Long-term weight loss effects of semaglutide in obesity without diabetes in the SELECT trial

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In the SELECT cardiovascular outcomes trial, semaglutide showed a 20% reduction in major adverse cardiovascular events in 17,604 adults with preexisting cardiovascular disease, overweight or obesity, without diabetes. Here in this prespecified analysis, we examined effects of semaglutide on weight and anthropometric outcomes, safety and tolerability by baseline body mass index (BMI). In patients treated with semaglutide, weight loss continued over 65 weeks and was sustained for up to 4 years. At 208 weeks, semaglutide was associated with mean reduction in weight (−10.2%), waist circumference (−7.7 cm) and waist-to-height ratio (−6.9%) versus placebo (−1.5%, −1.3 cm and −1.0%, respectively; $P < 0.0001$ for all comparisons versus placebo). Clinically meaningful weight loss occurred in both sexes and all races, body sizes and regions. Semaglutide was associated with fewer serious adverse events. For each BMI category (<30, 30 to <35, 35 to <40 and ≥40 kg m^{-2}) there were lower rates (events per 100 years of observation) of serious adverse events with semaglutide (43.23, 43.54, 51.07 and 47.06 for semaglutide and 50.48, 49.66, 52.73 and 60.85 for placebo). Semaglutide was associated with increased rates of trial product discontinuation. Discontinuations increased as BMI class decreased. In SELECT, at 208 weeks, semaglutide produced clinically significant weight loss and improvements in anthropometric measurements versus placebo. Weight loss was sustained over 4 years. ClinicalTrials.gov identifier: NCT03574597.

The worldwide obesity prevalence, defined by body mass index (BMI) ≥30 kg m^{-2}, has nearly tripled since 1975 (ref. 1). BMI is a good surveillance measure for population changes over time, given its strong correlation with body fat amount on a population level, but it may not accurately indicate the amount or location of body fat at the individual level[2]. In fact, the World Health Organization defines clinical obesity as 'abnormal or excessive fat accumulation that may impair health'[1]. Excess abnormal body fat, especially visceral adiposity and ectopic fat, is a driver of cardiovascular (CV) disease (CVD)[3–5], and contributes to the global chronic disease burden of diabetes, chronic kidney disease, cancer and other chronic conditions[6,7].

Remediating the adverse health effects of excess abnormal body fat through weight loss is a priority in addressing the global chronic disease burden. Improvements in CV risk factors, glycemia and quality-of-life measures including personal well-being and physical functioning generally begin with modest weight loss of 5%, whereas greater weight loss is associated with more improvement in
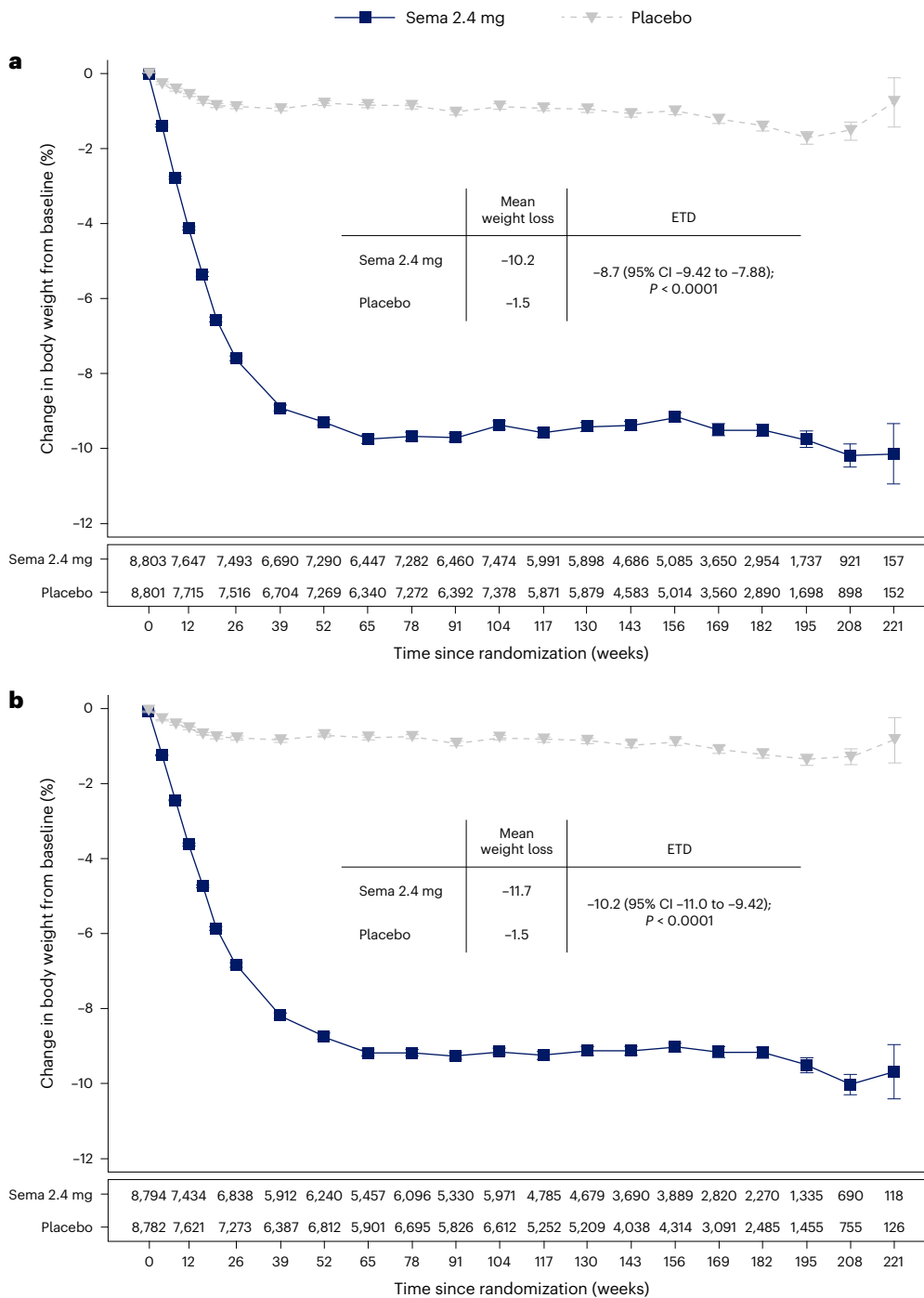
Fig. 1 | Percentage change in mean body weight from baseline through week 208 for all patients in-trial[21] and first on-treatment. a,b, Observed data from the in-trial period (**a**) and first on-treatment (**b**). The symbols are the observed means, and error bars are ±s.e.m. Numbers shown below each panel represent the number of patients contributing to the means. Analysis of covariance with treatment and baseline values was used to estimate the treatment difference. Exact *P* values are 1.323762×10^{-94} and 9.80035×10^{-100} for **a** and **b**, respectively. *P* values are two-sided and are not adjusted for multiplicity. ETD, estimated treatment difference; sema, semaglutide.

these measures[8–10]. Producing and sustaining durable and clinically significant weight loss with lifestyle intervention alone has been challenging[11]. However, weight-management medications that modify appetite can make attaining and sustaining clinically meaningful weight loss of ≥10% more likely[12]. Recently, weight-management medications, particularly those comprising glucagon-like peptide-1 receptor agonists, that help people achieve greater and more sustainable weight loss have been developed[13]. Once-weekly subcutaneous semaglutide 2.4 mg, a glucagon-like peptide-1 receptor agonist, is approved for chronic weight management[14–16] and at doses of up to 2.0 mg is approved for type 2 diabetes treatment[17–19]. In patients with type 2 diabetes and high CV risk, semaglutide at doses of 0.5 mg and 1.0 mg has been shown to significantly lower the risk of CV events[20]. The SELECT trial (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity) studied patients with established CVD and overweight or obesity but without diabetes. In SELECT, semaglutide was associated with a 20% reduction in major adverse CV events (hazard ratio 0.80, 95% confidence interval (CI) 0.72 to 0.90;
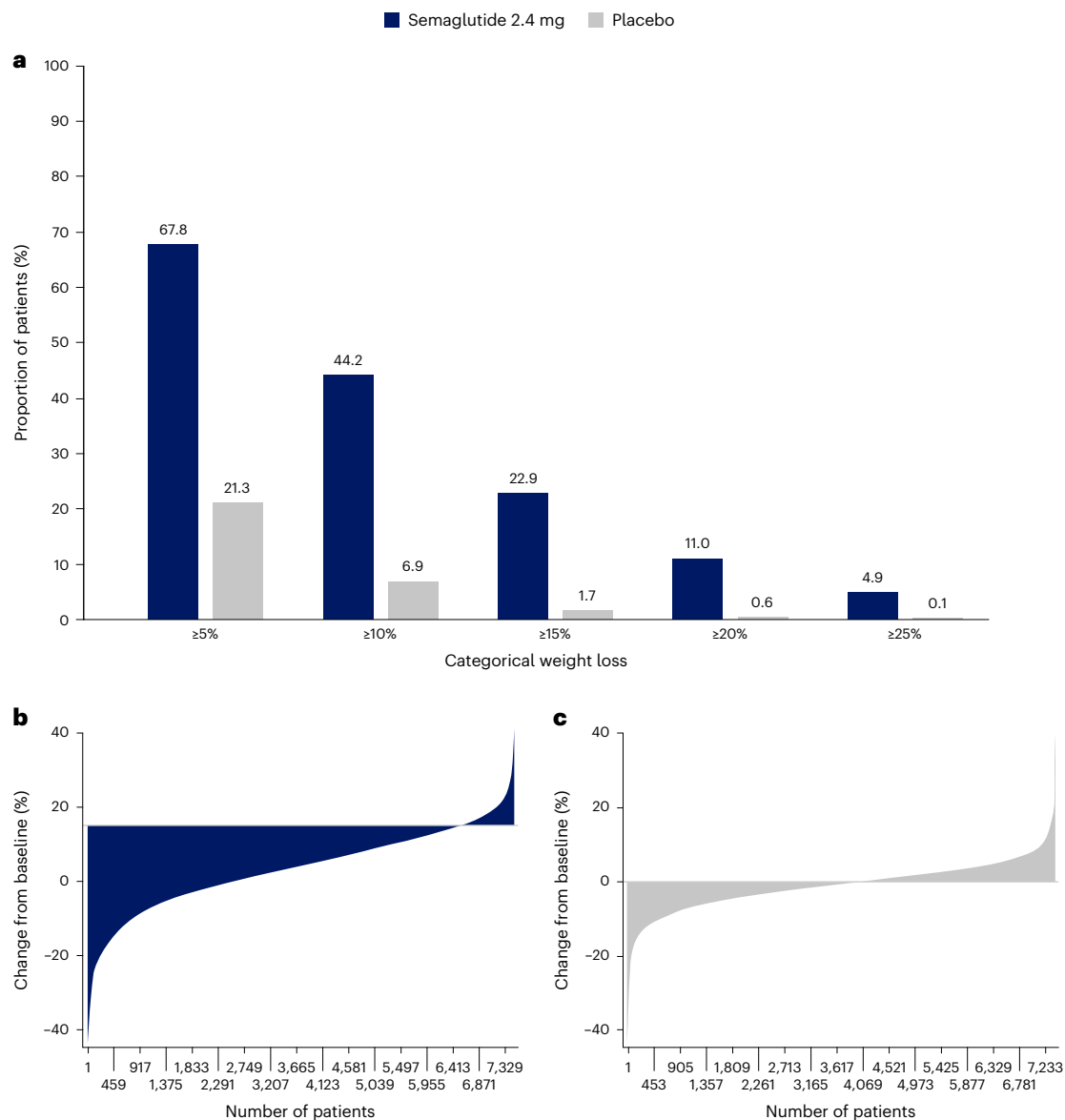
Fig. 2 | Variation in weight loss response for semaglutide and placebo.
a, Categorical weight loss from baseline at week 104 for semaglutide and placebo. Data from the in-trial period. Bars depict the proportion (%) of patients receiving semaglutide or placebo who achieved ≥5%, ≥10%, ≥15%, ≥20% and ≥25% weight loss. **b,c**, Percentage change in body weight for individual patients from baseline to week 104 for semaglutide (**b**) and placebo (**c**). Each patient's percentage change in body weight is plotted as a single bar.

$P < 0.001$)[21]. Data derived from the SELECT trial offer the opportunity to evaluate the weight loss efficacy, in a geographically and racially diverse population, of semaglutide compared with placebo over 208 weeks when both are given in addition to standard-of-care recommendations for secondary CVD prevention (but without a focus on targeting weight loss). Furthermore, the data allow examination of changes in anthropometric measures such as BMI, waist circumference (WC) and waist-to-height ratio (WHtR) as surrogates for body fat amount and location[22,23]. The diverse population can also be evaluated for changes in sex- and race-specific 'cutoff points' for BMI and WC, which have been identified as anthropometric measures that predict cardiometabolic risk[8,22,23].

This prespecified analysis of the SELECT trial investigated weight loss and changes in anthropometric indices in patients with established CVD and overweight or obesity without diabetes, who met inclusion and exclusion criteria, within a range of baseline categories for glycemia, renal function and body anthropometric measures.

Results

Study population

The SELECT study enrolled 17,604 patients (72.3% male) from 41 countries between October 2018 and March 2021, with a mean (s.d.) age of 61.6 (8.9) years and BMI of 33.3 (5.0) kg m^{-2} (ref. 21). The baseline characteristics of the population have been reported[24]. Supplementary Table 1 outlines SELECT patients according to baseline BMI categories. Of note, in the lower BMI categories (<30 kg m^{-2} (overweight) and 30 to <35 kg m^{-2} (class I obesity)), the proportion of Asian individuals was higher (14.5% and 7.4%, respectively) compared with the proportion of Asian individuals in the higher BMI categories (BMI 35 to <40 kg m^{-2} (class II obesity; 3.8%) and ≥40 kg m^{-2} (class III obesity; 2.2%), respectively). As the BMI categories increased, the proportion of women was higher: in the class III BMI category, 45.5% were female, compared with 20.8%, 25.7% and 33.0% in the overweight, class I and class II categories, respectively. Lower BMI categories were associated with a higher proportion of patients with normoglycemia and glycated hemoglobin
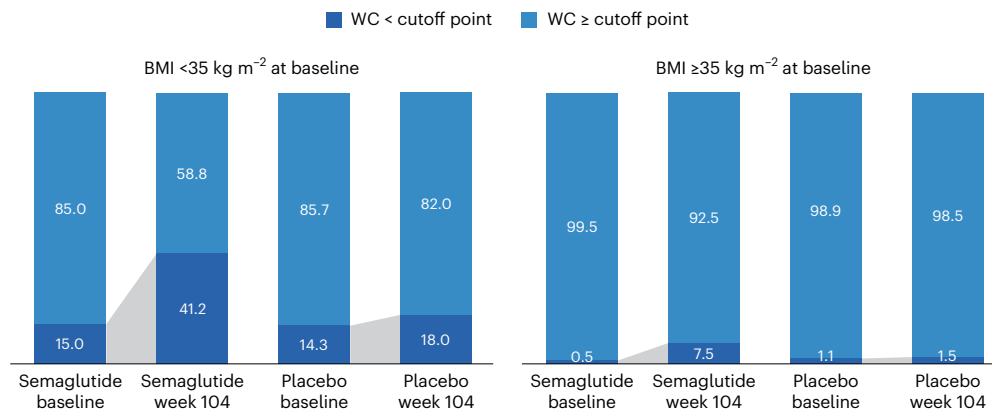
Fig. 3 | Proportion (%) of in-trial patients achieving sex- and race-specific WC cutoff points for increased metabolic risk according to baseline BMI <35 or ≥35 kg m⁻². WC cutoff points; Asian women <80 cm, non-Asian women <88 cm, Asian men <88 cm, non-Asian men <102 cm.

<5.7%. Although the proportions of patients with high cholesterol and history of smoking were similar across BMI categories, the proportion of patients with high-sensitivity C-reactive protein ≥2.0 mg dl⁻¹ increased as the BMI category increased. A high-sensitivity C-reactive protein >2.0 mg dl⁻¹ was present in 36.4% of patients in the overweight BMI category, with a progressive increase to 43.3%, 57.3% and 72.0% for patients in the class I, II and III obesity categories, respectively.

Weight and anthropometric outcomes
Percentage weight loss. The average percentage weight-loss trajectories with semaglutide and placebo over 4 years of observation are shown in Fig. 1a (ref. 21). For those in the semaglutide group, the weight-loss trajectory continued to week 65 and then was sustained for the study period through week 208 (−10.2% for the semaglutide group, −1.5% for the placebo group; treatment difference −8.7%; 95% CI −9.42 to −7.88; P < 0.0001). To estimate the treatment effect while on medication, we performed a first on-treatment analysis (observation period until the first time being off treatment for >35 days). At week 208, mean weight loss in the semaglutide group analyzed as first on-treatment was −11.7% compared with −1.5% for the placebo group (Fig. 1b; treatment difference −10.2%; 95% CI −11.0 to −9.42; P < 0.0001).

Categorical weight loss and individual body weight change. Among in-trial (intention-to-treat principle) patients at week 104, weight loss of ≥5%, ≥10%, ≥15%, ≥20% and ≥25% was achieved by 67.8%, 44.2%, 22.9%, 11.0% and 4.9%, respectively, of those treated with semaglutide compared with 21.3%, 6.9%, 1.7%, 0.6% and 0.1% of those receiving placebo (Fig. 2a). Individual weight changes at 104 weeks for the in-trial populations for semaglutide and placebo are depicted in Fig. 2b and Fig. 2c, respectively. These waterfall plots show the variation in weight-loss response that occurs with semaglutide and placebo and show that weight loss is more prominent with semaglutide than placebo.

Change in WC. WC change from baseline to 104 weeks has been reported previously in the primary outcome paper[21]. The trajectory of WC change mirrored that of the change in body weight. At week 208, average reduction in WC was −7.7 cm with semaglutide versus −1.3 cm with placebo, with a treatment difference of −6.4 cm (95% CI −7.18 to −5.61; P < 0.0001)[21].

WC cutoff points. We analyzed achievement of sex- and race-specific cutoff points for WC by BMI <35 kg m⁻² or ≥35 kg m⁻², because for BMI >35 kg m⁻², WC is more difficult technically and, thus, less accurate as a risk predictor[4,25,26]. Within the SELECT population with BMI <35 kg m⁻² at baseline, 15.0% and 14.3% of the semaglutide and placebo groups, respectively, were below the sex- and race-specific WC cutoff points. At week 104, 41.2% fell below the sex- and race-specific cutoff points

for the semaglutide group, compared with only 18.0% for the placebo group (Fig. 3).

Waist-to-height ratio. At baseline, mean WHtR was 0.66 for the study population. The lowest tertile of the SELECT population at baseline had a mean WHtR <0.62, which is higher than the cutoff point of 0.5 used to indicate increased cardiometabolic risk[27], suggesting that the trial population had high WCs. At week 208, in the group randomized to semaglutide, there was a relative reduction of 6.9% in WHtR compared with 1.0% in placebo (treatment difference −5.87% points; 95% CI −6.56 to −5.17; P < 0.0001).

BMI category change. At week 104, 52.4% of patients treated with semaglutide achieved improvement in BMI category compared with 15.7% of those receiving placebo. Proportions of patients in the BMI categories at baseline and week 104 are shown in Fig. 4, which depicts in-trial patients receiving semaglutide and placebo. The BMI category change reflects the superior weight loss with semaglutide, which resulted in fewer patients being in the higher BMI categories after 104 weeks. In the semaglutide group, 12.0% of patients achieved a BMI <25 kg m⁻², which is considered the healthy BMI category, compared with 1.2% for placebo; per study inclusion criteria, no patients were in this category at baseline. The proportion of patients with obesity (BMI ≥30 kg m⁻²) fell from 71.0% to 43.3% in the semaglutide group versus 71.9% to 67.9% in the placebo group.

Weight and anthropometric outcomes by subgroups
The forest plot illustrated in Fig. 5 displays mean body weight percentage change from baseline to week 104 for semaglutide relative to placebo in prespecified subgroups. Similar relationships are depicted for WC changes in prespecified subgroups shown in Extended Data Fig. 1. The effect of semaglutide (versus placebo) on mean percentage body weight loss as well as reduction in WC was found to be heterogeneous across several population subgroups. Women had a greater difference in mean weight loss with semaglutide versus placebo (−11.1% (95% CI −11.56 to −10.66) versus −7.5% in men (95% CI −7.78 to −7.23); P < 0.0001). There was a linear relationship between age category and degree of mean weight loss, with younger age being associated with progressively greater mean weight loss, but the actual mean difference by age group is small. Similarly, BMI category had small, although statistically significant, associations. Those with WHtR less than the median experienced slightly lower mean body weight change than those above the median, with estimated treatment differences −8.04% (95% CI −8.37 to −7.70) and −8.99% (95% CI −9.33 to −8.65), respectively (P < 0.0001). Patients from Asia and of Asian race experienced slightly lower mean weight loss (estimated treatment difference with semaglutide for Asian race −7.27% (95% CI −8.09 to −6.46; P = 0.0147) and for Asia −7.30 (95% CI −7.97 to
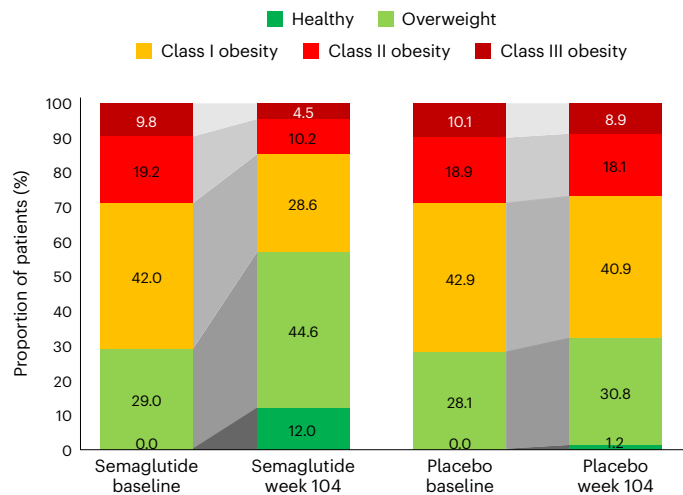
Fig. 4 | Change in BMI category (healthy, overweight, class I obesity, class II obesity and class III obesity) at baseline and week 104 for in-trial patients. In the semaglutide group, 12.0% of patients achieved normal weight status at week 104 (from 0% at baseline), compared with 1.2% (from 0% at baseline) for placebo. BMI classes: healthy (BMI <25 kg m^{-2}), overweight (25 to <30 kg m^{-2}), class I obesity (30 to <35 kg m^{-2}), class II obesity (35 to <40 kg m^{-2}) and class III obesity (BMI ≥40 kg m^{-2}).

−6.62; P = 0.0016)). There was no difference in weight loss with semaglutide associated with ethnicity (estimated treatment difference for Hispanic −8.53 (95% CI −9.28 to −7.76) or non-Hispanic −8.52 (95% CI −8.77 to 8.26); P = 0.9769), glycemic status (estimated treatment difference for prediabetes −8.53 (95% CI −8.83 to −8.24) or normoglycemia −8.48 (95% CI −8.88 to −8.07; P = 0.8188) or renal function (estimated treatment difference for estimated glomerular filtration rate (eGFR) <60 or ≥60 ml min^{-1} 1.73 m^{-2} being −8.50% (95% CI −9.23 to −7.76) and −8.52% (95% CI −8.77 to −8.26), respectively (P = 0.9519)).

Safety and tolerability according to baseline BMI category

We reported in the primary outcome of the SELECT trial that adverse events (AEs) leading to permanent discontinuation of the trial product occurred in 1,461 patients (16.6%) in the semaglutide group and 718 patients (8.2%) in the placebo group (P < 0.001)[21]. For this analysis, we evaluated the cumulative incidence of AEs leading to trial product discontinuation by treatment assignment and by BMI category (Fig. 6). For this analysis, with death modeled as a competing risk, we tracked the proportion of in-trial patients for whom drug was withdrawn or interrupted for the first time (Fig. 6, left) or cumulative discontinuations (Fig. 6, right). Both panels of Fig. 6 depict a graded increase in the proportion discontinuing semaglutide, but not placebo. For lower BMI classes, discontinuation rates are higher in the semaglutide group but not the placebo group.

We reported in the primary SELECT analysis that serious adverse events (SAEs) were reported by 2,941 patients (33.4%) in the semaglutide arm and by 3,204 patients (36.4%) in the placebo arm (P < 0.001)[21]. For this study, we analyzed SAE rates by person-years of treatment exposure for BMI classes (<30 kg m^{-2}, 30 to <35 kg m^{-2}, 35 to <40 kg m^{-2}, and ≥40 kg m^{-2}) and provide these data in Supplementary Table 2. We also provide an analysis of the most common categories of SAEs. Semaglutide was associated with lower SAEs, primarily driven by CV event and infections. Within each obesity class (<30 kg m^{-2}, 30 to <35 kg m^{-2}, 35 to <40 kg m^{-2}, and ≥40 kg m^{-2}), there were fewer SAEs in the group receiving semaglutide compared with placebo. Rates (events per 100 years of observation) of SAEs were 43.23, 43.54, 51.07 and 47.06 for semaglutide and 50.48, 49.66, 52.73 and 60.85 for placebo, with no evidence of heterogeneity. There was no detectable difference in hepatobiliary or gastrointestinal SAEs comparing semaglutide with placebo in any of the four BMI classes we evaluated.
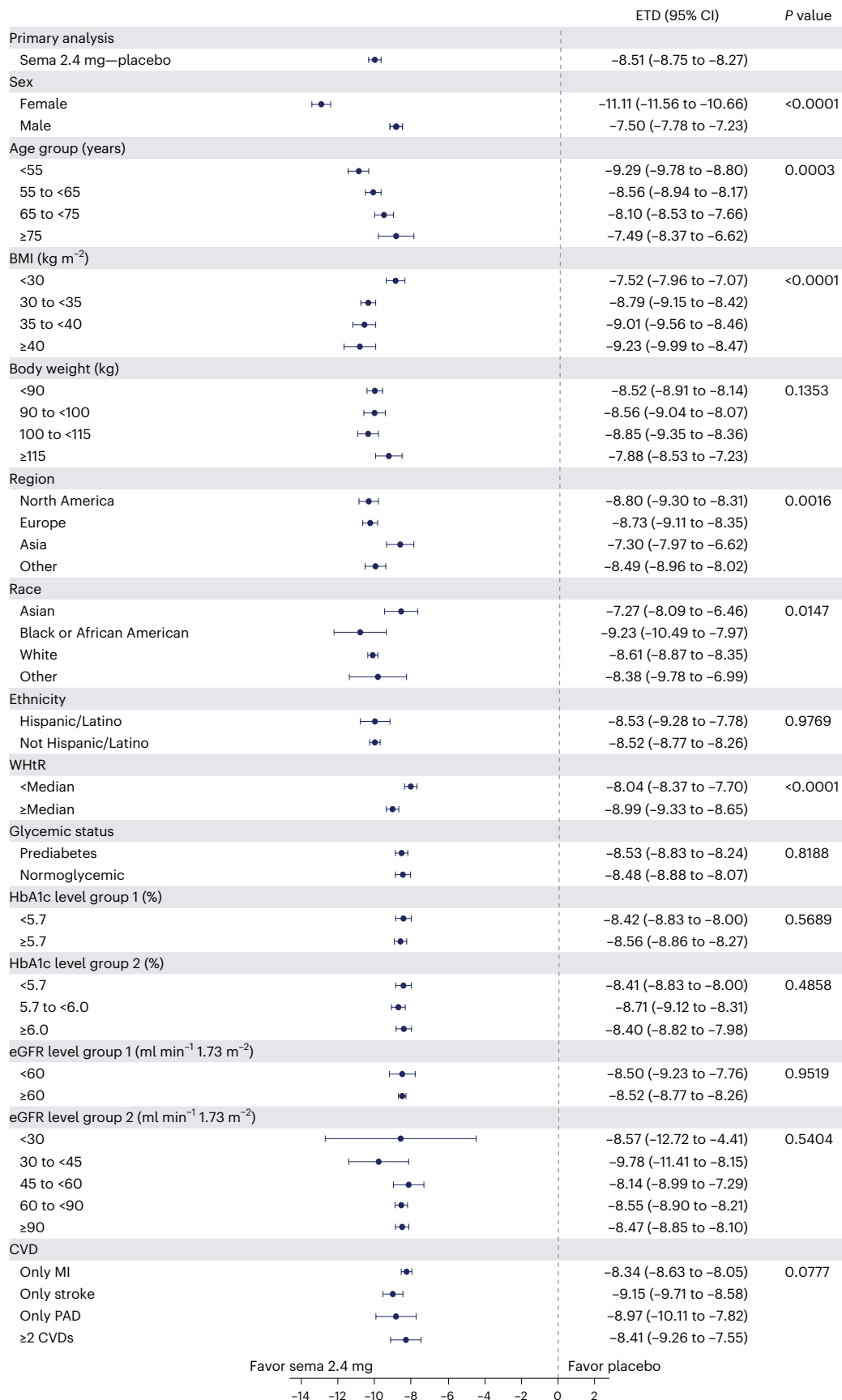
Discussion

The analyses of weight effects of the SELECT study presented here reveal that patients assigned to once-weekly subcutaneous semaglutide 2.4 mg lost significantly more weight than those receiving placebo. The weight-loss trajectory with semaglutide occurred over 65 weeks and was sustained up to 4 years. Likewise, there were similar improvements in the semaglutide group for anthropometrics (WC and WHtR). The weight loss was associated with a greater proportion of patients receiving semaglutide achieving improvement in BMI category, healthy BMI (<25 kg m^{-2}) and falling below the WC cutoff point above which increased cardiometabolic risk for the sex and race is greater[22,23]. Furthermore, both sexes, all races, all body sizes and those from all geographic regions were able to achieve clinically meaningful weight loss. There was no evidence of increased SAEs based on BMI categories, although lower BMI category was associated with increased rates of trial product discontinuation, probably reflecting exposure to a higher level of drug in lower BMI categories. These data, representing the longest clinical trial of the effects of semaglutide versus placebo on weight, establish the safety and durability of semaglutide effects on weight loss and maintenance in a geographically and racially diverse population of adult men and women with overweight and obesity but not diabetes. The implications of weight loss of this degree in such a diverse population suggests that it may be possible to impact the public health burden of the multiple morbidities associated with obesity. Although our trial focused on CV events, many chronic diseases would benefit from effective weight management[28].

There were variations in the weight-loss response. Individual changes in body weight with semaglutide and placebo were striking; still, 67.8% achieved 5% or more weight loss and 44.2% achieved 10% weight loss with semaglutide at 2 years, compared with 21.3% and 6.9%, respectively, for those receiving placebo. Our first on-treatment analysis demonstrated that those on-drug lost more weight than those in-trial, confirming the effect of drug exposure. With semaglutide, lower BMI was associated with less percentage weight loss, and women lost more weight on average than men (−11.1% versus −7.5% treatment difference from placebo); however, in all cases, clinically meaningful mean weight loss was achieved. Although Asian patients lost less weight on average than patients of other races (−7.3% more than placebo), Asian patients were more likely to be in the lowest BMI category (<30 kg m^{-2}), which is known to be associated with less weight loss, as discussed below. Clinically meaningful weight loss was evident in the semaglutide group within a broad range of baseline categories for glycemia and body anthropometrics. Interestingly, at 2 years, a significant proportion of the semaglutide-treated group fell below the sex- and race-specific WC cutoff points, especially in those with BMI <35 kg m^{-2}, and a notable proportion (12.0%) fell below the BMI cutoff point of 25 kg m^{-2}, which is deemed a healthy BMI in those without unintentional weight loss. As more robust weight loss is possible with newer medications, achieving and maintaining these cutoff point targets may become important benchmarks for tracking responses.

The overall safety profile did not reveal any new signals from prior studies, and there were no BMI category-related associations with AE reporting. The analysis did reveal that tolerability may differ among specific BMI classes, since more discontinuations occurred with semaglutide among lower BMI classes. Potential contributors may include a possibility of higher drug exposure in lower BMI classes, although other explanations, including differences in motivation and cultural mores regarding body size, cannot be excluded.

Is the weight loss in SELECT less than expected based on prior studies with the drug? In STEP 1, a large phase 3 study of once-weekly subcutaneous semaglutide 2.4 mg in individuals without diabetes but with BMI >30 kg m^{-2} or 27 kg m^{-2} with at least one obesity-related comorbidity, the mean weight loss was −14.9% at week 68, compared with −2.4% with placebo[14]. Several reasons may explain the observation that the mean treatment difference was −12.5% in STEP 1 and −8.7% in SELECT. First, SELECT was designed as a CV outcomes trial and not

		ETD (95% CI)	P value
Primary analysis			
Sema 2.4 mg—placebo		–8.51 (–8.75 to –8.27)	
Sex			
Female		–11.11 (–11.56 to –10.66)	<0.0001
Male		–7.50 (–7.78 to –7.23)	
Age group (years)			
<55		–9.29 (–9.78 to –8.80)	0.0003
55 to <65		–8.56 (–8.94 to –8.17)	
65 to <75		–8.10 (–8.53 to –7.66)	
≥75		–7.49 (–8.37 to –6.62)	
BMI (kg m^{-2})			
<30		–7.52 (–7.96 to –7.07)	<0.0001
30 to <35		–8.79 (–9.15 to –8.42)	
35 to <40		–9.01 (–9.56 to –8.46)	
≥40		–9.23 (–9.99 to –8.47)	
Body weight (kg)			
<90		–8.52 (–8.91 to –8.14)	0.1353
90 to <100		–8.56 (–9.04 to –8.07)	
100 to <115		–8.85 (–9.35 to –8.36)	
≥115		–7.88 (–8.53 to –7.23)	
Region			
North America		–8.80 (–9.30 to –8.31)	0.0016
Europe		–8.73 (–9.11 to –8.35)	
Asia		–7.30 (–7.97 to –6.62)	
Other		–8.49 (–8.96 to –8.02)	
Race			
Asian		–7.27 (–8.09 to –6.46)	0.0147
Black or African American		–9.23 (–10.49 to –7.97)	
White		–8.61 (–8.87 to –8.35)	
Other		–8.38 (–9.78 to –6.99)	
Ethnicity			
Hispanic/Latino		–8.53 (–9.28 to –7.78)	0.9769
Not Hispanic/Latino		–8.52 (–8.77 to –8.26)	
WHtR			
<Median		–8.04 (–8.37 to –7.70)	<0.0001
≥Median		–8.99 (–9.33 to –8.65)	
Glycemic status			
Prediabetes		–8.53 (–8.83 to –8.24)	0.8188
Normoglycemic		–8.48 (–8.88 to –8.07)	
HbA1c level group 1 (%)			
<5.7		–8.42 (–8.83 to –8.00)	0.5689
≥5.7		–8.56 (–8.86 to –8.27)	
HbA1c level group 2 (%)			
<5.7		–8.41 (–8.83 to –8.00)	0.4858
5.7 to <6.0		–8.71 (–9.12 to –8.31)	
≥6.0		–8.40 (–8.82 to –7.98)	
eGFR level group 1 (ml min^{-1} 1.73 m^{-2})			
<60		–8.50 (–9.23 to –7.76)	0.9519
≥60		–8.52 (–8.77 to –8.26)	
eGFR level group 2 (ml min^{-1} 1.73 m^{-2})			
<30		–8.57 (–12.72 to –4.41)	0.5404
30 to <45		–9.78 (–11.41 to –8.15)	
45 to <60		–8.14 (–8.99 to –7.29)	
60 to <90		–8.55 (–8.90 to –8.21)	
≥90		–8.47 (–8.85 to –8.10)	
CVD			
Only MI		–8.34 (–8.63 to –8.05)	0.0777
Only stroke		–9.15 (–9.71 to –8.58)	
Only PAD		–8.97 (–10.11 to –7.82)	
≥2 CVDs		–8.41 (–9.26 to –7.55)	

Favor sema 2.4 mg   Favor placebo

–14   –12   –10   –8   –6   –4   –2   0   2

Fig. 5 | Effect of semaglutide treatment or placebo on mean percentage change in body weight from baseline to week 104 by subgroups. Data from the in-trial period. *N* = 17,604. *P* values represent test of no interaction effect. *P* values are two-sided and are not adjusted for multiplicity. The dots show estimated treatment differences, and the error bars show 95% CIs. Details of the statistical models are available in Methods. ETD, estimated treatment difference; HbA1c, glycated hemoglobin; MI, myocardial infarction; PAD, peripheral artery disease; sema, semaglutide.
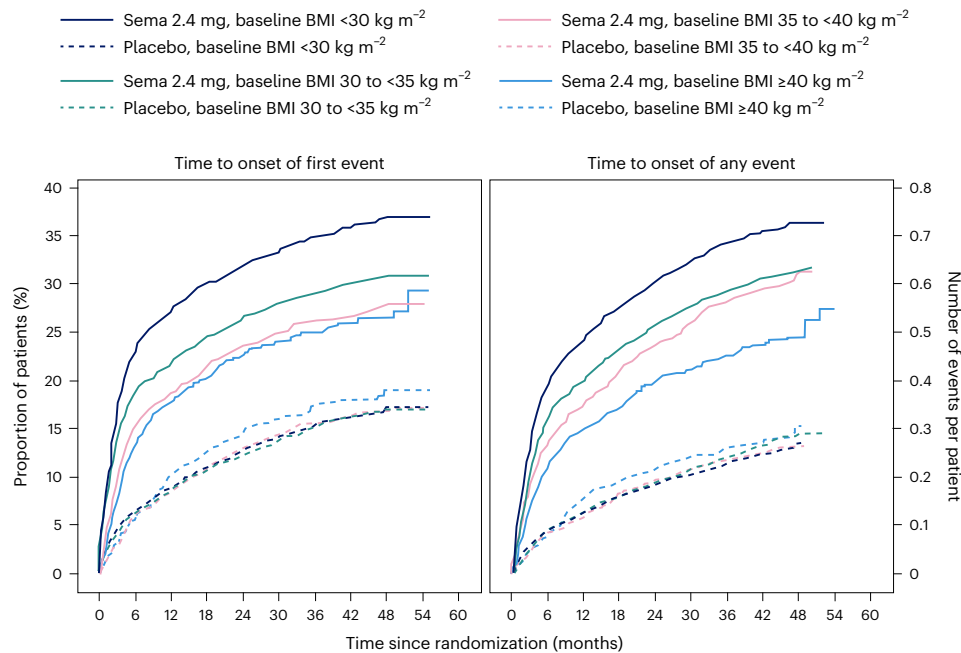
Fig. 6 | AEs leading to trial product discontinuation for baseline BMI class (<30 kg m^{-2}, 30 to <35 kg m^{-2}, 35 to <40 kg m^{-2}, and ≥40 kg m^{-2}); cumulative incidence for first event over time (left) and cumulative mean number of events over time (right). Data are in-trial from the full analysis set. sema, semaglutide.

a weight-loss trial, and weight loss was only a supportive secondary endpoint in the trial design. Patients in STEP 1 were desirous of weight loss as a reason for study participation and received structured lifestyle intervention (which included a −500 kcal per day diet with 150 min per week of physical activity). In the SELECT trial, patients did not enroll for the specific purpose of weight loss and received standard of care covering management of CV risk factors, including medical treatment and healthy lifestyle counseling, but without a specific focus on weight loss. Second, the respective study populations were quite different, with STEP 1 including a younger, healthier population with more women (73.1% of the semaglutide arm in STEP 1 versus 27.7% in SELECT) and higher mean BMI (37.8 kg m^{-2} versus 33.3 kg m^{-2}, respectively)[14,21]. Third, major differences existed between the respective trial protocols. Patients in the semaglutide treatment arm of STEP 1 were more likely to be exposed to the medication at the full dose of 2.4 mg than those in SELECT. In SELECT, investigators were allowed to slow, decrease or pause treatment. By 104 weeks, approximately 77% of SELECT patients on dose were receiving the target semaglutide 2.4 mg weekly dose, which is lower than the corresponding proportion of patients in STEP 1 (89.6% were receiving the target dose at week 68)[14,21]. Indeed, in our first on-treatment analysis at week 208, weight loss was greater (−11.7% for semaglutide) compared with the in-trial analysis (−10.2% for semaglutide). Taken together, all these issues make less weight loss an expected finding in SELECT, compared with STEP 1.

The SELECT study has some limitations. First, SELECT was not a primary prevention trial, and the data should not be extrapolated to all individuals with overweight and obesity to prevent major adverse CV events. Although the data set is rich in numbers and diversity, it does not have the numbers of individuals in racial subgroups that may have revealed potential differential effects. SELECT also did not include individuals who have excess abnormal body fat but a BMI <27 kg m^{-2}. Not all individuals with increased CV risk have BMI ≥27 kg m^{-2}. Thus, the study did not include Asian patients who qualify for treatment with obesity medications at lower BMI and WC cutoff points according to guidelines in their countries[29]. We observed that Asian patients were less likely to be in the higher BMI categories of SELECT and that the population of those with BMI <30 kg m^{-2} had a higher percentage of Asian race. Asian individuals would probably benefit from weight

loss and medication approaches undertaken at lower BMI levels in the secondary prevention of CVD. Future studies should evaluate CV risk reduction in Asian individuals with high CV risk and BMI <27 kg m^{-2}. Another limitation is the lack of information on body composition, beyond the anthropometric measures we used. It would be meaningful to have quantitation of fat mass, lean mass and muscle mass, especially given the wide range of body size in the SELECT population.

An interesting observation from this SELECT weight loss data is that when BMI is ≤30 kg m^{-2}, weight loss on a percentage basis is less than that observed across higher classes of BMI severity. Furthermore, as BMI exceeds 30 kg m^{-2}, weight loss amounts are more similar for class I, II and III obesity. This was also observed in Look AHEAD, a lifestyle intervention study for weight loss[30]. The proportion (percentage) of weight loss seems to be less, on average, in the BMI <30 kg m^{-2} category relative to higher BMI categories, despite their receiving of the same treatment and even potentially higher exposure to the drug for weight loss[30]. Weight loss cannot continue indefinitely. There is a plateau of weight that occurs after weight loss with all treatments for weight management. This plateau has been termed the 'set point' or 'settling point', a body weight that is in harmony with the genetic and environmental determinants of body weight and adiposity[31]. Perhaps persons with BMI <30 kg m^{-2} are closer to their settling point and have less weight to lose to reach it. Furthermore, the cardiometabolic benefits of weight loss are driven by reduction in the abnormal ectopic and visceral depots of fat, not by reduction of subcutaneous fat stores in the hips and thighs. The phenotype of cardiometabolic disease but lower BMI (<30 kg m^{-2}) may be one where reduction of excess abnormal and dysfunctional body fat does not require as much body mass reduction to achieve health improvement. We suspect this may be the case and suggest further studies to explore this aspect of weight-loss physiology.

In conclusion, this analysis of the SELECT study supports the broad use of once-weekly subcutaneous semaglutide 2.4 mg as an aid to CV event reduction in individuals with overweight or obesity without diabetes but with preexisting CVD. Semaglutide 2.4 mg safely and effectively produced clinically significant weight loss in all subgroups based on age, sex, race, glycemia, renal function and anthropometric categories. Furthermore, the weight loss was sustained over 4 years during the trial.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-02996-7.

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Methods

Trial design and participants

The current work complies with all relevant ethical regulations and reports a prespecified analysis of the randomized, double-blind, placebo-controlled SELECT trial (NCT03574597), details of which have been reported in papers describing study design and rationale[32], baseline characteristics[24] and the primary outcome[21]. SELECT evaluated once-weekly subcutaneous semaglutide 2.4 mg versus placebo to reduce the risk of major adverse cardiac events (a composite endpoint comprising CV death, nonfatal myocardial infarction or nonfatal stroke) in individuals with established CVD and overweight or obesity, without diabetes. The protocol for SELECT was approved by national and institutional regulatory and ethical authorities in each participating country. All patients provided written informed consent before beginning any trial-specific activity. Eligible patients were aged ≥45 years, with a BMI of ≥27 kg m^{-2} and established CVD defined as at least one of the following: prior myocardial infarction, prior ischemic or hemorrhagic stroke, or symptomatic peripheral artery disease. Additional inclusion and exclusion criteria can be found elsewhere[32].

Human participants research

The trial protocol was designed by the trial sponsor, Novo Nordisk, and the academic Steering Committee. A global expert panel of physician leaders in participating countries advised on regional operational issues. National and institutional regulatory and ethical authorities approved the protocol, and all patients provided written informed consent.

Study intervention and patient management

Patients were randomly assigned in a double-blind manner and 1:1 ratio to receive once-weekly subcutaneous semaglutide 2.4 mg or placebo. The starting dose was 0.24 mg once weekly, with dose increases every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg per week) until the target dose of 2.4 mg was reached after 16 weeks. Patients who were unable to tolerate dose escalation due to AEs could be managed by extension of dose-escalation intervals, treatment pauses or maintenance at doses below the 2.4 mg per week target dose. Investigators were allowed to reduce the dose of study product if tolerability issues arose. Investigators were provided with guidelines for, and encouraged to follow, evidence-based recommendations for medical treatment and lifestyle counseling to optimize management of underlying CVD as part of the standard of care. The lifestyle counseling was not targeted at weight loss. Additional intervention descriptions are available[32].

Sex, race, body weight, height and WC measurements

Sex and race were self-reported. Body weight was measured without shoes and only wearing light clothing; it was measured on a digital scale and recorded in kilograms or pounds (one decimal with a precision of 0.1 kg or lb), with preference for using the same scale throughout the trial. The scale was calibrated yearly as a minimum unless the manufacturer certified that calibration of the weight scales was valid for the lifetime of the scale. Height was measured without shoes in centimeters or inches (one decimal with a precision of 0.1 cm or inches). At screening, BMI was calculated by the electronic case report form. WC was defined as the abdominal circumference located midway between the lower rib margin and the iliac crest. Measures were obtained in a standing position with a nonstretchable measuring tape and to the nearest centimeter or inch. The patient was asked to breathe normally. The tape touched the skin but did not compress soft tissue, and twists in the tape were avoided.

Endpoints

The following endpoints relevant to this paper were assessed at randomization (week 0) to years 2, 3 and 4: change in body weight (%); proportion achieving weight loss ≥5%, ≥10%, ≥15% and ≥20%; change in WC (cm); and percentage change in WHtR (cm cm^{-1}). Improvement

in BMI category (defined as being in a lower BMI class) was assessed at week 104 compared with baseline according to BMI classes: healthy (BMI <25 kg m^{-2}), overweight (25 to <30 kg m^{-2}), class I obesity (30 to <35 kg m^{-2}), class II obesity (35 to <40 kg m^{-2}) and class III obesity (≥40 kg m^{-2}). The proportions of individuals with BMI <35 or ≥35 kg m^{-2} who achieved sex- and race-specific cutoff points for WC (indicating increased metabolic risk) were evaluated at week 104. The WC cutoff points were as follows: Asian women <80 cm, non-Asian women <88 cm, Asian men <88 cm and non-Asian men <102 cm.

Overall, 97.1% of the semaglutide group and 96.8% of the placebo group completed the trial. During the study, 30.6% of those assigned to semaglutide did not complete drug treatment, compared with 27.0% for placebo.

Statistical analysis

The statistical analyses for the in-trial period were based on the intention-to-treat principle and included all randomized patients irrespective of adherence to semaglutide or placebo or changes to background medications. Continuous endpoints were analyzed using an analysis of covariance model with treatment as a fixed factor and baseline value of the endpoint as a covariate. Missing data at the landmark visit, for example, week 104, were imputed using a multiple imputation model and done separately for each treatment arm and included baseline value as a covariate and fit to patients having an observed data point (irrespective of adherence to randomized treatment) at week 104. The fit model is used to impute values for all patients with missing data at week 104 to create 500 complete data sets. Rubin's rules were used to combine the results. Estimated means are provided with s.e.m., and estimated treatment differences are provided with 95% CI. Binary endpoints were analyzed using logistic regression with treatment and baseline value as a covariate, where missing data were imputed by first using multiple imputation as described above and then categorizing the imputed data according to the endpoint, for example, body weight percentage change at week 104 of <0%. Subgroup analyses for continuous and binary endpoints also included the subgroup and interaction between treatment and subgroup as fixed factors. Because some patients in both arms continued to be followed but were off treatment, we also analyzed weight loss by first on-treatment group (observation period until first time being off treatment for >35 days) to assess a more realistic picture of weight loss in those adhering to treatment. CIs were not adjusted for multiplicity and should therefore not be used to infer definitive treatment effects. All statistical analyses were performed with SAS software, version 9.4 TS1M5 (SAS Institute).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

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

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Author contributions

D.H.R., I.L. and S.E.K. contributed to the study design. D.B.H., I.L., D.D., A.K., S.M.M., A.P.v.B., C.C. and J.P.H.W. were study investigators. D.B.H., I.L., D.D., A.K., S.M.M., A.P.v.B., C.C. and J.P.H.W. enrolled patients. D.H.R. was responsible for data analysis and manuscript preparation. All authors contributed to data interpretation, review, revisions and final approval of the manuscript.

Competing interests

D.H.R. declares having received consulting honoraria from Altimmune, Amgen, Biohaven, Boehringer Ingelheim, Calibrate, Carmot Therapeutics, CinRx, Eli Lilly, Epitomee, Gila Therapeutics, IFA Celtics, Novo Nordisk, Pfizer, Rhythm, Scientific Intake, Wondr Health and Zealand Pharma; she declares she received stock options from Calibrate, Epitomee, Scientific Intake and Xeno Bioscience. I.L. declares having received research funding (paid to institution) from Novo Nordisk, Sanofi, Mylan and Boehringer Ingelheim. I.L. received advisory/consulting fees and/or other support from Altimmune, AstraZeneca, Bayer, Biomea, Boehringer Ingelheim, Carmot Therapeutics, Cytoki Pharma, Eli Lilly, Intercept, Janssen/Johnson & Johnson, Mannkind, Mediflix, Merck, Metsera, Novo Nordisk, Pharmaventures, Pfizer, Regeneron, Sanofi, Shionogi, Structure Therapeutics, Target RWE, Terns Pharmaceuticals, The Comm Group, Valeritas, WebMD and Zealand Pharma. J.D. declares having received consulting honoraria from Amgen, Boehringer Ingelheim, Merck, Pfizer, Aegerion, Novartis, Sanofi, Takeda, Novo Nordisk and Bayer, and research grants from British Heart Foundation, MRC (UK), NIHR, PHE, MSD, Pfizer, Aegerion, Colgate and Roche. S.E.K. declares having received consulting honoraria from ANI Pharmaceuticals, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk and Oramed, and stock options from AltPep. B.B. declares having received honoraria related to participation on this trial and has no financial conflicts related to this publication. H.M.C. declares being a stockholder and serving on an advisory panel for Bayer; receiving research grants from Chief Scientist Office, Diabetes UK, European Commission, IQVIA, Juvenile Diabetes Research Foundation and Medical Research Council; serving on an advisory board and speaker's bureau for Novo Nordisk; and holding stock in Roche Pharmaceuticals. C.C. declares having received consulting honoraria from Novo Nordisk, Eli Lilly, Merck, Brace Pharma and Eurofarma. D.D. declares having received consulting honoraria from Novo Nordisk, Eli Lilly, Boehringer Ingelheim and AstraZeneca, and received research grants through his affiliation from Novo Nordisk, Eli Lilly, Boehringer Ingelheim and Rhythm. D.B.H. declares having received research grants through her academic affiliation from Novo Nordisk and Eli Lilly, and advisory/consulting honoraria from Novo Nordisk, Eli Lilly and Gelesis. A.K. declares having received research grants through his affiliation from Novo Nordisk and Pharmaserve Lilly, and consulting honoraria from Pharmaserve Lilly, Sanofi-Aventis, Novo Nordisk, MSD, AstraZeneca, ELPEN Pharma, Boehringer Ingelheim, Galenica Pharma, Epsilon Health and WinMedica. A.M.L. declares having received honoraria from Novo Nordisk, Eli Lilly, Akebia Therapeutics, Ardelyx, Becton Dickinson, Endologix, FibroGen, GSK, Medtronic, Neovasc, Provention Bio, ReCor, BrainStorm Cell Therapeutics, Alnylam and Intarcia for consulting activities, and research funding to his institution from AbbVie, Esperion, AstraZeneca, CSL Behring, Novartis and Eli Lilly. S.M.M. declares having received consulting honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daichii-Sankyo, esanum, Gilead, Ipsen, Eli Lilly, Novartis, Novo Nordisk, Sandoz and Sanofi; he declares he received research grants from AstraZeneca, Eli Lilly and Novo Nordisk. J.P. declares having received consulting honoraria from Altimmune, Amgen, Esperion, Merck, MJH Life Sciences, Novartis and Novo Nordisk; he has received a grant, paid to his institution, from Boehringer Ingelheim and holds the position of Director, Preventive Cardiology, at Brigham and Women's Hospital. A.P.v.B. is contracted via the University of Groningen (no personal payment) to undertake consultancy for Novo Nordisk, Eli Lilly and Boehringer Ingelheim. J.P.H.W. is contracted via the University of Liverpool (no personal payment) to undertake consultancy for Altimmune, AstraZeneca, Boehringer Ingelheim, Cytoki, Eli Lilly, Napp, Novo Nordisk, Menarini, Pfizer, Rhythm Pharmaceuticals, Sanofi, Saniona, Tern Pharmaceuticals, Shionogi and Ysopia. J.P.H.W. also declares personal honoraria/lecture fees from AstraZeneca, Boehringer Ingelheim, Medscape, Napp, Menarini, Novo Nordisk and Rhythm. R.F.K. declares having received consulting honoraria from Novo Nordisk, Weight Watchers, Eli Lilly, Boehringer Ingelheim, Pfizer, Structure and Altimmune. E.B., G.K.H., O.K.J. and T.K.O. are employees of Novo Nordisk A/S.
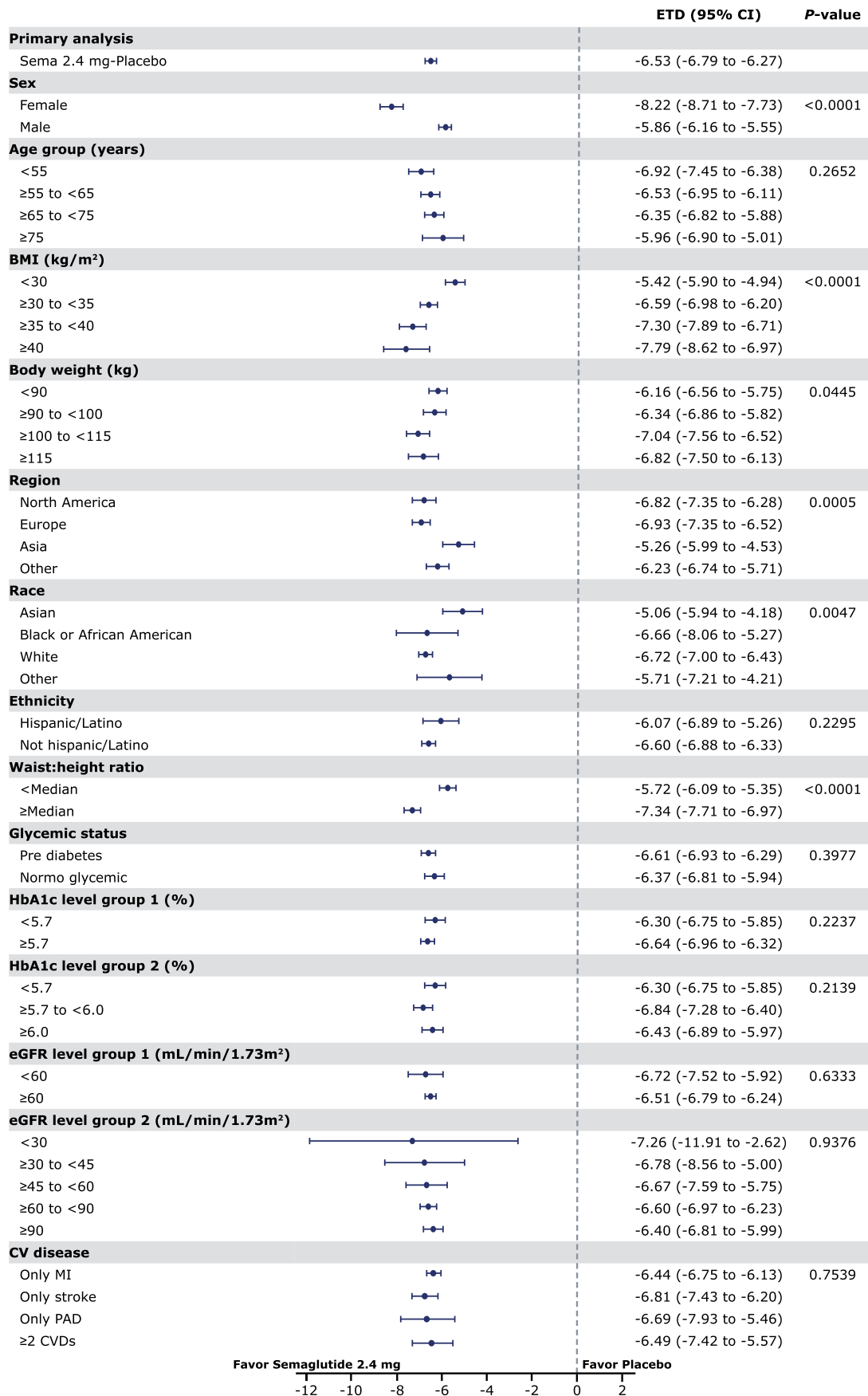
Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-024-02996-7.

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	ETD (95% CI)	*P*-value
Primary analysis		
Sema 2.4 mg-Placebo	-6.53 (-6.79 to -6.27)	
Sex		
Female	-8.22 (-8.71 to -7.73)	<0.0001
Male	-5.86 (-6.16 to -5.55)	
Age group (years)		
<55	-6.92 (-7.45 to -6.38)	0.2652
≥55 to <65	-6.53 (-6.95 to -6.11)	
≥65 to <75	-6.35 (-6.82 to -5.88)	
≥75	-5.96 (-6.90 to -5.01)	
BMI (kg/m²)		
<30	-5.42 (-5.90 to -4.94)	<0.0001
≥30 to <35	-6.59 (-6.98 to -6.20)	
≥35 to <40	-7.30 (-7.89 to -6.71)	
≥40	-7.79 (-8.62 to -6.97)	
Body weight (kg)		
<90	-6.16 (-6.56 to -5.75)	0.0445
≥90 to <100	-6.34 (-6.86 to -5.82)	
≥100 to <115	-7.04 (-7.56 to -6.52)	
≥115	-6.82 (-7.50 to -6.13)	
Region		
North America	-6.82 (-7.35 to -6.28)	0.0005
Europe	-6.93 (-7.35 to -6.52)	
Asia	-5.26 (-5.99 to -4.53)	
Other	-6.23 (-6.74 to -5.71)	
Race		
Asian	-5.06 (-5.94 to -4.18)	0.0047
Black or African American	-6.66 (-8.06 to -5.27)	
White	-6.72 (-7.00 to -6.43)	
Other	-5.71 (-7.21 to -4.21)	
Ethnicity		
Hispanic/Latino	-6.07 (-6.89 to -5.26)	0.2295
Not hispanic/Latino	-6.60 (-6.88 to -6.33)	
Waist:height ratio		
<Median	-5.72 (-6.09 to -5.35)	<0.0001
≥Median	-7.34 (-7.71 to -6.97)	
Glycemic status		
Pre diabetes	-6.61 (-6.93 to -6.29)	0.3977
Normo glycemic	-6.37 (-6.81 to -5.94)	
HbA1c level group 1 (%)		
<5.7	-6.30 (-6.75 to -5.85)	0.2237
≥5.7	-6.64 (-6.96 to -6.32)	
HbA1c level group 2 (%)		
<5.7	-6.30 (-6.75 to -5.85)	0.2139
≥5.7 to <6.0	-6.84 (-7.28 to -6.40)	
≥6.0	-6.43 (-6.89 to -5.97)	
eGFR level group 1 (mL/min/1.73m²)		
<60	-6.72 (-7.52 to -5.92)	0.6333
≥60	-6.51 (-6.79 to -6.24)	
eGFR level group 2 (mL/min/1.73m²)		
<30	-7.26 (-11.91 to -2.62)	0.9376
≥30 to <45	-6.78 (-8.56 to -5.00)	
≥45 to <60	-6.67 (-7.59 to -5.75)	
≥60 to <90	-6.60 (-6.97 to -6.23)	
≥90	-6.40 (-6.81 to -5.99)	
CV disease		
Only MI	-6.44 (-6.75 to -6.13)	0.7539
Only stroke	-6.81 (-7.43 to -6.20)	
Only PAD	-6.69 (-7.93 to -5.46)	
≥2 CVDs	-6.49 (-7.42 to -5.57)	

Favor Semaglutide 2.4 mg   Favor Placebo

-12 -10 -8 -6 -4 -2 0 2

Extended Data Fig. 1 | See next page for caption.

Extended Data Fig. 1 | Effect of semaglutide treatment or placebo on waist circumference from baseline to week 104 by subgroups. Data from the in-trial period. N = 17,604. P values represent test of no interaction effect. P values are two-sided and not adjusted for multiplicity. The dots show estimated treatment differences and the error bars show 95% confidence intervals. Details of the statistical models are available in Methods. BMI, body mass index; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; HbA1c, glycated hemoglobin; MI, myocardial infarction; PAD, peripheral artery disease; sema, semaglutide.

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☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	
Data analysis	All statistical analyses were performed with SAS software, version 9.4 TS1M5 (SAS Institute)

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:
- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

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

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Biologic sex was reported for trial participants; information on gender was not collected.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were reported for trial participants.
Population characteristics	Reported in Supplementary Table 1
Recruitment	Detailed in Methods section
Ethics oversight	National and institutional regulatory and ethical authorities approved the protocol, and all patients provided written and informed consent.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

[x] Life sciences   ☐ Behavioural & social sciences   ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	17,604. Sample size determination was provided in the primary publication (Lincoff AM et al. NEJM 389; 2221-2232 (2023).
Data exclusions	No data were excluded
Replication	This is an international, randomized, double-blind trial; thus replication is not possible
Randomization	Participants were randomized in a 1:1 ratio
Blinding	Participants and investigators were blinded to treatment allocation

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	
Research sample	
Sampling strategy	
Data collection	
Timing	
Data exclusions	
Non-participation	
Randomization	

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	
Research sample	
Sampling strategy	
Data collection	
Timing and spatial scale	
Data exclusions	
Reproducibility	
Randomization	
Blinding	

Did the study involve field work? ☐ Yes ☐ No

Field work, collection and transport

Field conditions	
Location	
Access & import/export	
Disturbance	

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
X	☐ Antibodies
X	☐ Eukaryotic cell lines
X	☐ Palaeontology and archaeology
X	☐ Animals and other organisms
☐	X Clinical data
X	☐ Dual use research of concern
X	☐ Plants

Methods

n/a	Involved in the study
X	☐ ChIP-seq
X	☐ Flow cytometry
X	☐ MRI-based neuroimaging

Antibodies

Antibodies used	
Validation	

Eukaryotic cell lines

Cell line source(s)	
Authentication	
Mycoplasma contamination	
Commonly misidentified lines (See ICLAC register)	

Palaeontology and Archaeology

Specimen provenance	
Specimen deposition	
Dating methods	

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight	

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Laboratory animals	
Wild animals	
Reporting on sex	
Field-collected samples	
Ethics oversight	

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Clinical trial registration	NCT03574597
Study protocol	Provided in the primary publication (Lincoff AM et al. NEJM 389; 2221-2232 (2023)
Data collection	The SELECT study enrolled participants from 41 countries between October 2018 through March 2021.All potentially eligible patients were eligible to take part, thereby minimizing any potential self-selection bias
Outcomes	All of the primary and secondary outcomes, and the statistical methodologies used to analyze them, were prespecified in the Statistical Analysis Plan. All statistical analyses performed for all outcome measures were thus predefined.

Dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
x	☐	Public health
x	☐	National security
x	☐	Crops and/or livestock
x	☐	Ecosystems
x	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
x	☐	Demonstrate how to render a vaccine ineffective
x	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
x	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
x	☐	Increase transmissibility of a pathogen
x	☐	Alter the host range of a pathogen
x	☐	Enable evasion of diagnostic/detection modalities
x	☐	Enable the weaponization of a biological agent or toxin
x	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks	
Novel plant genotypes	
Authentication	

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

| Data access links
May remain private before publication.	
Files in database submission	
Genome browser session
(e.g. UCSC)	

Methodology

Replicates	
Sequencing depth	
Antibodies	
Peak calling parameters	
Data quality	
Software	

Flow Cytometry

Plots

Confirm that:

☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☐ All plots are contour plots with outliers or pseudocolor plots.

☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	
Instrument	
Software	
Cell population abundance	
Gating strategy	

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	
Design specifications	
Behavioral performance measures	

Imaging type(s)	
Field strength	
Sequence & imaging parameters	
Area of acquisition	

Diffusion MRI   ☐ Used   ☐ Not used

Preprocessing

Preprocessing software	
Normalization	
Normalization template	
Noise and artifact removal	
Volume censoring	

Statistical modeling & inference

Model type and settings	
Effect(s) tested	

Specify type of analysis: ☐ Whole brain   ☐ ROI-based   ☐ Both

Statistic type for inference

(See Eklund et al. 2016)

Correction

Models & analysis

n/a	Involved in the study
X	☐ Functional and/or effective connectivity
X	☐ Graph analysis
☐	X Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Graph analysis

Multivariate modeling and predictive analysis