Supplementary Online Content

Larsen JR, Vedtofte L, Jakobsen MSL, et al. Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder: a randomized clinical trial [published online June 10, 2017]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2017.1220

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Informed oral and written consent Age ≥18 years and ≤65 years Diagnosed with schizophrenia, schizotypal disorder or paranoid psychosis according to the criteria of ICD-10 (International Classification of Diseases, World Health Organization) or the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, the American Psychiatric Association) Stable antipsychotic treatment with either clozapine or olanzapine for at least 6 months (without dose change for at least 30 days) Stable co-medications for at least 30 days Body mass index ≥27 kg/m^2 Stable body weight (defined as less than 5% change in weight over the last three months before inclusion) Prediabetes (fasting plasma glucose level of 6.1 mmol/l to 6.9 mmol/l (110-125 mg/dL) *and/or* a two-hour plasma glucose >7.8 mmol/l (140 mg/dL) following a 75-grams oral glucose tolerance test *and/or* HbA1c of 43 mmol/mol to 47 mmol/mol (6.1-6.4%)	Compulsory treatment Type 1 or 2 diabetes *and/or* HbA1c >47 mmol/mol (6.4%) *and/or* receiving diabetes medication Impaired hepatic function (liver transaminases >2 times upper normal limit) Impaired renal function (se-creatinine >150 μM *and/or* macroalbuminuria) Impaired pancreatic function (acute or chronic pancreatitis and/or amylase >2 times upper normal limit) Cardiac problems defined as decompensated heart failure (NYHA class III or IV), unstable angina pectoris and/or myocardial infarction within the last 12 months Uncontrolled hypertension (systolic blood pressure >180 mmHg, diastolic blood pressure >100 mmHg) Treatment with corticosteroids or other hormone therapy (except estrogens) Use of body weight-lowering pharmacotherapy within the preceding three months Females of child bearing potential who are pregnant, breast-feeding or have intention of becoming pregnant or are not using adequate contraceptive measures Any active substance abuse or dependence for the past six months (except for nicotine) Any condition that the investigator feels would

	interfere with trial participation Receiving any investigational drug within the last three months

eTable 2. Additional Baseline Characteristics

	Liraglutide n=47	Placebo n=50
Intervention		
Days of treatment	112.0 ± 0.4	113.7 ± 0.6
Number of patients on 1.2 mg of liraglutide[a]	3 (6.5)	0.0 (0.0)
Number of patients on lipid-lowering agents[a]	11 (23.4)	13 (26.0)
Number of patients on antihypertensive agents[a]	11 (23.4)	13 (26.0)
Liver function[b]		
Alanine transaminase (U/L)	34.0 [31.0]	32.0 [21.0]
Aspartate transaminase (U/L)	25.0 [12.0]	27.0 [10.0]
Alkaline phosphatase (U/L)	86.0 [32.0]	84.0 [29.0]
Amylase (U/L)	19.0 [12.0]	20.0 [11.0]
Kidney function		
Creatinine	81.1 ± 15.5	82.2 ± 13.3
Albumin/creatinine-ratio	3.1 ± 2.0	2.7 ± 1.9
Alcohol		
AUDIT	4.4 ± 4.8	4.6 ± 4.9
Drinks per week	3.7 ± 7.4	4.7 ± 11.7

Baseline values are calculated for participants, who were randomized, received at least one dose of the trial compound (liraglutide or placebo), and who had at least one assessment after baseline. For alanine transaminase, aspartate transaminase and amylase differences were based on logarithmic transformed data because of screwed distributions. There were no significant differences between the two groups for any of the characteristics with the exception of days of treatment (P=.03).

Plus-minus values are observed means ± SD.

[a] are numbers (percentage) .

[b] are medians [interquartile range] .

SD denotes standard deviation and AUDIT Alcohol Use Disorder Identification Test.

eTable 3. Additional Change in End Points Between Baseline and Week 16[a]

	Liraglutide n=47	Placebo n=50	Estimated Treatment Difference, Liraglutide vs. Placebo (95% CI)[b]	*P* Value
Liver function				
Alanine transaminase	0.89	0.91	0.94 (0.79 to 1.12)	.48
Aspartate transaminase	0.91	0.86	0.99 (0.86 to 1.13)	.84
Alkaline phosphatase (U/L)	-5.3 ± 1.9	-2.8 ± 1.4	-2.6 (-7.5 to 2.4)	.30
Amylase	1.27	0.98	1.27 (1.13 to 1.43)	<.001
Kidney function				
Creatinine	1.6 ± 1.2	-1.5 ± 1.2	3.4 (-0.5 to 7.3)	.08
Alcohol				
AUDIT	-0.5 ± 0.4	-1.1 ± 0.4	0.7 (-0.6 to 2.0)	.30
Drinks per week	0.1 ± 0.7	-1.3 ± 1.4	0.4 (-1.7 to 2.6)	.69

[a] Plus-minus values are differences in means ± SE from baseline to week 16 calculated by a repeated mixed model analysis of covariance for participants, who were randomized, received at least one dose of the trial compound (liraglutide or placebo), and who had at least one assessment after baseline. For alanine transaminase, aspartate transaminase and amylase the relative change from baseline is presented.

[b] Estimated treatment differences between the two groups calculated by a repeated mixed model analysis of covariance. The model includes the baseline value of the relevant variable together with the covariates: age, gender, illness duration, treatment with olanzapine, clozapine or both, baseline body mass index and baseline CGI-S.

SE denotes standard error, AUDIT Alcohol Use Disorder Identification Test and CGI-S Clinical Global Impressions-Severity.

eTable 4. Prevalence of the Most Common Adverse Events During the 16 Weeks[a]

	Liraglutide (n=52)				Placebo (n=51)			
	Week 4	**Week 8**	**Week 12**	**Week 16**	**Week 4**	**Week 8**	**Week 12**	**Week 16**
Gastrointestinal								
Nausea	51.0	27.1	19.1	23.9	20.0	12.0	6.1	8.0
Diarrhea	16.3	2.1	10.6	6.5	8.0	4.0	6.1	4.0
Constipation	22.4	27.1	19.1	15.2	14.0	10.0	10.2	6.0
Vomiting	22.4	16.7	10.6	13.0	6.0	4.0	6.1	6.0
Dyspepsia	20.4	8.3	8.5	15.2	10.0	10.0	10.2	8.0
Abdominal pain	26.5	14.6	25.5	10.9	8.0	8.0	6.1	8.0
Other								
Headache	12.2	6.3	8.5	4.3	4.0	8.0	10.2	6.0
Upper respiratory tract infection	6.1	4.2	2.1	13.0	6.0	6.0	4.1	10.0
Serious Adverse Events	4.1	2.1	4.3	0.0	5.9	6.0	10.2	8.0

[a] Values are percentage of individuals with a given common adverse event reported at control visits every four weeks during the 16 weeks of intervention for participants, who were randomized and received at least one dose of the trial compound (liraglutide or placebo).

eTable 5. Sensitivity Analyses of the Plasma Glucose Excursion, C-Peptide, and Glucagon Secretion During the Oral Glucose Tolerance Test Between Baseline and Week 16

	Unadjusted Treatment Difference, Liraglutide vs. Placebo[a] (n=97)	Covariate Adjusted Treatment Difference, Liraglutide vs. Placebo[b] (n=97)	Full ITT Treatment Difference, Liraglutide vs. Placebo[c] (n=103)
Primary endpoint Plasma glucose excursion	*P* < .001	*P* < .001	*P* < .001
Secondary endpoints C-peptide secretion	*P* = .01	*P* = .06	*P* = .02
Glucagon secretion	*P* = .01	*P* = .13	*P* = .02

Plasma glucose excursion, C-peptide and glucagon secretion were evaluated at fixed time point before and after ingestion of 75-g glucose at baseline and after 16 week for the liraglutide and the placebo group.

[a] Estimated treatment differences between the two groups are calculated by a repeated mixed model analysis of covariance for participants, who were randomized, received at least one dose of the trial compound (liraglutide or placebo), and who had at least one assessment after baseline.

[b] Estimated treatment differences between the two groups are calculated by a repeated mixed model analysis of covariance for participants, who were randomized, received at least one dose of the trial compound (liraglutide or placebo), and who had at least one assessment after baseline. The model includes the baseline value of the relevant variable together with the covariates: age, gender, illness duration, treatment with olanzapine, clozapine or both, baseline body mass index and baseline CGI-S.

[c] Estimated treatment differences between the two groups are calculated by a repeated mixed model analysis of covariance for all participants, who were randomized (n=103). For participants with no assessments after baseline, the baseline values are carried forward to end of treatment. ITT Intention To Treat, CGI-S Clinical Global Impressions-Severity.

eTable 6. Sensitivity Analyses for the Secondary End Points Between Baseline and Week 16

	Unadjusted Treatment Difference, Liraglutide vs. Placebo (95% CI)[a] (n=97)	Covariate Adjusted Treatment Difference, Liraglutide vs. Placebo (95% CI)[b] (n=97)	Full ITT Treatment Difference, Liraglutide vs. Placebo (95% CI)[c] (n=103)
Clinical			
Body weight (kg)	-5.3 (-6.9 to -3.6)	-5.3 (-7.0 to -3.7)	-4.7 (-6.3 to -3.1)
Waist circumference (cm)	-4.5 (-6.4 to -2.7)	-4.1 (-6.0 to -2.3)	-4.1 (-5.9 to -2.4)
Body mass index (kg/m^2)	-1.7 (-2.2 to 1.2)	-1.8 (-2.4 to -1.3)	-1.5 (-2.0 to -1.0)
Systolic blood pressure (mmHg)	-2.1 (-6.7 to 2.5)	-4.9 (-9.5 to -0.3)	-1.6 (-6.0 to 2.8)
Diastolic blood pressure (mmHg)	-2.1 (-5.2 to 1.0)	-3.0 (-6.8 to 0.9)	-1.9 (-4.8 to 1.1)
Glucose metabolism			
Glycated hemoglobin (%)	-0.2 (-0.3 to -0.1)	-0.2 (-0.3 to -0.1)	-0.2 (-0.3 to -0.1)
Fasting plasma glucose level	0.93 (0.90 to 0.96)	0.90 (0.88 to 0.95)	0.94 (0.91 to 0.97)
Fasting C-peptide (ng/mL)	0.55 (0.17 to 0.93)	0.46 (-0.02 to 0.94)	0.53 (0.17 to 0.88)
Fasting glucagon (pg/mL)	-7.3 (-11.1 to -3.8)	-4.7 (-8.6 to -0.05)	-7.0 (-10.8 to -3.5)
Insulin resistance[d]	1.07 (0.96 to 1.20)	1.08 (0.96 to 1.22)	1.08 (0.97 to 1.20)
Beta cell function[d]	1.23 (1.14 to 1.32)	1.29 (1.18 to 1.42)	1.20 (1.12 to 1.29)
Insulin sensitivity[d]	0.88 (0.80 to 0.98)	0.93 (0.82 to 1.06)	0.89 (0.80 to 0.98)
75-grams OGTT			
Two-hour value	0.73 (0.66 to 0.81)	0.77 (0.70 to 0.85)	0.76 (0.69 to 0.83)
Body composition			
Visceral fat (gram)	-295.0 (-467.0 to -122.9)	-250.2 (-459.9 to -40.5)	-253.4 (-414.6 to -92.1)
Android/gynoid-ratio	1.00 (0.97 to 1.03)	0.98 (0.94 to 1.01)	1.00 (0.97 to 1.03)
Total body fat	0.97 (0.95 to 0.99)	0.96 (0.94 to 0.99)	0.97 (0.95 to 0.99)
Cholesterol			
Total cholesterol (mg/dL)	-15.1 (-24.3 to -5.4)	-19.3 (-30.9 to -7.7)	-13.9 (-22.8 to -4.6)
LDL (mg/dL)	-13.9 (-21.6 to -6.2)	-15.4 (-23.2 to -7.7)	-12.7 (-20.5 to -5.4)
HDL	0.96 (0.90 to 1.02)	0.96 (0.90 to 1.03)	0.96 (0.91 to 1.02)
VLDL	0.93 (0.83 to 1.06)	0.93 (0.79 to 1.10)	0.94 (0.84 to 1.06)
Fasting triglycerides	0.88 (0.77 to 1.01)	0.90 (0.76 to 1.07)	0.90 (0.80 to 1.02)
Rating Scales			
Schizophrenia Quality of Life Scale (SQLS)			
Psychosocial	0.9 (-5.1 to 6.9)	2.2 (-5.0 to 9.3)	1.3 (-4.4 to 7.1)
Motivation and energy	-2.6 (-10.1 to 4.9)	-3.5 (-12.3 to 5.2)	-1.7 (-8.7 to 5.4)
Side-effects	-1.7 (-8.8 to 5.4)	4.0 (-3.6 to 11.6)	-1.5 (-8.4 to 5.4)
Clinical Global Impressions–Severity (CGI-S)	-0.1 (-0.3 to 0.08)	-0.1 (-0.3 to 0.2)	-0.1 (-0.3 to 0.1)
Global Assessment of Function (GAF)	-1.3 (-2.8 to 0.2)	-1.7 (-3.5 to 0.05)	-1.2 (-2.6 to 0.2)

[a] Estimated treatment differences between the two groups are calculated by a repeated mixed model analysis of covariance for participants, who were randomized, received at least one dose of the trial compound (liraglutide or placebo), and who had at least one assessment after baseline.

[b] Estimated treatment differences between the two groups are calculated by a repeated mixed model analysis of covariance for participants, who were randomized, received at least one dose of the trial compound (liraglutide or placebo), and who had at least one assessment after baseline. The model includes the baseline value of the relevant variable together with the covariates: age, gender, illness duration, treatment with olanzapine, clozapine or both, baseline body mass index and baseline CGI-S.

[c] Estimated treatment differences between the two groups are calculated by a repeated mixed model analysis of covariance for all participants, who were randomized (n=103). For participants with no assessments after baseline, the baseline values are carried forward to end of treatment.

[d] Estimated by HOMA2

For fasting plasma glucose, two-hour value during the OGTT, android/gynoid-ratio, total body fat, HDL, VLDL, triglycerides and HOMA2 measures, the relative change from baseline is presented. ITT denotes Intention To Treat,

HOMA homeostatic model assessment 2, OGTT oral glucose tolerance test, LDL low density lipoprotein, HDL high density lipoprotein, VLDL very low density lipoprotein, SE standard error, CGI-S Clinical Global Impressions-Severity. SI conversion factors: Total cholesterol and LDL: 0,0259; To covert to pmol/L multiply values by: C-peptide; 331; Glucagon: 0.287.

eTable 7. Mean Changes for the Major Outcomes Between Baseline and Week 16 by Olanzapine and Clozapine Treatment

	Patients treated with olanzapine (n=21)			Patients treated with clozapine (n=73)			
	Liraglutide (n=15)	**Placebo (n=6)**	**Estimated Treatment Difference, Liraglutide vs. Placebo (95% CI)[a]**	**Liraglutide (n=32)**	**Placebo (n=41)**	**Estimated Treatment Difference, Liraglutide vs. Placebo (95% CI)[a]**	**Interaction *P* Value[b]**
Body weight (kg)	-4.6 (-6.4 to -2.8)	1.2 (-1.2 to 3.5)	-6.7 (-10.0 to -3.3)	-4.8 (-6.1 to -3.5)	0.7 (-0.7 to 2.1)	-5.2 (-7.1 to -3.3)	.16
BMI (kg/m^2)	-1.8 (-2.5 to -1.1)	0.5 (-0.1 to 1.1)	-2.5 (-3.7 to -1.4)	-1.5 (-2.0 to -1.1)	0.1 (-0.3 to 0.5)	-1.6 (-2.2 to -0.9)	.35
Waist circumference (cm)	-4.1 (-6.3 to -1.9)	2.2 (-0.9 to 5.3)	-5.9 (-10.4 to -1.4)	-4.0 (-5.6 to -2.3)	0.5 (-1.0 to 2.0)	-3.8 (-5.9 to -1.6)	.49
Systolic blood pressure (mmHg)	2.4 (-4.2 to 9.0)	-5.7 (-22.5 to 11.2)	4.6 (-3.1 to 12.3)	-3.2 (-8.4 to 1.9)	1.2 (-2.6 to 5.1)	-6.1 (-12.2 to -0.01)	.40
Visceral fat (grams)	-252.7 (-529.8 to 24.3)	-24.0 (-109.2 to 61.2)	-152.9 (-782.4 to 476.5)	-352.3 (-549.9 to -154.7)	5.1 (-102.4 to 112.7)	-316.6 (-582.1 to -51.1)	.76
Percentage of body fat	0.94 (0.89 to 0.98)	1.02 (0.98 to 1.05)	0.91 (0.83 to 0.99)	0.97 (0.96 to 0.99)	1.0 (0.99 to 1.01)	0.98 (0.96 to 1.01)	.14
Hemoglobin A1c (%)	-0.2 (-0.3 to -0.05)	0.1 (-0.05 to 0.3)	-0.3 (-0.5 to -0.1)	-0.2 (-0.3 to -0.1)	0.05 (-0.03 to 0.1)	-0.2 (-0.3 to -0.08)	.94
Fasting plasma glucose	0.91 (0.86 to 0.96)	0.98 (0.82 to 1.17)	0.93 (0.85 to 1.01)	0.87 (0.85 to 0.92)	1.00 (0.97 to 1.03)	0.90 (0.86 to 0.95)	.38
Two-hour value during the OGTT	0.73 (0.66 to 0.82)	1.09 (0.90 to 1.32)	0.69 (0.54 to 0.87)	0.72 (0.63 to 0.81)	0.96 (0.90 to 1.03)	0.81 (0.72 to 0.92)	.34
Total cholesterol (mg/dL)	-27.0 (-42.5 to -15.4)	-3.9 (-19.3 to 11.6)	-19.3 (-42.5 to 3.9)	-11.6 (-19.3 to -3.9)	-3.1 (-11.6 to 3.9)	-15.4 (-27.0 to -2.3)	.74
LDL (mg/dL)	-19.3 (-30.9 to -7.7)	-0.8 (-11.6 to 7.7)	-15.4 (-38.6 to 7.7)	-11.6 (-19.3 to -3.5)	-2.3 (-7.7 to 2.3)	-11.6 (-19.3 to -2.7)	.48
Amylase	1.20 (1.07 to 1.35)	0.92 (0.76 to 1.12)	1.35 (1.11 to 1.65)	1.30 (1.19 to 1.42)	0.99 (0.91 to 1.07)	1.26 (1.08 to 1.47)	.22

Values are differences in means (95% CI) from baseline to week 16 calculated by a repeated mixed model analysis of covariance for participants, who were randomized, received at least one dose of the trial compound (liraglutide or placebo), and who had at least one assessment after baseline. For percentage of body fat, fasting plasma glucose, two-hour value during the OGTT and amylase, the relative change from baseline is presented.

[a] Estimated treatment differences between the two groups calculated by a repeated mixed model analysis of covariance. The model includes the baseline value of the relevant variable together with the covariates: age, gender, illness duration, treatment with olanzapine, clozapine or both, baseline body mass index and baseline CGI-S.
[b] Estimated differences in effect according to treatment with olanzapine, clozapine or both.
BMI denotes body mass index, OGTT oral glucose tolerance test, LDL low density lipoprotein and CGI-S Clinical Global Impressions-Severity.

eTable 8. Mean Changes for the Major Outcomes Between Baseline and Week 16 by Change in Dose of Olanzapine or Clozapine

	Patients with change of dose <20% (n=89)			Patients with no change of dose (n=82)			
	Liraglutide (n=42)	**Placebo (n=47)**	**Estimated Treatment Difference, Liraglutide vs. Placebo (95% CI)[a]**	**Liraglutide (n=32)**	**Placebo (n=41)**	**Estimated Treatment Difference, Liraglutide vs. Placebo (95% CI)[a]**	**Inter-action *P* Value[b]**
Body weight (kg)	-4.5 (-5.6 to -3.5)	0.7 (-0.7 to 2.1)	-5.4 (-7.2 to -3.6)	-4.6 (-5.8 to -3.4)	0.4 (-0.6 to 1.5)	-5.5 (-7.4 to -3.6)	.57
BMI (kg/m^2)	-1.6 (-1.9 to -1.2)	0.1 (-0.3 to 0.6)	-1.8 (-2.4 to -1.2)	-1.6 (-2.0 to -1.2)	0.07 (-0.3 to 0.4)	-1.9 (-2.5 to -1.2)	.97
Waist circumference (cm)	-3.9 (-5.3 to -2.6)	0.7 (-0.6 to 2.1)	-4.4 (-6.4 to -2.5)	-4.2 (-5.6 to -2.8)	0.5 (-0.6 to 1.7)	-4.8 (-6.9 to -2.8)	.69
Systolic blood pressure (mmHg)	-0.7 (-4.8 to 3.5)	1.2 (-2.6 to 5.1)	-3.5 (-8.2 to 1.2)	0.4 (-3.8 to 4.6)	2.0 (-1.9 to 5.9)	-1.9 (-6.5 to 2.7)	.06
Visceral fat (grams)	-279.7 (-441.8 to -117.7)	-31.6 (-118.7 to 55.4)	-165.2 (-381.5 to 51.2)	-315.8 (-484.8 to -146.9)	-18.4 (-109.8 to 72.9)	-180.2 (-400.5 to 40.0)	.47
Percentage of body fat	0.96 (0.94 to 0.98)	1.00 (0.99 to 1.01)	0.96 (0.94 to 0.99)	0.96 (0.94 to 0.98)	1.00 (0.99 to 1.01)	0.96 (0.93 to 0.99)	.38
Hemoglobin A1c (%)	-0.2 (-0.3 to -0.1)	0.06 (-0.006 to 0.1)	-0.2 (-0.3 to -0.1)	-0.2 (-0.3 to -0.1)	0.06 (-0.005 to 0.1)	-0.2 (-0.3 to -0.1)	.46
Fasting plasma glucose	0.90 (0.87 to 0.93)	0.99 (0.96 to 1.02)	0.91 (0.88 to 0.95)	0.91 (0.90 to 0.94)	0.99 (0.96 to 1.02)	0.92 (0.88 to 0.96)	.09
Two-hour value during the OGTT	0.74 (0.69 to 0.80)	0.97 (0.91 to 1.03)	0.78 (0.70 to 0.87)	0.74 (0.69 to 0.80)	0.98 (0.92 to 1.04)	0.77 (0.69 to 0.86)	.49
Total cholesterol (mg/dL)	-19.3 (-23.2 to -11.6)	-3.1 (-7.7 to3.5)	-15.4 (-27.0 to -3.9)	-15.4 (-23.2 to -7.7)	-3.9 (-11.6 to 2.7)	-15.4 (-27.0 to -3.9)	.10
LDL(mg/dL)	-11.6 (-19.3 to -7.7)	-1.9 (-7.7 to 2.3)	-11.6 (-19.3 to -3.9)	-11.6 (-19.3 to -3.9)	-2.3 (-7.7 to 2.3)	-11.6 (-19.3 to -2.7)	.15
Amylase	1.25 (1.16 to 1.34)	0.99 (0.92 to 1.07)	1.25 (1.10 to 1.41)	1.25 (1.15 to 1.36)	0.99 (0.91 to 1.07)	1.24 (1.09 to 1.41)	.98

Values are differences in means (95% CI) from baseline to week 16 calculated by a repeated mixed model analysis of covariance for participants, who were randomized, received at least one dose of the trial compound (liraglutide or liraglutide placebo), and who had at least one assessment after baseline. For percentage of body fat, fasting plasma glucose, two-hour value during the OGTT and amylase, the relative change from baseline is presented.

[a] Estimated treatment differences between the two groups calculated by a repeated mixed model analysis of covariance. The model includes the baseline value of the relevant variable together with the covariates: age, gender, illness duration, treatment with olanzapine, clozapine or both, baseline body mass index and baseline CGI-S.
[b] Estimated differences in effect according to change in dose of olanzapine or clozapine one month prior to inclusion and during the 16 weeks of treatment. The differences in effect were calculated for patients with no dose change vs small change of dose (<20%) vs large change of dose (≥20%).
BMI denotes body mass index, OGTT oral glucose tolerance test, LDL low density lipoprotein and CGI-S Clinical Global Impressions-Severity.

eTable 9. Mean Changes for the Major Outcomes Between Baseline and Week 16 by the 2-Hour Value During the OGTT

	Patients with a two-hour value ≤11.0 mmol/L (199 mg/dL) (n=73)			Patients with a two-hour value >11.0 mmol/L (199 mg/dL) (n=24)			
	Liraglutide (n=36)	**Placebo (n=37)**	**Estimated Treatment Difference, Liraglutide vs. Placebo (95% CI)[a]**	**Liraglutide (n=11)**	**Placebo (n=13)**	**Estimated Treatment Difference, Liraglutide vs. Placebo (95% CI)[a]**	**Interaction *P* Value[b]**
Body weight (kg)	-4.7 (-5.9 to -3.5)	1.1 (-0.6 to 2.8)	-5.8 (-7.7 to -3.9)	-4.9 (-7.5 to -2.3)	-1.2 (-3.1 to 0.6)	-4.7 (-10.9 to 1.6)	.75
BMI (kg/m^2)	-1.7 (-2.1 to 1.2)	0.2 (-0.3 to 0.7)	-1.9 (-2.6 to -1.3)	-1.5 (-2.3 to -0.7)	-0.3 (-1.1 to 0.4)	-1.4 (-3.1 to 0.3)	.70
Waist circumference (cm)	-4.1 (-5.6 to -2.5)	1.2 (-0.3 to 27)	-4.9 (-7.1 to -2.7)	-3.7 (-6.3 to -1.2)	-1.6 (-4.1 to 0.9)	0.5 (-3.1 to 4.1)	.75
Systolic blood pressure (mmHg)	-0.5 (-5.3 to 4.3)	2.2 (-1.6 to 6.0)	-4.4 (-9.9 to 1.0)	-5.3 (-13.5 to 2.9)	-2.0 (-11.7 to 7.7)	-1.2 (-15.6 to 13.2)	.48
Visceral fat (grams)	-299.6 (-469.2 to -130.0)	-37.3 (-134.6 to 59.2)	-218.5 (-439.4 to 2.3)	NA (small sample)	NA (small sample)	NA	.08
Percentage of body fat	0.96 (0.94 to 0.98)	1.00 (0.98 to 1.01)	0.96 (0.94 to 0.99)	NA (small sample)	NA (small sample)	NA	.27
Hemoglobin A1c (%)	-0.2 (-0.2 to -0.1)	0.05 (-0.03 to 0.1)	-0.2 (-0.3 to 0.1)	-0.3 (-0.5 to -0.1)	0.1 (-0.05 to 0.3)	0.009 (-0.6 to 0.6)	.35
Fasting plasma glucose	0.90 (0.87 to 0.93)	0.99 (0.96 to 1.02)	0.91 (0.87 to 0.96)	0.89 (0.83 to 0.95)	1.01 (0.94 to 1.09)	0.92 (0.86 to 0.99)	.16
Two-hour value during the OGTT	0.77 (0.71 to 0.84)	0.99 (0.93 to 1.06)	0.77 (0.70 to 0.87)	0.57 (0.42 to 0.78)	0.93 (0.82 to 1.07)	0.73 (0.43 to 1.27)	.39
Total cholesterol (mg/dL)	-19.3 (-30.9 to -11.6)	-0.8 (-7.7 to 7.7)	-19.3 (-34.7 to -7.7)	-11.6 (-23.2 to 0.1)	-11.6 (-19.3 to -3.1)	7.7 (-30.9 to 42.5)	.94
LDL (mg/dL)	-15.4 (-23.2 to -7.7)	-0.4 (-3.9 to 3.9)	-15.4 (-23.2 to -7.7)	-7.7 (-19.3 to 1.9)	-7.7 (-0.01 to 0.8)	3.9 (-38.6 to 50.2)	.84
Amylase	1.21 (1.13 to 1.30)	0.98 (0.89 to 1.07)	1.29 (1.14 to 1.47)	1.44 (1.21 to 1.72)	1.00 (0.89 to 1.13)	1.00 (0.64 to 1.55)	.11

Values are differences in means (95% CI) from baseline to week 16 calculated by a repeated mixed model analysis of covariance for participants, who were randomized, received at least one dose of the trial compound (liraglutide or placebo), and who had at least one assessment after baseline. For percentage of body fat, fasting plasma glucose, two-hour value during the OGTT and amylase the relative change from baseline is presented.

[a] Estimated treatment differences between the two groups calculated by a repeated mixed model analysis of covariance. The model includes the baseline value of the relevant variable together with the covariates: age, gender, illness duration, treatment with olanzapine, clozapine or both, baseline body mass index and baseline CGI-S.
[b] Estimated differences in effect according to a two-hour value above 11.0 mmol/L vs. below 11.1 mmol/L.
BMI denotes body mass index, OGTT oral glucose tolerance test, LDL low density lipoprotein and CGI-S Clinical Global Impressions-Severity.

eMethods. Data Analysis

Full statistical analyses

A sample size of 96 participants (48 in each group) was estimated, with two-sided t-testing, an α of 5% and a power of 90%. The power calculation was based on the primary outcome measurement: Change in glucose tolerance. The glucose tolerance was estimated by the total area under the curve (AUC) following a four-hour 75-grams oral glucose tolerance test (OGTT). The expected mean total AUC for the plasma glucose excursion following a four-hour 75-grams OGTT was estimated as 1695 (SD 158) and 1800 (SD 158) after 16 weeks of treatment for the liraglutide and the placebo group, respectively. The difference in total AUC was based on unpublished data in participants with and without impaired glucose tolerance (IGT) following a four-hour 75-grams OGTT at baseline from the study: "*The Impact of Liraglutide on Glucose Tolerance and the Risk of Type 2 Diabetes in Women With Previous Pregnancy-induced Diabetes*".[1]

Procedure

All analyses were carried out with the treatment groups still blinded and labeled as "treatment group A" and "treatment group B". Before dividing participants into group A and group B, the statistical plan was completed and uploaded on clinicaltrials.gov, and the data set was locked. The final unblinding of treatment groups (liraglutide or placebo), was not carried out until all statistical analyses were performed. All analyses were performed using SAS 9.4, with α set at 0.05 and two-sided testing.

All efficacy analyses were performed using a modified intention-to-treat principle. All randomized participants who received at least one dose of the trial compound (liraglutide or placebo) and who

had at least one assessment after baseline were included in the efficacy analyses. All safety analyses were performed in the intent-to-treat sample that included all participants, who were randomized and received at least one dose of the trial compound (liraglutide or placebo).

Primary end point

The primary endpoint was the change in glucose tolerance following a four-hour 75-grams OGTT from week 0 to week 16. During the four-hour 75-grams OGTT, blood was sampled at fixed time points: -15, -10, 0, 5, 10, 15, 20, 30, 40, 50, 60, 90, 120, 150, 180, and 240 minutes. An analysis of covariance was used to analyze change in glucose tolerance from week 0 to week 16 using repeated mixed model analyses for the plasma glucose levels for the liraglutide and the placebo group, respectively. In case of relevant baseline differences between the two groups, demographic, illness or treatment parameters were included in the model together with the baseline value of the OGTTs as a covariate.

Secondary end points

Blood was also sampled for analyses of C-peptide and glucagon in response to the glucose load at the same fixed time points during the OGTT. Change in secretion of C-peptide and glucagon from week 0 to week 16 was evaluated using repeated mixed model analyses for the liraglutide and the placebo group, respectively. In case of relevant baseline differences between the two groups, demographic, illness or treatment parameters were included in the model together with the baseline value of the relevant variable as a covariate.

Most secondary endpoints were repeated every four weeks. Few secondary endpoints were only repeated at week 0 and 16. For all repeated measurements, a repeated mixed model analyses were

used to analyze mean change in continuous outcomes from week 0 to week 16 for the liraglutide and the placebo group, respectively. In case of relevant baseline differences between the two groups, demographic, illness or treatment parameters were included in the model together with the baseline value of the relevant variable as a covariate. Change in categorical outcomes from week 0 to week 16 was analyzed using repeated mixed model logistic regression with the same covariates as described for the continuous outcomes.

For secondary endpoints without repeated measurements, missing data imputations were made using multiple imputations of chained equations (MICE).

For continuous outcomes without repeated measurements, outcomes were analyzed using analysis of covariance to detect differences between the liraglutide and the placebo group. In the model baseline demographic, illness or treatment parameters were included. Categorical outcomes without repeated measurements were analyzed using a multiple mixed effect logistic regression analysis model, where baseline demographic, illness or treatment parameters were included.

Number-needed-to-treat (NNT) for normalization of prediabetes was calculated by dividing 1 by the risk difference. Effect sizes (Cohen's d) for lowering glycated hemoglobin levels and reducing body weight were calculated dividing the difference of the means in change from baseline to end of trial (treatment - placebo) by the common standard deviation.

Subgroup and sensitivity analyses

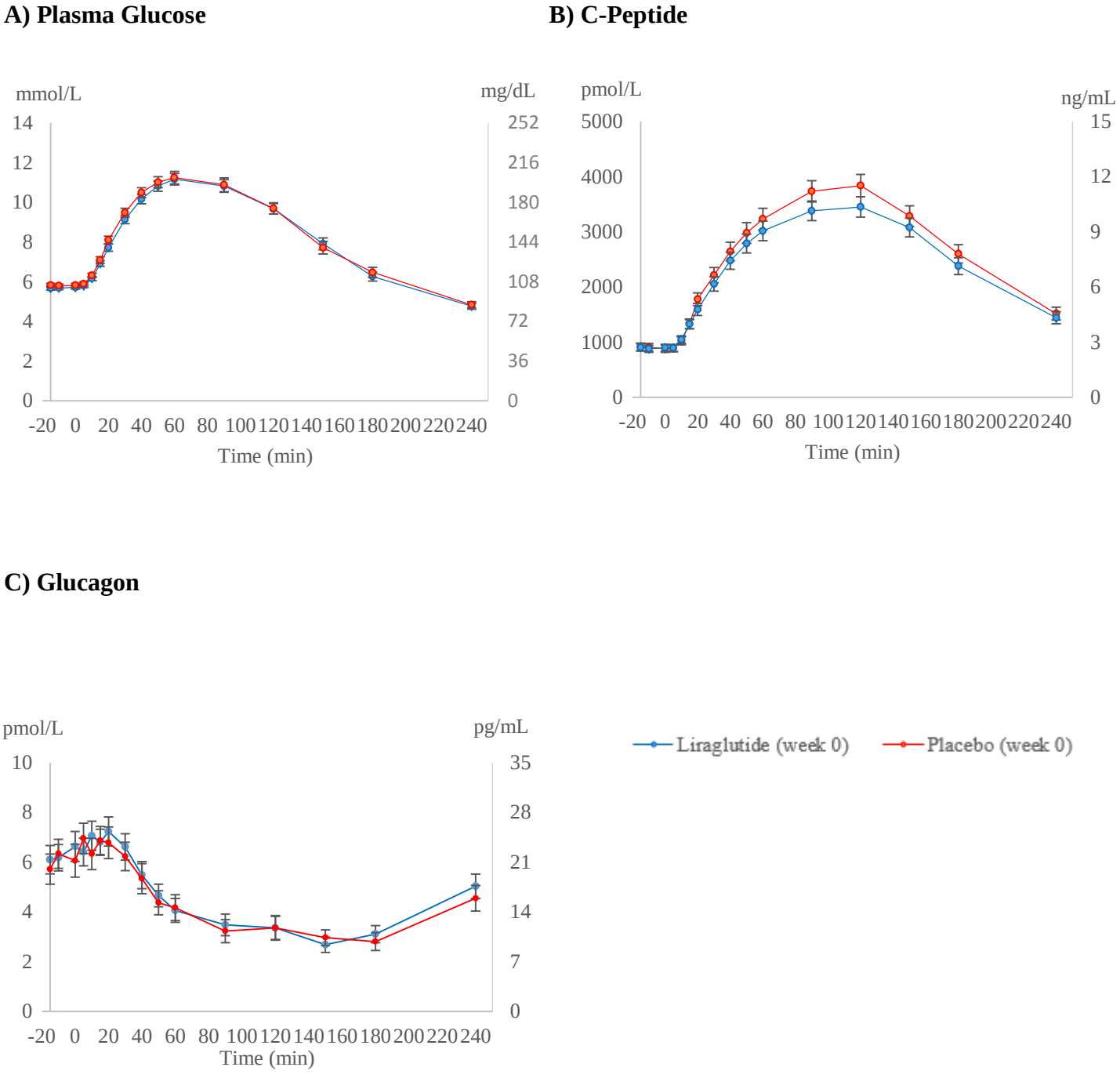
Subgroup and sensitivity analyses were performed to assess the robustness of the primary analyses. These analyses were performed using regression analysis for continuous outcomes and logistic regression for categorical outcomes. The analyses considered clinically or mechanistically relevant baseline and intra-treatment variables, including:

- Gender
- Age
- Smoking
- Antipsychotics (clozapine vs. olanzapine; monopharmacy vs. polypharmacy with other antipsychotic medications)
- Lipid profile
- Liver function
- Different groups of dysglycemia:
    1. Glycated hemoglobin (HbA1c): 43 mmol/mol (6.1%) ≤ HbA1c ≤47 mmol/mol (6.4%), vs.
    2. Elevated fasting plasma glucose (FPG): 6.1 mmol/L (110 mg/dL) ≤ FPG ≤6.9 mmol/L (125 mg/dL) and HbA1c <48 mmol/mol (6.5%), vs.
    3. Impaired glucose tolerance (IGT): two-hour plasma glucose after 75-grams oral glucose tolerance test >7.8 mmol/l (140 mg/dL) with a FPG <7.0 mmol/L (125 mg/dL) and HbA1c <48 mmol/mol (6.5%)
- IGT >11.1 mmol/l (200 mg/dL) vs. IGT <11.0 mmol/l (199 mg/dL)
- Liraglutide treatment (1.2 mg vs. 1.8 mg liraglutide)
- Body weight
- Add-on psychotropic drugs/classes (antidepressants, anxiolytics etc. vs. no add-on)
- Antihypertensive treatment vs. no antihypertensive treatment
- Lipid lowering treatment vs. no lipid lowering treatment

- Changes in antipsychotic medication (>20% change in dose vs. <20% change in dose vs no changes in dose for clozapine or olanzapine, respectively)
- Inhalation steroid vs. no inhalation steroid
- Body composition
- Insulin resistance
- Beta cell function
- Incretin hormones
- Psychopathologic rating scales
- Alcohol consumption
- Length of disease
- Diagnosis (schizophrenia vs. schizotypal disorder vs. paranoid psychosis)
- Side effects
- Serious adverse events

eFigure 1. Baseline Oral Glucose Tolerance Test for the Liraglutide and the Placebo Groups

Plasma glucose excursion, C-peptide and glucagon secretion evaluated at fixed time point before and after ingestion of 75-g glucose at baseline for the liraglutide and the placebo group. Values are means ± SEM calculated by a repeated mixed model analyses of covariance. When comparing liraglutide with placebo, the covariates: age, gender, illness duration, treatment with olanzapine, clozapine or both, baseline body mass index and baseline CGI-S were included. No differences were found between the two groups at baseline (Panel A: $P > .99$, Panel B: $P = .93$, Panel C: $P > .99$). The analyses include all participants, who were randomized, received at least one dose of the trial compound (liraglutide or placebo), and who had at least one assessment after baseline.
SEM denotes standard error of the mean and CGI-S Clinical Global Impressions Scale-Severity.



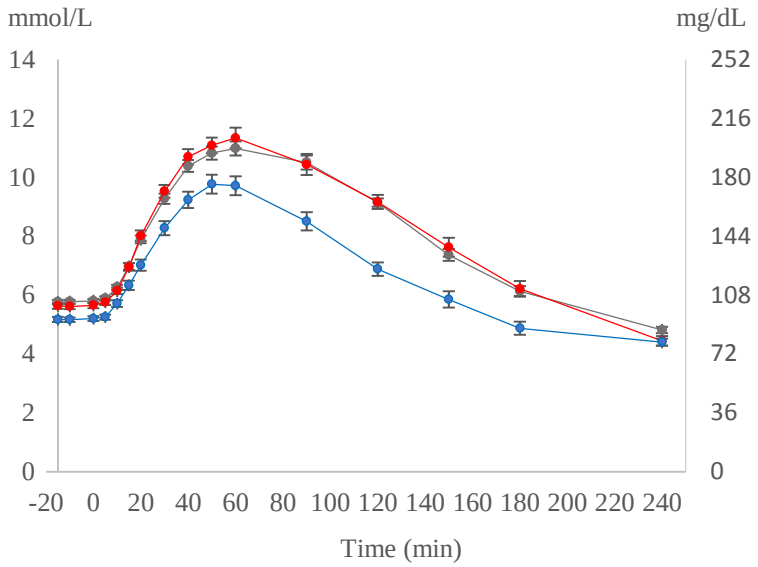
eFigure 2. Exploratory Analyses for the Primary Outcome

Plasma glucose excursion evaluated at fixed time point before and after ingestion of 75-g glucose in different exploratory analyses for the liraglutide and the placebo group. Values are means ± SEM calculated by a repeated mixed model analyses of covariance. The analyses include all participants, who were randomized, received at least one dose of the trial compound (liraglutide or placebo), and who had at least one assessment after baseline.
SEM denotes standard error of the mean, OGTT oral glucose tolerance, CGI-S Clinical Global Impressions Scale-Severity.

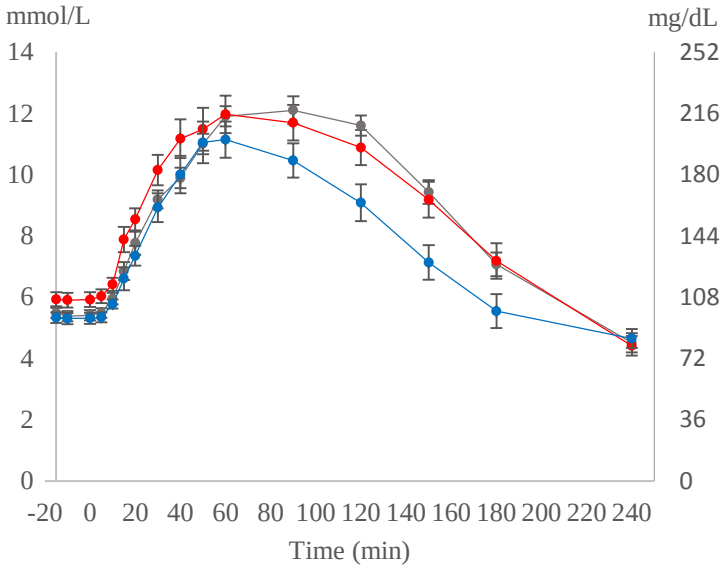
P values for change in glucose tolerance (all time values) from baseline to week 16:
A) Liraglutide group: $P < .001$ vs. Placebo group: $P = .98$
B) Liraglutide group: $P < .001$ vs. Placebo group: $P = .37$
C) Liraglutide group: $P = .03$ vs. Placebo group: $P > .99$
D) Liraglutide group: $P = .005$ vs. Placebo group: $P = .94$
E) Liraglutide group: $P = .005$ vs. Placebo group: $P = .94$
F) Liraglutide group: $P < .001$ vs. Placebo group: $P = .93$

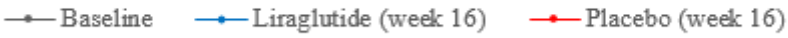
Patients with Two-Hour ≤11.0 mmol/l vs. Two-Hour Value >11.0 mmol/l during OGTTs

A) Two-Hour Value ≤11.0 mmol/l (n=73)



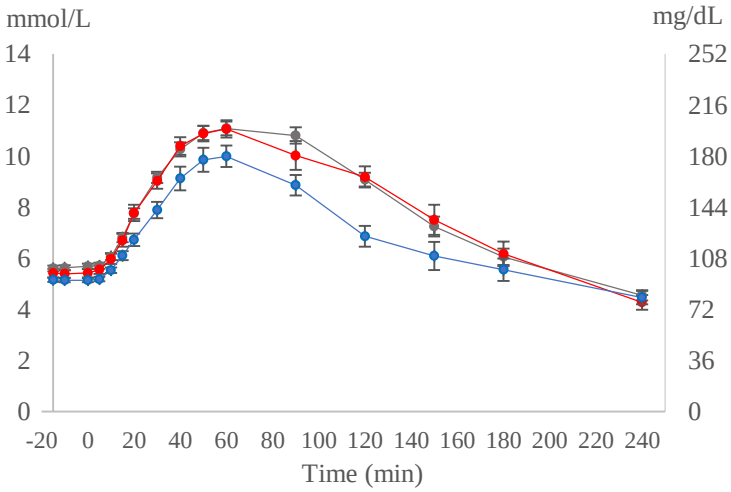
B) Two-Hour Value >11.0 mmol/l (n=24)



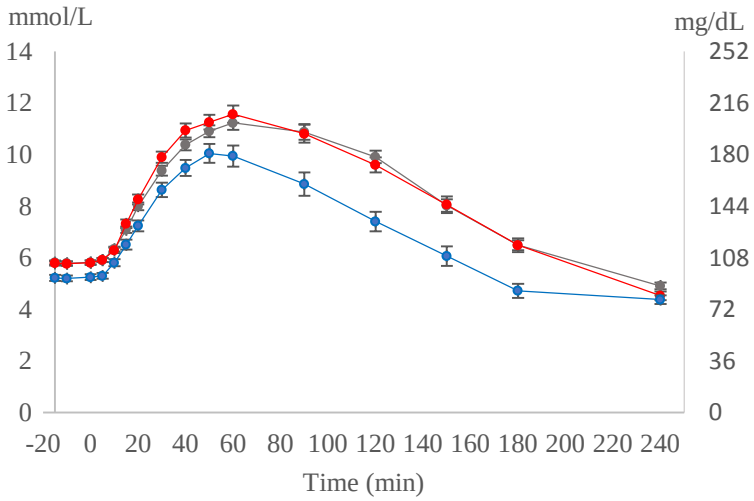


Participants Treated with Olanzapine vs. Clozapine

C) Olanzapine-Treated Participants (n=21)

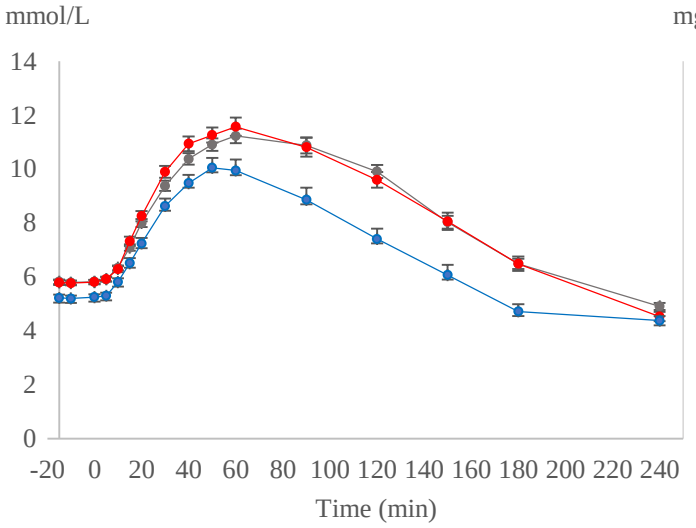


D) Clozapine-Treated Participants (n=73)

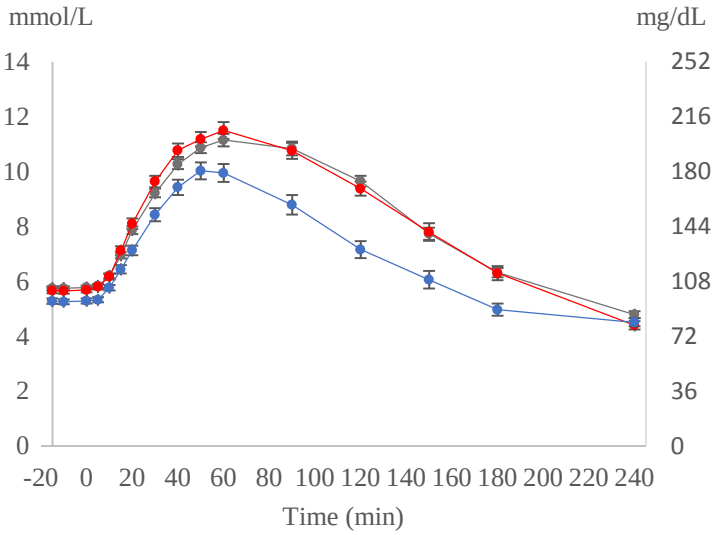


Patients with Change of Dose of Clozapine or Olanzapine One Month Prior to Inclusion or during the 16 Weeks of Treatment

E) Patients without Change of Dose >20% (n=89)



F) Patients without Change of Dose (n=82)



Reference

1. Foghsgaard S, Vedtofte L, Mathiesen ER et al. The effect of a glucagon-like peptide-1 receptor agonist on glucose tolerance in women with previous gestational diabetes mellitus: protocol for an investigator-initiated, randomised, placebo-controlled, double-blinded, parallel intervention trial. *BMJ Open* 2013;3:e003834.