Online-only Supplementary Materials

Effect of semaglutide on insulin sensitivity and cardiometabolic risk factors in adolescents with obesity: The STEP TEENS study

Running title: STEP TEENS Cardiometabolic Risk Factors

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Characteristic	BMI reduction category		
	<5% (*n* = 29)	**≥5–<20% (*n* = 44)**	**≥20% (*n* = 53)**
Female	13 (44.8)	31 (70.5)	34 (64.2)
Age, years	15.9 (1.3)	15.5 (1.4)	15.2 (1.6)
Tanner stage,* *n* (%)			
2–3	2 (6.8)	5 (11.4)	6 (11.3)
4–5	27 (93.1)	39 (88.6)	47 (88.7)
Body weight, kg	115.8 (28.7)	114.9 (24.7)	103.8 (23.8)
BMI, kg/m^2	39.0 (8.0)	34.5 (6.3)	35.7 (5.7)
Waist circumference, cm	114.9 (19.5)	114.5 (15.9)	107.5 (16.1)
FPG, mmol/L	5.0 (0.5)	5.0 (0.5)	4.9 (0.4)
HOMA-IR, score, geometric mean (CV)	5.4 (61.0)	4.8 (63.7)	4.2 (47.0)
FSI, pmol/L, geometric mean (CV)	171.7 (53.6)	157.3 (60.6)	139.5 (44.1)
HbA_{1c} (SD), %	5.4 (0.2)	5.5 (0.3)	5.4 (0.3)
Glycemic category,† *n* (%)			
Normoglycemia	22 (75.9)	38 (86.4)	48 (90.6)
Prediabetes	7 (24.1)	6 (13.6)	5 (9.4)
Type 2 diabetes	0	0	0
SBP (SD), mmHg	118 (9)	122 (12)	120 (11)
Lipids, mmol/L, geometric mean (CV)			
Total cholesterol	4.2 (20.3)	4.2 (19.3)	4.1 (18.4)
HDL cholesterol	1.1 (28.3)	1.1 (23.8)	1.2 (20.0)
LDL cholesterol	2.4 (28.1)	2.4 (30.5)	2.3 (29.0)
VLDL cholesterol	0.6 (55.3)	0.5 (44.3)	0.6 (47.8)
Triglycerides	1.4 (55.0)	1.2 (44.0)	1.3 (47.6)
ALT (SD), %	27 (73.6)	22 (61.4)	23 (69.9)

Supplementary Table 1. Baseline demographics and clinical characteristics stratified by BMI reduction categories in the semaglutide 2.4 mg group (excluding participants with T2D)

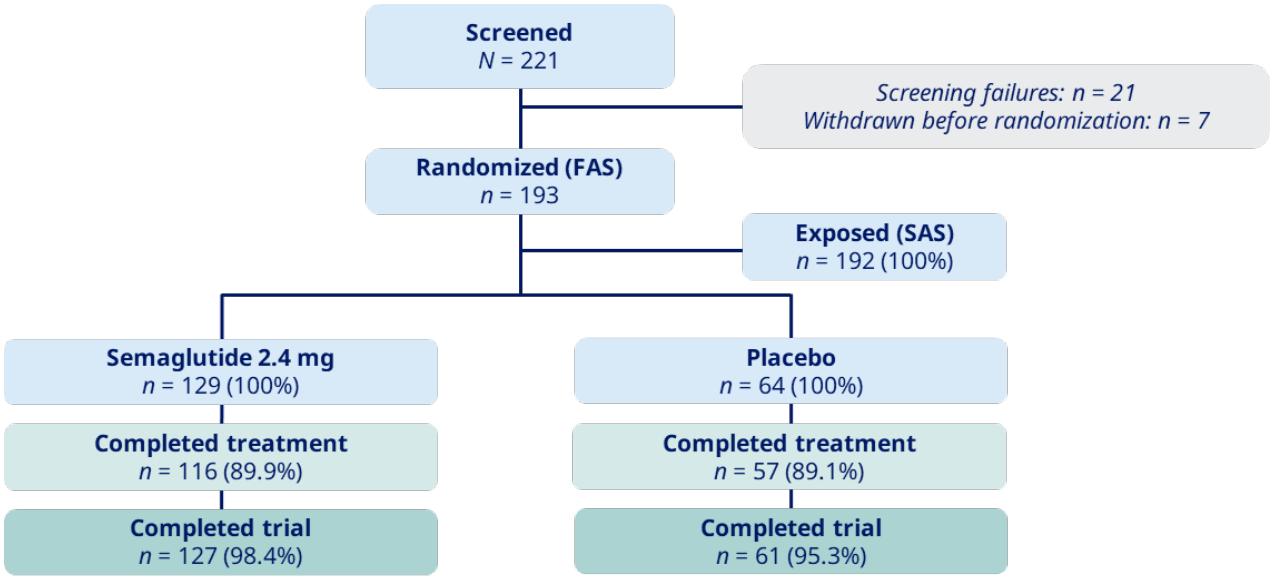
All data are mean (SD) unless otherwise stated. *Tanner stages 2 and 3 indicate early puberty, stage 4 indicates late puberty, and stage 5 indicates adult-level maturity (1). †Glycemic category was determined from HbA_{1c} assessments, per American Diabetes Association HbA_{1c} criteria. Normoglycemia was defined as HbA_{1c} <5.7% (39 mmol/mol); prediabetes was defined as HbA_{1c} 5.7–6.4% (39–47 mmol/mol); type 2 diabetes was defined as HbA_{1c} ≥6.5% (48 mmol/mol) (2).
ALT, alanine aminotransferase; CV, coefficient of variation; FSI, fasting insulin; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostatic model for insulin resistance; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation; VLDL, very low-density lipoprotein.

Outcome	<5% BMI reduction (*n* = 29)	≥5–<20% BMI reduction (*n* = 44)	≥20% BMI reduction (*n* = 53)
BMI, %	0.9 (4.4)	–13.0 (4.8)	–28.9 (6.5)
Waist circumference, cm	1.6 (6.4)	–10.8 (7.2)	–22.4 (9.5)
Waist-to-height ratio	0.00 (0.04)	–0.07 (0.04)	–0.14 (0.06)
eGFR*	–2.6 (9.6)	–3.7 (10.7)	–0.98 (8.9)
SBP, mmHg	2 (11)	–1 (9)	–7 (12)
DBP, mmHg	1 (12)	–2 (9)	–3 (7)
ALT*	1.15 (54.9)	0.80 (55.4)	0.65 (66.2)

Supplementary Table 2. Change in cardiometabolic risk factors from baseline to week 68 by BMI reduction in the semaglutide 2.4 mg group (excluding participants with T2D)

Data are from the in-trial observation period. Data are mean (SD) unless otherwise stated. *Data are mean (SD) ratio to baseline.

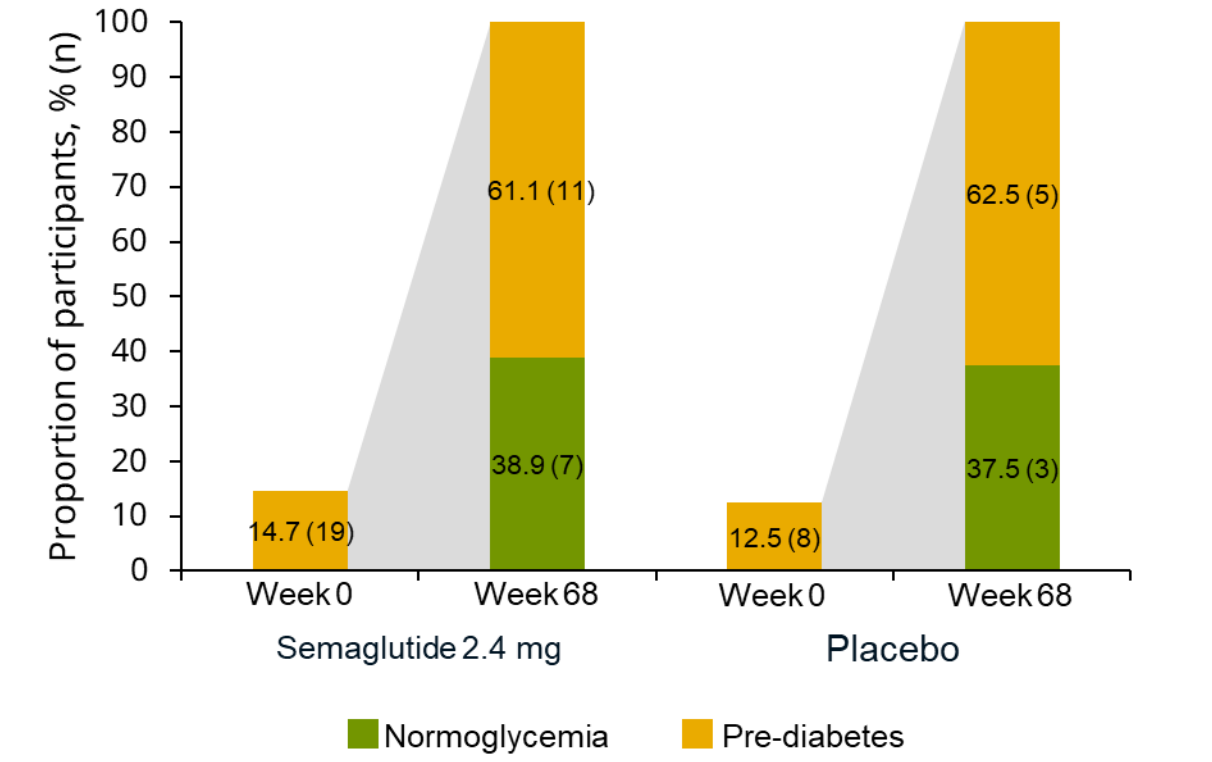
ALT, alanine aminotransferase; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SD, standard deviation.



Supplementary Figure 1. Participant disposition (excluding participants with type 2 diabetes).

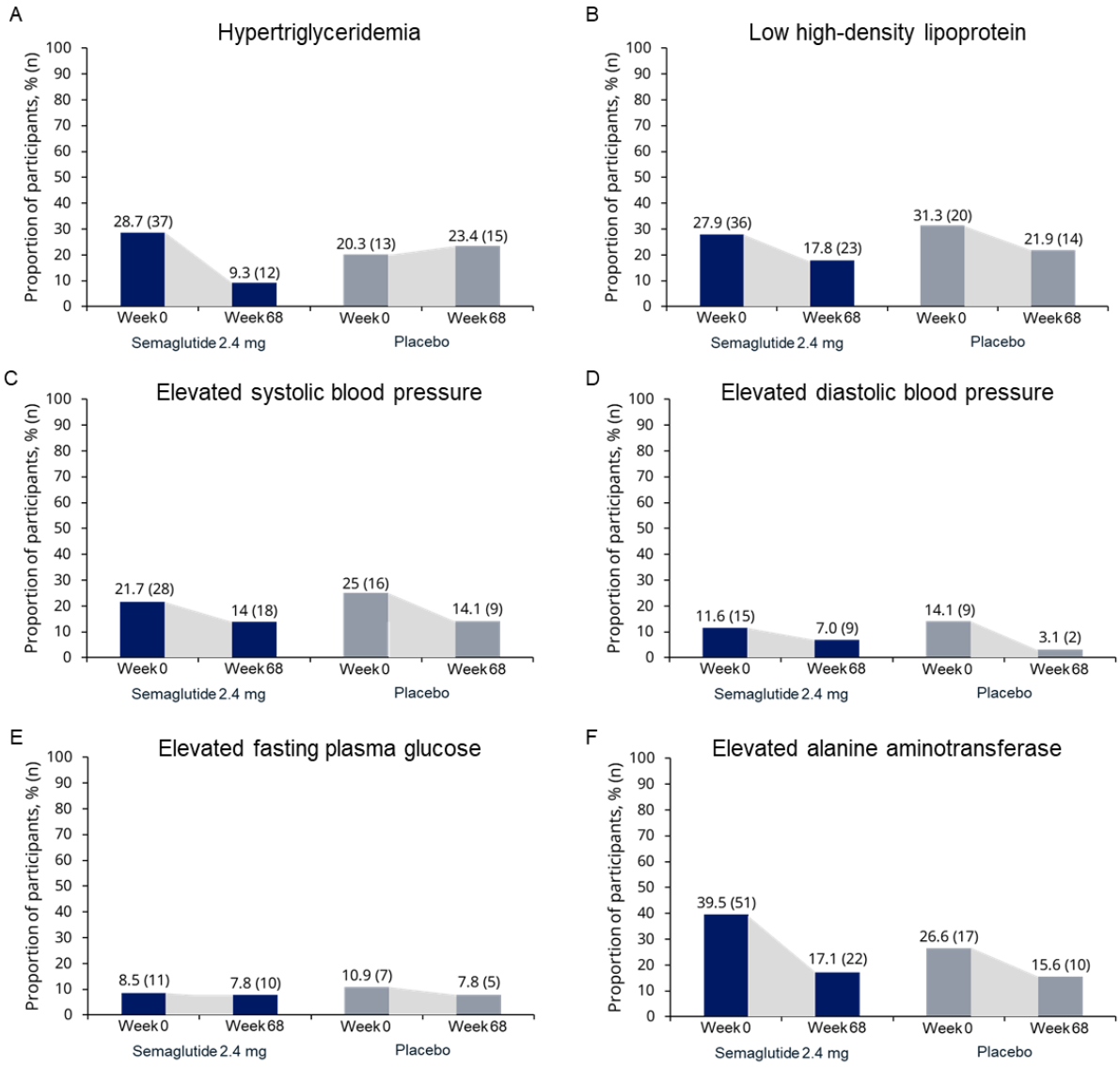
%, proportion of participants of full analysis set.

FAS, full analysis set; SAS, safety analysis set.



Supplementary Figure 2. Proportion of participants with baseline prediabetes achieving normoglycemia at week 68.

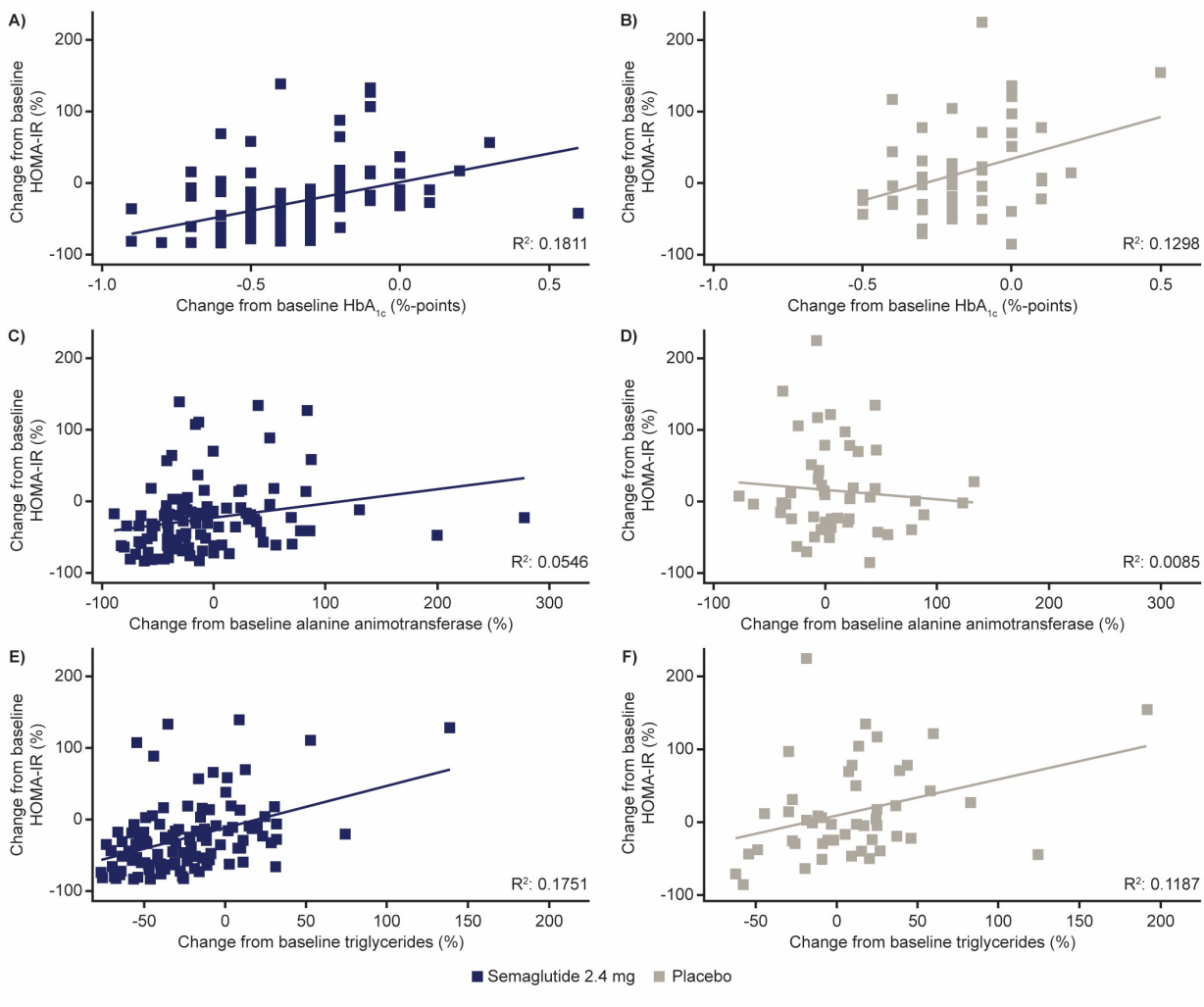
Data are from the in-trial period. Percentages are based on subjects with an observation at the visit. Normoglycemia was defined as HbA_{1c} <5.7%, pre-diabetes was defined as ≥5.7%.



Supplementary Figure 3. Proportion of participants with cardiometabolic risk factors at baseline and at week 68.

Data are from the in-trial period showing proportion of participants with hypertriglyceridemia (A), low-HDL (B), high systolic and diastolic blood pressure (C and D, respectively), hyperglycemia (E), and ALT (F). Thresholds for risk were defined as; hypertriglyceridemia as serum triglyceride levels of ≥1.7 mmol/L (≥150 mg/dL), low-HDL as ≤1.0 mmol/L (≤40 mg/dL), high systolic and diastolic blood pressures as ≥130 and ≥80 mmHg, respectively, high FPG as ≥5.6 mmol/L, and ALT as >25.8 U/L in male participants, >22.1 U/L in female participants.

ALT, alanine aminotransferase; FPG, fasting plasma glucose; HDL, high-density lipoprotein.



Supplementary Figure 4. Associations between change from baseline to week 68 in HOMA-IR and change from baseline in cardiometabolic parameters HbA_{1c}, triglycerides, and ALT.

ALT, alanine aminotransferase; HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance.

References

1. Weghuber D, Barrett T, Barrientos-Pérez M, et al. Once-weekly semaglutide in adolescents with obesity. N Engl J Med 2022;387:2245–2257
2. American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S27–S49.