsuccessful dietary efforts to lose weight, and BMI ≥ 30 kg/m² or ≥ 27 kg/m², with one or more weight-related comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease), without diabetes (13,15,16). All participants provided written informed consent.

Analyses

The primary objective of each trial was to compare the effect of semaglutide 2.4 mg with placebo on body weight in participants with overweight/obesity. The objective of the present post hoc analysis was to evaluate whether a higher proportion of participants with prediabetes at week 0 had normoglycemia after 68 weeks' treatment with semaglutide 2.4 mg versus placebo and assess changes in glucose metabolism with semaglutide 2.4 mg versus placebo in participants with prediabetes at week 0 across STEP 1, 3, and 4. Analyses included change from week 0 to 68 in glycemic status, HbA_{1c}, FPG, HOMA-IR, HOMA-B, and change from week 0 to 68 in percentage of body weight according to glycemic status at week 0. For most outcomes, data from each trial were analyzed separately. However, for post hoc outcomes of a descriptive nature, where there was no intention of directly comparing the effect of semaglutide versus placebo, the semaglutide arms were pooled to increase the power. Placebo arms were not pooled due to differences in the design of STEP 4, whereby the placebo arm had a 20-week semaglutide run-in before switching to placebo at week 20.

Glycemic status (normoglycemia, prediabetes, or type 2 diabetes) was assessed by the investigator according to ADA definitions at weeks 0 and 68, based on all available relevant information (e.g., concomitant medication, medical records, and blood glucose parameters). Prediabetes was defined as FPG 5.6–6.9 mmol/L or HbA_{1c} 5.7–6.4% (39–47 mmol/mol). The final dose of trial product was administered at week 68; there was no formal washout period before the week 68 glycemic status assessment.

Statistical Analyses

Change from week 0 to 68 in glycemic status was a prespecified exploratory end point in STEP 1 and 3 (in which week 0 was baseline) and was analyzed post hoc in STEP 4 due to differences in the study design, whereby baseline was at week 20. Changes from week 0 to 68 in HbA_{1c} and FPG were prespecified supportive secondary efficacy end points in STEP 1 and 3 that were analyzed post hoc among participants with baseline prediabetes. Changes from week 0 to 68 in HbA_{1c} and FPG in participants with

prediabetes at week 0 in STEP 4 were post hoc analyses. All other outcomes—that is, change from week 0 to 68 in HOMA-IR and HOMA-B in participants with prediabetes at week 0, and change in the percentage of body weight according to glycemic status at week 0—were post hoc analyses.

Two estimands (“treatment policy” and “trial product,” as described elsewhere [19,20]) were used in the STEP trials to evaluate the treatment effects of semaglutide from different perspectives, in line with guidance from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (21,22). In this analysis, we used the treatment policy estimand, as this was the primary estimand in the STEP program. It evaluates the trial population average treatment effect of semaglutide or placebo and includes all randomized participants regardless of adherence or unplanned interventions, such as use of any other antiobesity medications or bariatric surgery. Analyses used observed data from the in-trial period (the time from random assignment to last contact with a trial site, regardless of treatment discontinuation/rescue intervention). Continuous end points were analyzed using ANCOVA (with randomized treatment as a factor and week 0 value as a covariate). Missing data were imputed using a multiple imputation approach.

Tests for differences in the proportions of participants changing glycemic status from week 0 to 68 (i.e., prediabetes to normoglycemia, normoglycemia to prediabetes, and prediabetes to type 2 diabetes) were performed using the χ^2 test for independence. Statistical analyses were not adjusted for multiplicity.

Data and Resource Availability

Data will be shared with bona fide researchers submitting a research proposal approved by the independent review board. Access request proposals can be found at novonordisk-trials.com. Data will be made available after research completion, and approval of the product and product use in the European Union and the U.S. Individual participant data will be shared in data sets in a de-identified/anonymized format.

RESULTS

Participant Demographics and Baseline Characteristics

Overall, 1,961 participants were randomized in STEP 1 (semaglutide, $n = 1,306$; placebo, $n = 655$) and 611 in STEP 3 (semaglutide, $n = 407$; placebo, $n = 204$). In STEP 4, 902 participants entered the 20-week semaglutide run-in; of these, 803 were randomized to continued semaglutide or placebo for 48 weeks—the present analysis of STEP 4 was restricted to these randomized participants.

Approximately half of each study population had prediabetes at week 0 (STEP 1: 43.7%; STEP 3: 49.8%; STEP 4: 46.8%). Baseline characteristics of participants with prediabetes at week 0 are summarized in Table 1.

Glycemic Status From Week 0 to 68

At week 68, most participants in the three semaglutide groups were classed as having normoglycemia. By week 68 in STEP 1, 84.1% of those with prediabetes at week 0 had normoglycemia with semaglutide versus 47.8% with placebo ($P < 0.0001$) (Fig. 1A). At week 68, type 2 diabetes was observed in 0.5% of participants who had prediabetes at week 0 in the semaglutide group versus 3.0% in the placebo group ($P = 0.0045$). Among participants with normoglycemia at week 0, fewer participants on semaglutide had prediabetes by week 68 than on placebo (2.9% vs. 10.9%; $P < 0.0001$) (Supplementary Fig. 2).

Similar findings were observed in STEP 3. Among participants with prediabetes at week 0, 89.5% in the semaglutide group had normoglycemia by week 68 compared with 55.0% on placebo ($P < 0.0001$) (Fig. 1B). No participants with prediabetes at week 0 in the semaglutide group had type 2 diabetes at week 68 versus one participant (1.0%) in the placebo group ($P = 0.1777$). By week 68, 3.2% of participants on semaglutide who had normoglycemia at week 0 had prediabetes compared with 5.8% on placebo ($P = 0.3048$) (Supplementary Fig. 2).

In STEP 4, 89.8% and 70.4% of participants with prediabetes at week 0 had normoglycemia after 68 weeks of continued treatment with semaglutide and placebo (48 weeks of placebo after the 20-week semaglutide run-in), respectively ($P < 0.0001$) (Fig. 1C). No participants

with prediabetes in the semaglutide group had type 2 diabetes at week 68 versus one participant (0.9%) in the placebo group ($P = 0.1231$). Among participants with normoglycemia at week 0, fewer participants on semaglutide had prediabetes by week 68 versus those on placebo (1.1% vs. 5.0%; $P = 0.0171$) (Supplementary Fig. 2).

Across all three trials, most participants on semaglutide whose glycemic status changed from normoglycemia to prediabetes or from prediabetes to type 2 diabetes between week 0 and 68 had completed treatment.

Body Weight Change and Glycemic Status at Week 68 (Participants With Prediabetes at Week 0)

Pooling individual participant-level data across the three semaglutide arms demonstrated that most participants who had prediabetes at week 0 and weight loss associated with 68 weeks' semaglutide treatment had normoglycemia at week 68 (Supplementary Fig. 3A). A relationship between the greater percentage weight loss and the likelihood of normoglycemia at week 68 was also evident in the pooled semaglutide data and in the placebo arms of each individual study (Supplementary Fig. 3A–D). This relationship was also observed in an analysis of change in glycemic status by categorical weight loss, whereby the proportion of participants with prediabetes at week 0 who changed to normoglycemia at week 68 with semaglutide increased with larger losses of body weight from week 0 to 68 in STEP 1 and 4 (Fig. 2).

Effects on Glucose Metabolism and Body Weight (Participants With Prediabetes at Week 0)

In STEP 1, treatment with semaglutide versus placebo lowered HbA_{1c} (estimated treatment difference [ETD]: -0.35 percentage points, -3.78 mmol/mol; $P < 0.0001$), FPG (ETD: -8.49 mg/dL [-0.47 mmol/L]; $P < 0.0001$), and HOMA-IR (estimated relative percentage difference: -28% ; $P < 0.0001$) from week 0 to 68 (Fig. 3). In participants treated with semaglutide, geometric mean HOMA-B was 151.4 at week 0 vs. 155.5 at week 68, with corresponding values of 155.4 and 145.0 in placebo-treated participants (estimated relative percentage difference: 5.7% ; $P = 0.1532$). Body weight reduced by -13.7% with

Table 1—Demographics and clinical characteristics of study participants with prediabetes at week 0*

	STEP 1		STEP 3		STEP 4	
	Semaglutide 2.4 mg OW (n = 593)	Placebo (n = 263)	Semaglutide 2.4 mg OW (n = 196)	Placebo (n = 108)	Semaglutide 2.4 mg OW (n = 262)	Placebo (n = 114)
Age, years	48.5 ± 12.5	49.4 ± 12.1	48.8 ± 11.9	49.7 ± 12.3	49.9 ± 11.6	50.0 ± 10.6
Female sex, n (%)	407 (68.6)	196 (74.5)	153 (78.1)	88 (81.5)	208 (79.4)	81 (71.1)
Race, n (%)						
White	417 (70.3)	183 (69.6)	146 (74.5)	84 (77.8)	212 (80.9)	94 (82.5)
Black or African American	42 (7.1)	22 (8.4)	45 (23.0)	19 (17.6)	42 (16.0)	17 (14.9)
Asian	100 (16.9)	41 (15.6)	1 (0.5)	4 (3.7)	4 (1.5)	1 (0.9)
Other	34 (5.7)	17 (6.5)	4 (2.0)	1 (0.9)	4 (1.5)	2 (1.8)
Ethnicity, n (%)						
Not Hispanic or Latino	508 (85.7)	216 (82.1)	154 (78.6)	87 (80.6)	239 (91.2)	108 (94.7)
Hispanic or Latino	75 (12.6)	41 (15.6)	42 (21.4)	21 (19.4)	23 (8.8)	6 (5.3)
Body weight, kg	106.9 ± 22.4	106.9 ± 21.1	108.7 ± 22.9	106.9 ± 23.3	109.7 ± 25.1	109.6 ± 24.6
BMI, kg/m ²	38.4 ± 6.6	38.9 ± 6.5	39.0 ± 6.8	38.5 ± 6.9	39.3 ± 7.8	39.1 ± 7.6
HbA _{1c} , %	5.9 ± 0.2	5.9 ± 0.2	6.0 ± 0.2	6.0 ± 0.2	5.9 ± 0.2	5.9 ± 0.2
HbA _{1c} , mmol/mol	41.2 ± 2.4	41.4 ± 2.7	41.6 ± 2.6	41.6 ± 2.4	41.5 ± 2.5	41.3 ± 2.3
FPG, mg/dL	98.7 ± 11.0	97.6 ± 11.8	96.8 ± 9.4	96.7 ± 9.2	100.9 ± 11.5	98.5 ± 9.3
FPG, mmol/L	5.5 ± 0.6	5.4 ± 0.7	5.4 ± 0.5	5.4 ± 0.5	5.6 ± 0.6	5.5 ± 0.5
HOMA-IR	3.46 (63.7)	3.38 (65.8)	3.32 (65.3)	3.20 (66.1)	3.44 (58.4)	3.39 (50.4)
HOMA-B	151.4 (63.0)	155.4 (64.9)	155.4 (55.8)	150.6 (68.4)	139.2 (61.2)	147.6 (54.1)

Data are mean ± SD or geometric mean (coefficient of variation), unless indicated otherwise. OW, once weekly. *Glycemic status was determined by investigators based on available information (e.g., medical records, concomitant medication, and blood glucose parameters) and in accordance with ADA definitions.

semaglutide versus -2.4% with placebo from week 0 to 68 (ETD: -11.31 percentage points; $P < 0.0001$) (Fig. 3).

Treatment with semaglutide versus placebo in STEP 3 also lowered HbA_{1c} (ETD: -0.29 percentage points, -3.13 mmol/mol; $P < 0.0001$), FPG (ETD: -7.97 mg/dL [-0.44 mmol/L]; $P < 0.0001$), and HOMA-IR (estimated relative percentage difference: -29.7% ; $P = 0.0018$) from week 0 to 68 (Fig. 3). Geometric mean HOMA-B was 155.4 and 140.4 at weeks 0 and 68, respectively, in semaglutide-treated participants and 150.6 and 129.1 in placebo-treated participants (estimated relative percentage difference: 5.9% ; $P = 0.3521$). Body weight reduced by -15.5% with semaglutide and -6.4% with placebo from week 0 to 68 (ETD: -9.08 percentage points; $P < 0.0001$) (Fig. 3).

In STEP 4, treatment with semaglutide versus placebo lowered HbA_{1c} (ETD: -0.30 percentage points, -3.23 mmol/mol; $P < 0.0001$), FPG (ETD: -8.82 mg/dL [-0.49 mmol/L]; $P < 0.0001$), and HOMA-IR (estimated relative percentage difference: -30.4% ; $P < 0.0001$) from week 0 to 68 (Fig. 3). The trajectories of HbA_{1c} and FPG are shown in Supplementary

Fig. 4. Predictably, the mean values for both end points increased in the placebo group from week 20 when semaglutide was discontinued but had not returned to week 0 levels at week 68. In participants continuing semaglutide, both HbA_{1c} and FPG appeared to have leveled out by 52 weeks. In participants on semaglutide, the geometric mean HOMA-B was 139.2 at week 0 and 147.0 at week 68 vs. 147.6 and 132.7 in placebo-treated participants (estimated relative percentage difference: 15.26% ; $P = 0.0843$). Body weight reduced by -16.5% with semaglutide and by -5.2% with placebo from week 0 to 68 (ETD: -11.30 percentage points; $P < 0.0001$) (Fig. 3).

Supplementary Fig. 5 shows the cumulative distribution curves for absolute observed values at week 68 and the change from baseline in HbA_{1c} for semaglutide pooled across studies and the individual study placebo groups. This analysis shows the greater overall glucose-lowering effect of semaglutide versus placebo. The higher proportion of participants with a lower change in HbA_{1c} from baseline at week 68 in the STEP 4 placebo group is explained by the fact

that the baseline for this study was at 20 weeks and that participants randomized to placebo were withdrawn from semaglutide at this point.

CONCLUSIONS

In the STEP 1, 3, and 4 trials in individuals with overweight/obesity, treatment with once-weekly subcutaneous semaglutide, as an adjunct to standard-of-care lifestyle intervention or IBT, appeared to improve glucose parameters with a greater likelihood of achieving normoglycemia among participants with prediabetes at week 0 compared with placebo plus lifestyle intervention. In addition, weight loss was associated with normoglycemia, and semaglutide-treated weight loss rendered more normoglycemia at a given weight loss compared with placebo.

Baseline levels of prediabetes over 68 weeks were similar across all three studies. Most participants with prediabetes at week 0 who were treated with semaglutide for 68 weeks had normoglycemia at week 68 (STEP 1, 84.1%; STEP 3, 89.5%; STEP 4, 89.8%). In comparison, other

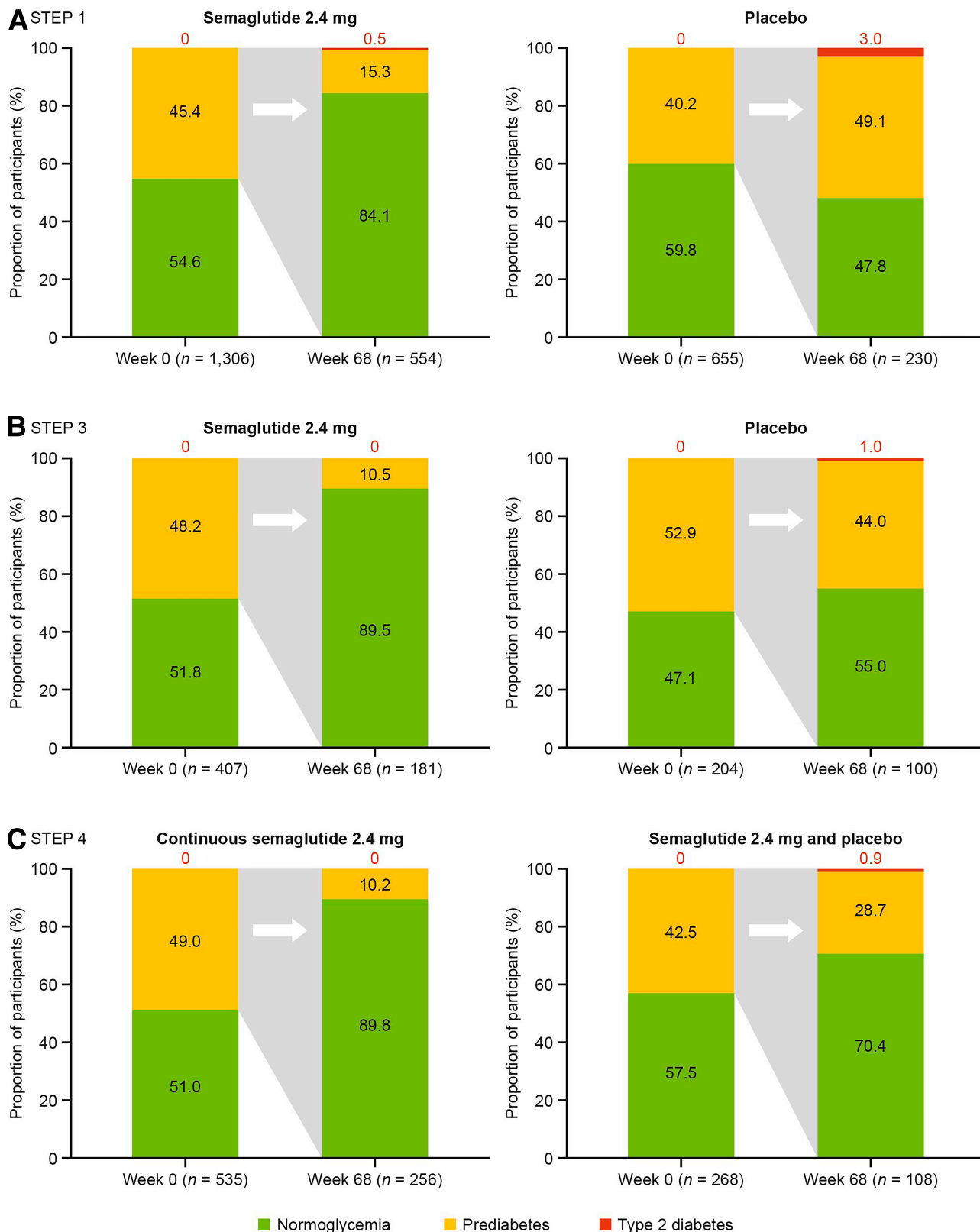


Figure 1—Glycemic status—changes in proportions of participants from week 0 to week 68 in participants with prediabetes at week 0 in STEP 1 (A), STEP 3 (B), and STEP 4 (C). Data are observed data during the in-trial period (regardless of treatment discontinuation or rescue intervention). Glycemic category was evaluated by the investigator based on all available relevant information (e.g., concomitant medication, medical records, and blood glucose parameters) in accordance with ADA definitions.

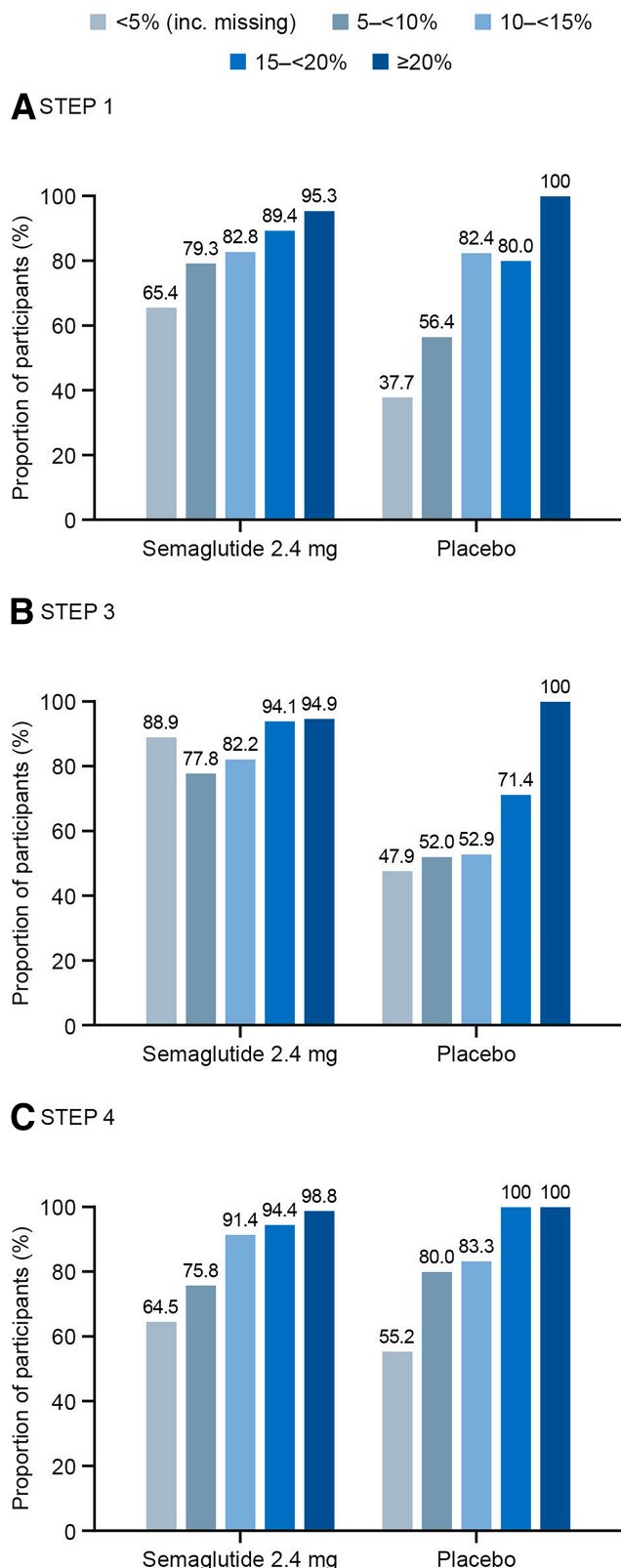


Figure 2—Glycemic status—proportion of participants with prediabetes at week 0 and normoglycemia at week 68 by weight-loss categories in STEP 1 (A), STEP 3 (B), and STEP 4 (C). Data are observed data during the in-trial period (regardless of treatment discontinuation or rescue intervention). Glycemic category was evaluated by the investigator based on all available relevant information (e.g., concomitant medication, medical records, and blood glucose parameters) in accordance with ADA definitions.

studies report reversion rates of 31–52% with lifestyle intervention only, 20% with metformin, 35% with acarbose, ~50% with rosiglitazone or pioglitazone, and 66% with liraglutide (23,24). Although these studies cannot be directly compared and may have differed in participant characteristics, design, and washout (or not), the magnitude of the effect with semaglutide was robust nevertheless.

Additionally, in STEP 1, 3, and 4, the number of participants with prediabetes at week 0 who had type 2 diabetes at week 68 was few/none among those treated with semaglutide, and most had normoglycemia at week 68. Similarly, the number of participants with normoglycemia at week 0 who had prediabetes at week 68 on semaglutide was low. These findings indicate that once-weekly semaglutide may slow the trajectory to type 2 diabetes in adults with overweight/obesity and has the potential to disrupt the pathophysiology of type 2 diabetes.

In each of the STEP trials, participants with prediabetes at week 0 in the semaglutide groups had greater reductions in HbA_{1c} and FPG and more improvement with respect to insulin resistance (HOMA-IR) than the respective placebo groups. The ADA defines prediabetes as FPG 5.6–6.9 mmol/L, HbA_{1c} 5.7–6.4% (39–47 mmol/mol), or 2-h plasma glucose during 75-g oral glucose tolerance test of 7.8–11.0 mmol/L (25). FPG and HbA_{1c} are the two most used diagnostic tests for type 2 diabetes (26); therefore, these were evaluated (rather than 2-h plasma glucose) in accordance with ADA definitions in this analysis.

Insulin resistance is associated with a higher risk of cardiovascular disease (27). In addition to beneficial effects on glucose control, improving insulin resistance may also reduce the risk of cardiovascular disease in those with prediabetes or type 2 diabetes. For example, a post hoc analysis of the Insulin Resistance Intervention after Stroke (IRIS) trial found that in people with prediabetes and a HOMA-IR >3.0 who experienced an ischemic stroke or transient ischemic attack within 6 months of randomization, insulin-sensitizing medication (pioglitazone) significantly reduced the risk of progression to diabetes (4.7% vs. 9.9%; *P* < 0.001) and of stroke or myocardial infarction (8.9% vs. 12.5%; *P* = 0.002) versus placebo (28).

Improvements in glycemic status were observed in the placebo arms of each

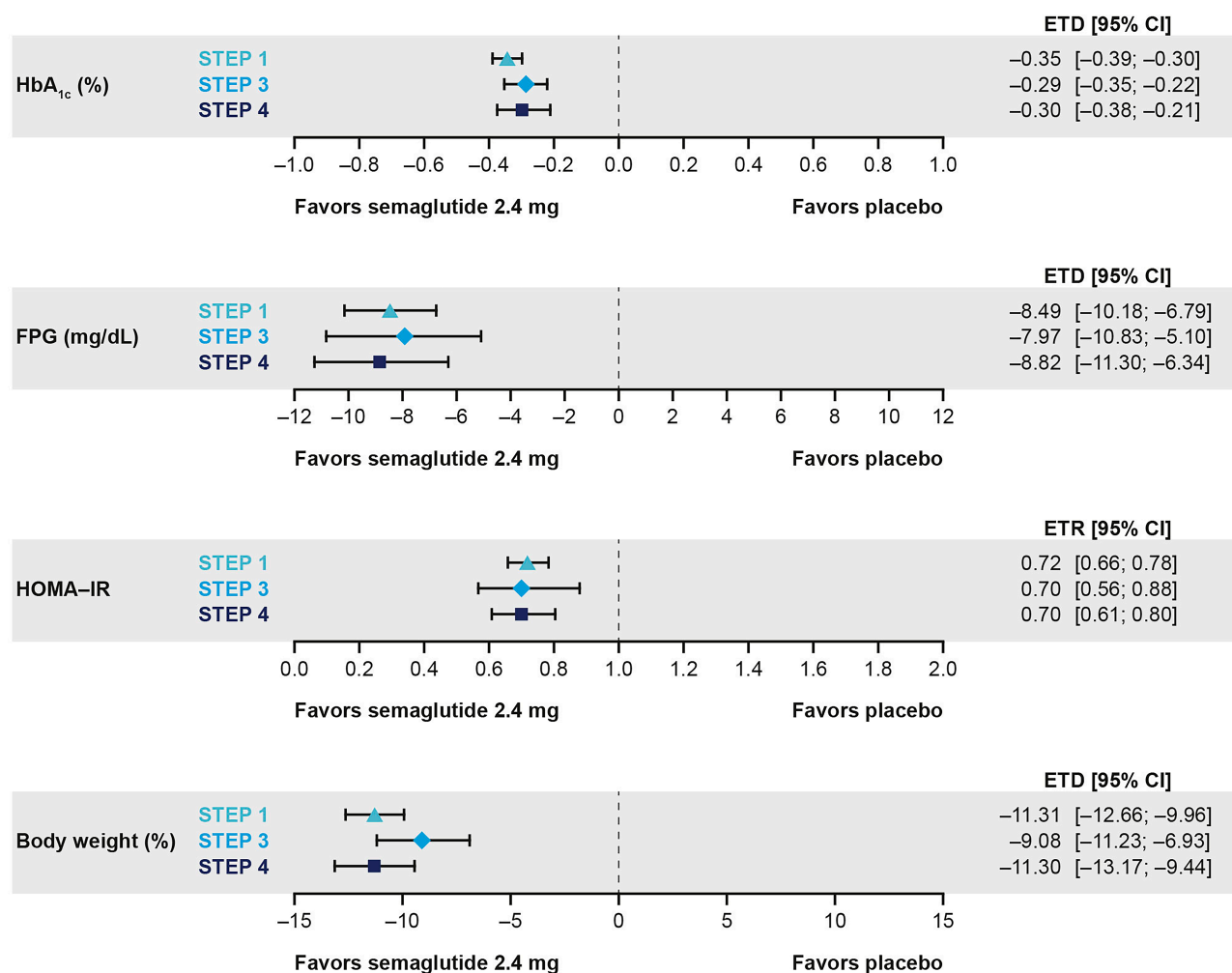


Figure 3—Effects on glucose metabolism (HbA_{1c}, FPG, HOMA-IR) and body weight in participants with prediabetes at week 0 (all studies). HbA_{1c} % to mmol/mol conversion formula: $10.929 * (\text{HbA}_{1c} \text{ value in } \% - 2.15) = \text{HbA}_{1c} \text{ mmol/mol}$; FPG mg/dL to mmol/L conversion formula: $\text{FPG value in mg/dL} * 0.0555 = \text{FPG mmol/L}$. ETR, estimated treatment ratio (semaglutide 2.4 mg vs. placebo).

study; 48–70% of participants with prediabetes at week 0 who were randomized to placebo had normoglycemia at week 68. While this is partly due to reclassification among those patients in the placebo arm who did not have marked weight loss, the findings demonstrated the value of standard-of-care preventative weight-loss measures (i.e., lifestyle intervention) and IBT, as well as short-term (20 weeks') treatment with semaglutide in the STEP 4 placebo arm. Improvements in glycemic status in the placebo arms of current analyses were similar to or higher than the optimum levels seen in earlier studies of lifestyle intervention alone, suggesting that participants in the STEP trials were well managed. Results also suggest that improvements in glycemic status in the semaglutide arm may be interpreted as substantial additional benefits beyond those achieved with state-of-the-art care

(i.e., optimal lifestyle intervention). This finding is noteworthy considering that participants in STEP 3 received IBT rather than standard-of-care lifestyle intervention as an adjunct to treatment. In STEP 1 and 3, in which all participants received lifestyle intervention (diet and exercise) or IBT, respectively, there were considerable but similar changes in the proportions of participants with prediabetes at week 0 who had normoglycemia at week 68 in the placebo groups (48% and 55%, respectively). In the STEP 4 placebo arm, 70.4% of participants with prediabetes at week 0 had normoglycemia at week 68, suggesting a potential sustained effect of the initial 20 weeks' treatment with semaglutide that was maintained until week 68. That, overall, the vast majority of participants benefited during this time in terms of glycemia is also shown by the divergence and increase in the HbA_{1c}

and FPG trajectories that occurred after 20 weeks in participants switched from semaglutide to placebo at randomization (Supplementary Fig. 4).

In individuals with overweight/obesity and type 2 diabetes undergoing intensive lifestyle intervention in the Look AHEAD (Action for Health in Diabetes) study, a greater benefit on glycemic outcomes was reported with greater weight loss (29) (this was also observed in participants with prediabetes at week 0 in STEP 1 and 4) (Fig. 2). However, as mentioned above, reported conversion rates from prediabetes to normoglycemia range between 31 and 52% with lifestyle intervention only (22,23). The superior reductions in body weight achieved with lifestyle intervention plus semaglutide compared with lifestyle intervention plus placebo in STEP 1, 3, and 4 indicate the greater weight loss with

semaglutide was associated with greater improvements in glycemic outcomes, at least for the duration of the trials. This translates into a higher proportion of participants with prediabetes at week 0 having normoglycemia at week 68 (~85%). This is supported by the observation that the proportion of participants with prediabetes at week 0 who had normoglycemia at week 68 with semaglutide increased with larger losses of body weight from week 0 to 68 in STEP 1 and 4. Furthermore, although it is not possible to directly compare the STEP and SCALE (Satiety and Clinical Adipose-Liraglutide Evidence) clinical trial programs, the magnitude of weight loss among participants with prediabetes appeared to be greater with semaglutide in STEP 1 (14.9%) than with liraglutide in SCALE Obesity and Prediabetes (7.4%) (13,30).

Similarly, the proportion of participants with normoglycemia at week 0 who had prediabetes by the end of treatment was greater with semaglutide in STEP 1 than with liraglutide in SCALE Obesity and Prediabetes. This suggests that greater weight loss may be associated with improvements in glycemic status during treatment with glucagon-like peptide-1 analogs. However, as semaglutide is a more potent glucose-lowering agent than liraglutide, it remains unclear whether the additional benefit of semaglutide is due to the greater magnitude of weight loss or a direct effect on glucose metabolism.

Our findings from STEP 3 also show that semaglutide provides further clinical value when added to IBT, which until now has been regarded as the gold standard for prevention of diabetes in people with overweight/obesity and prediabetes. However, despite use of IBT in STEP 3, as opposed to standard-of-care lifestyle intervention in STEP 1, changes in glycemic status and glucose metabolism with semaglutide were similar across the two trials. This is not surprising, as reductions in baseline body weight with semaglutide were also similar across these trials. Nonetheless, it suggests that IBT as an adjunct to semaglutide may not provide substantial additional benefits compared with less intensive lifestyle intervention.

Limitations include the fact that most analyses were post hoc and that the STEP trials represent a controlled clinical

trial environment with regular follow-up, which may differ from clinical practice. Furthermore, these studies were not able to determine the contribution of weight loss alone to the improvement of glycemia or how much of the benefit pertained to weight loss independent of the incretin effect of glucagon-like peptide-1 analogs. Moreover, investigator-assessed glycemic status was based on ADA definitions only, so results may differ according to World Health Organization or International Expert Committee definitions (31,32); we also considered more than just HbA_{1c}, preventing direct inference of changes in HbA_{1c} in relation to body weight and glycemic status. Additionally, analyses were not designed to evaluate whether improvements in glycemic status at the end of treatment represented complete reversion to normoglycemia in terms of reversion of the underlying pathophysiology associated with prediabetes. In STEP 1, 3, and 4, there was no washout period between the end of treatment and the final glycemic status assessment at week 68, consistent with a number of other trials investigating approaches to diabetes prevention and reversion of prediabetes (33–39); therefore, it is not possible to conclude whether improvements in glycemic status would be sustained after treatment discontinuation. As such, improvements could, in part, reflect short-term benefits of improved glucose control while on treatment. However, in the STEP 4 placebo arm—which had a 20-week semaglutide run-in period—a greater proportion of participants with prediabetes at week 0 had normoglycemia at week 68 than in the STEP 1 and 3 placebo arms. This suggests that glycemic status improvements were not limited to improved glucose control while on treatment, especially as the proportion of participants with prediabetes at week 0 who had normoglycemia at week 68 with semaglutide increased with larger losses of body weight in STEP 1 and 4. The off-treatment STEP 1 extension phase (NCT03548935) is anticipated to provide further insight into the effect of semaglutide treatment withdrawal on glycemic status. Finally, in STEP 4, treatment group comparisons over 68 weeks are confounded by the withdrawal design in which all participants (including the placebo group) received a 20-week semaglutide run-in.

Data for week 0 to 68 were evaluated only in participants who completed the run-in period and were randomized; thus, this is a selected population able to tolerate semaglutide treatment. However, collectively, STEP 1, 3, and 4 provide a robust assessment of the effects of semaglutide on glucose metabolism and prediabetes in a large cohort of >2,200 adults allocated with regular follow-up for over 1 year.

In conclusion, most adults with overweight/obesity and prediabetes at week 0 had normoglycemia after 68 weeks' treatment with once-weekly semaglutide 2.4 mg, and the proportions of these participants with normoglycemia at week 68 increased with larger losses of body weight from week 0 to 68 in STEP 1 and 4. Conversely, fewer participants with normoglycemia at week 0 had prediabetes at week 68 with semaglutide versus placebo. These findings support the concept that weight loss may alter the pathophysiology of type 2 diabetes. The role of semaglutide warrants further investigation in addition to an evaluation of predictors of treatment response to identify variables that can predict patient response in terms of weight loss and improvement in glucose metabolism. Finally, semaglutide-induced weight loss was associated with improvements in glucose metabolism and prediabetes in the respective STEP trials.

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Investigators were responsible for data collection, and the sponsor undertook site monitoring, data collation, and analysis. All authors had access to study data, participated in manuscript drafting (assisted by a sponsor-funded medical writer), approved its submission, and can vouch for data accuracy and fidelity to the protocol.

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References

- Miao Z, Alvarez M, Ko A, et al. The causal effect of obesity on prediabetes and insulin resistance reveals the important role of adipose tissue in insulin resistance. *PLoS Genet* 2020; 16:e1009018
- Centers for Diseases Control and Prevention. National Diabetes Statistics Report 2020. Estimates of Diabetes and Its Burden in the United States 2020. Accessed 11 May 2021. Available from <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>
- Herman WH, Pan Q, Edelstein SL, et al.; Diabetes Prevention Program Research Group. Impact of lifestyle and metformin interventions on the risk of progression to diabetes and regression to normal glucose regulation in overweight or obese people with impaired glucose regulation. *Diabetes Care* 2017;40:1668–1677
- le Roux CW, Astrup A, Fujioka K, et al.; SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* 2017;389:1399–1409
- Nesto R, Fain R, Li Y, Shanahan W. Evaluation of lorcaserin on progression of prediabetes to type 2 diabetes and reversion to euglycemia. *Postgrad Med* 2016;128:364–370
- Garvey WT, Ryan DH, Henry R, et al. Prevention of type 2 diabetes in subjects with prediabetes and metabolic syndrome treated with phentermine and topiramate extended release. *Diabetes Care* 2014;37:912–921
- Perreault L, Kahn SE, Christophi CA, Knowler WC, Hamman RF; Diabetes Prevention Program Research Group. Regression from pre-diabetes to normal glucose regulation in the diabetes prevention program. *Diabetes Care* 2009;32:1583–1588
- Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *BMJ* 2016;355:i5953
- Emerging Risk Factors Collaboration; Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215–2222
- Ratner R, Goldberg R, Haffner S, et al.; Diabetes Prevention Program Research Group. Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the Diabetes Prevention Program. *Diabetes Care* 2005;28:888–894
- Diabetes Prevention Program Outcomes Study Research Group; Orchard TJ, Temprosa M, Barrett-Connor E, et al. Long-term effects of the Diabetes Prevention Program interventions on cardiovascular risk factors: a report from the DPP Outcomes Study. *Diabet Med* 2013;30:46–55
- U.S. Food and Drug Administration. Ozempic (semaglutide) prescribing information. Revised January 2020. Accessed 11 May 2021. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209637s003lbl.pdf
- Wilding JPH, Batterham RL, Calanna S, et al.; STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021;384:989–1002
- Davies M, Færch L, Jeppesen OK, et al.; STEP 2 Study Group. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021;397:971–984
- Wadden TA, Bailey TS, Billings LK, et al.; STEP 3 Investigators. Effect on body weight of semaglutide 2.4 mg versus placebo as adjunct to intensive behavioral therapy in adults with overweight or obesity: the STEP 3 randomized clinical trial. *JAMA* 2021;325:1403–1413
- Rubino D, Abrahamsson N, Davies M, et al.; STEP 4 Investigators. Effect of continued once-weekly semaglutide 2.4 mg on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical maintenance trial. *JAMA* 2021;325:1414–1425
- U.S. Food and Drug Administration. Wegovy (semaglutide) prescribing information. Revised June 2021. Accessed 22 June 2021. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215256s000lbl.pdf
- UK Medicines and Healthcare products Regulatory Agency. Wegovy (semaglutide 2.4 mg) summary of product characteristics (SmPC). 2021. Approval date: 24 September 2021. Accessed 7 January 2022. Available from <https://products.mhra.gov.uk/product/?product=WEGOVY%202.4%20MG%20SOLUTION%20FOR%20INJECTION%20IN%20PRE-FILLED%20PEN>
- Aroda VR, Saugstrup T, Buse JB, Donsmark M, Zacho J, Davies MJ. Incorporating and interpreting regulatory guidance on estimands in diabetes clinical trials: the PIONEER 1 randomized clinical trial as an example. *Diabetes Obes Metab* 2019;21:2203–2210
- Wharton S, Astrup A, Endahl L, et al. Estimating and reporting treatment effects in clinical trials for weight management: using estimands to interpret effects of intercurrent events and missing data. *Int J Obes (Lond)* 2021;45:923–933

21. International Council for Harmonisation. ICH Harmonised Guideline E9 (R1): Estimands and Sensitivity Analysis in Clinical Trials. Current Step 2 version. 16 June 2017. Accessed 11 May 2021. Available from https://database.ich.org/sites/default/files/E9-R1_EWG_Draft_Guideline.pdf
22. U.S. Food and Drug Administration. Harmonised Guideline E9 (R1): Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials, 2017. Accessed 11 May 2021. Available from <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM582738.pdf>
23. Röhling M, Kempf K, Banzer W, et al.; ACOORH Study Group. Prediabetes conversion to normoglycemia is superior adding a low-carbohydrate and energy deficit formula diet to lifestyle intervention - a 12-month subanalysis of the ACOORH trial. *Nutrients* 2020;12:2022
24. Sallar A, Dagogo-Jack S. Regression from prediabetes to normal glucose regulation: state of the science. *Exp Biol Med (Maywood)* 2020; 245:889–896
25. American Diabetes Association. 2. Classification and diagnosis of diabetes: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care* 2020;43(Suppl. 1):S14–S31
26. Saleh A. Diagnosis of type 2 diabetes using serial fasting plasma glucose versus HbA1c in the primary care setting. *Aust J Gen Pract* 2019;48:269–271
27. Gast KB, Tjeerdema N, Stijnen T, Smit JW, Dekkers OM. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. *PLoS One* 2012;7:e52036
28. Spence JD, Viscoli CM, Inzucchi SE, et al.; IRIS Investigators. Pioglitazone therapy in patients with stroke and prediabetes: a post hoc analysis of the IRIS randomized clinical trial. *JAMA Neurol* 2019;76:526–535
29. Wing RR, Lang W, Wadden TA, et al.; Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 2011;34:1481–1486
30. Pi-Sunyer X, Astrup A, Fujioka K, et al.; SCALE Obesity and Prediabetes NN8022-1839 Study Group. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. *N Engl J Med* 2015;373:11–22
31. World Health Organization. Global Report on Diabetes. 21 April 2016. Accessed 11 May 2021. Available from <https://www.who.int/publications/i/item/9789241565257>
32. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 2009;32:1327–1334
33. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403
34. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004;27:155–161
35. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators; Gerstein HC, Yusuf S, Bosch J, et al. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 2006;368:1096–1105
36. NAVIGATOR Study Group; McMurray JJ, Holman RR, Haffner SM, et al. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010;362:1477–1490
37. DeFronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 2011;364:1104–1115
38. Garvey WT, Ryan DH, Look M, et al. Two-year sustained weight loss and metabolic benefits with controlled-release phentermine/topiramate in obese and overweight adults (SEQUEL): a randomized, placebo-controlled, phase 3 extension study. *Am J Clin Nutr* 2012;95:297–308
39. Inzucchi SE, Docherty KF, Køber L, et al.; DAPA-HF Investigators and Committees. Dapagliflozin and the incidence of type 2 diabetes in patients with heart failure and reduced ejection fraction: an exploratory analysis from DAPA-HF. *Diabetes Care* 2021;44:586–594