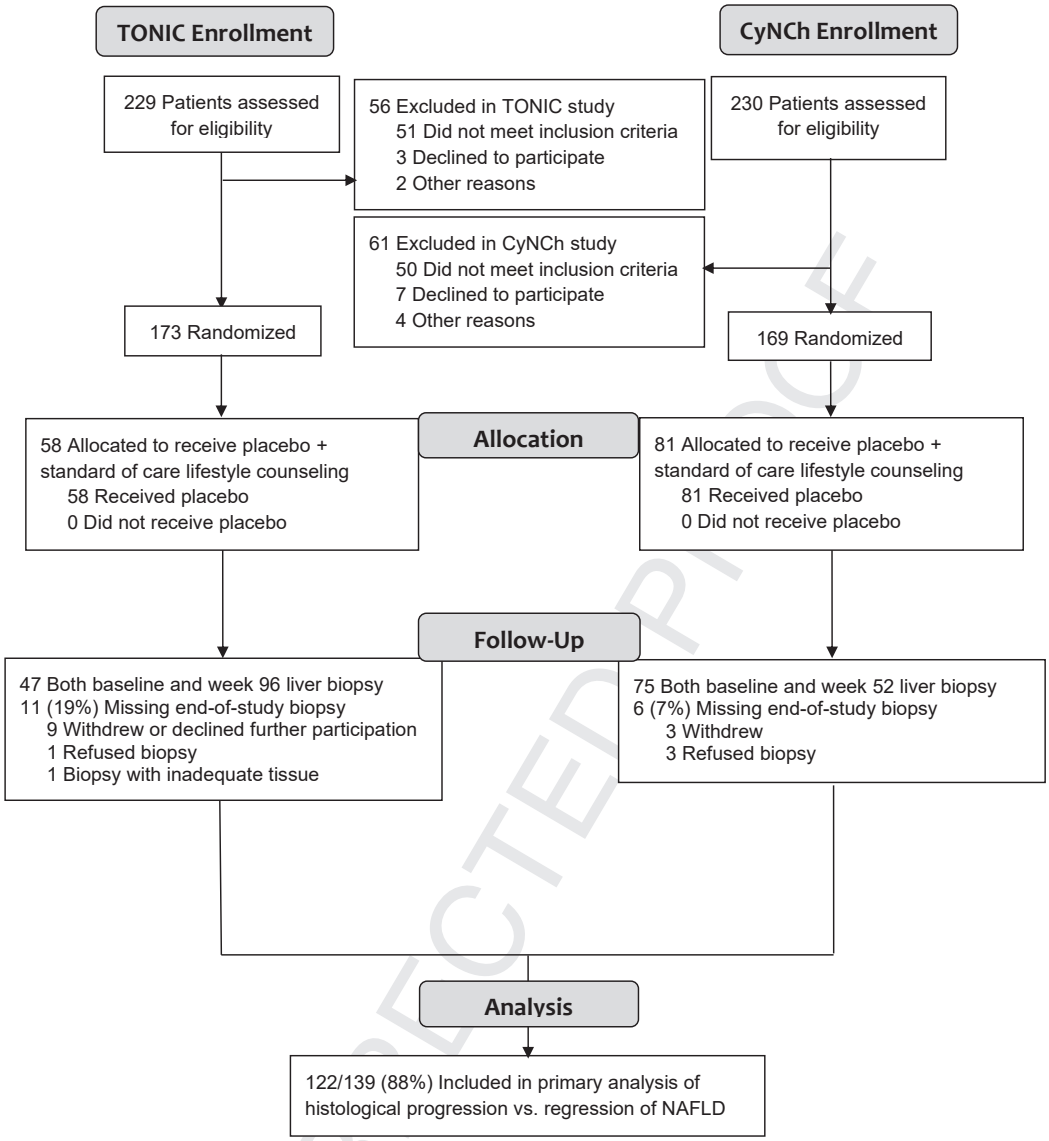
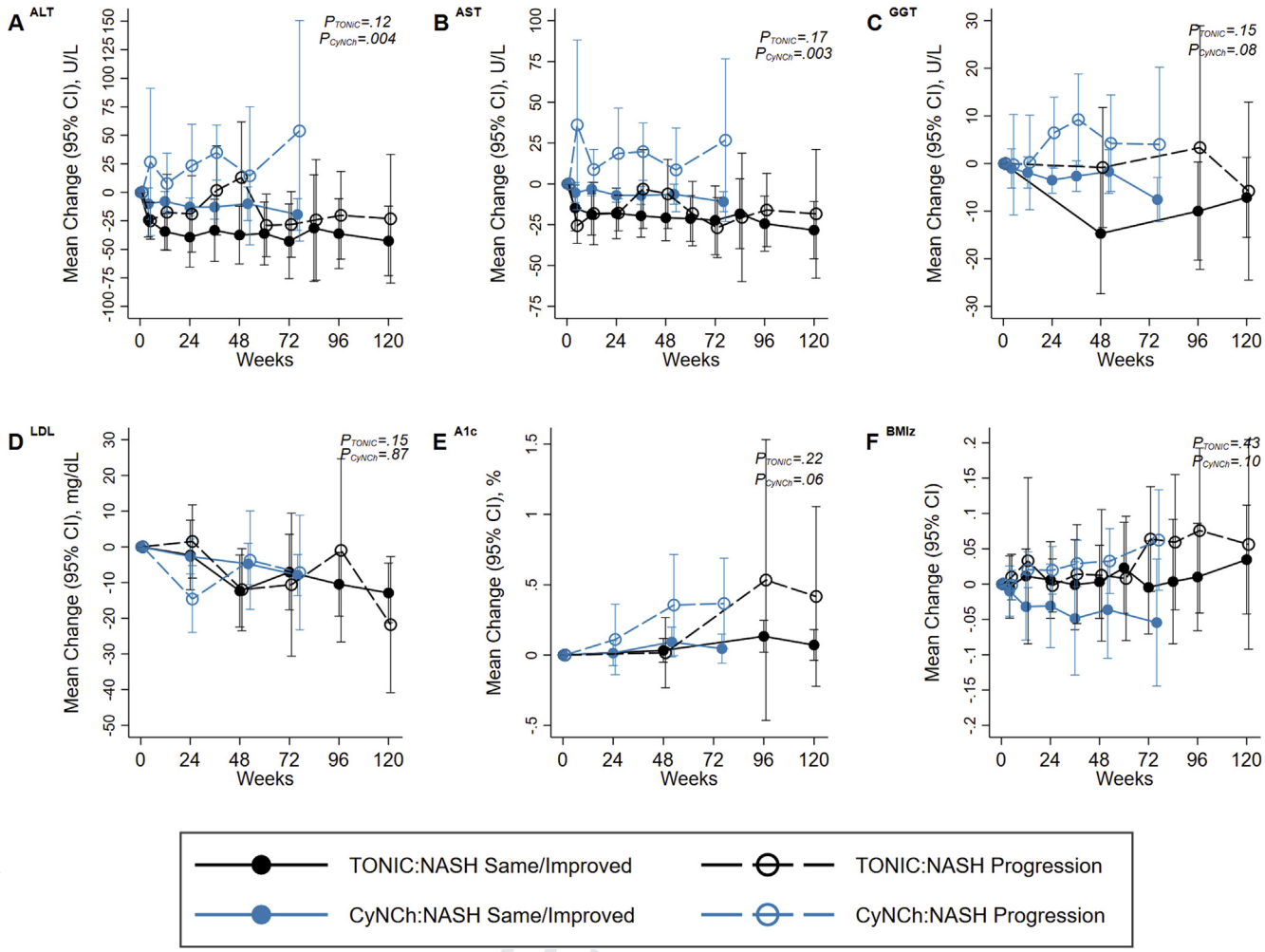
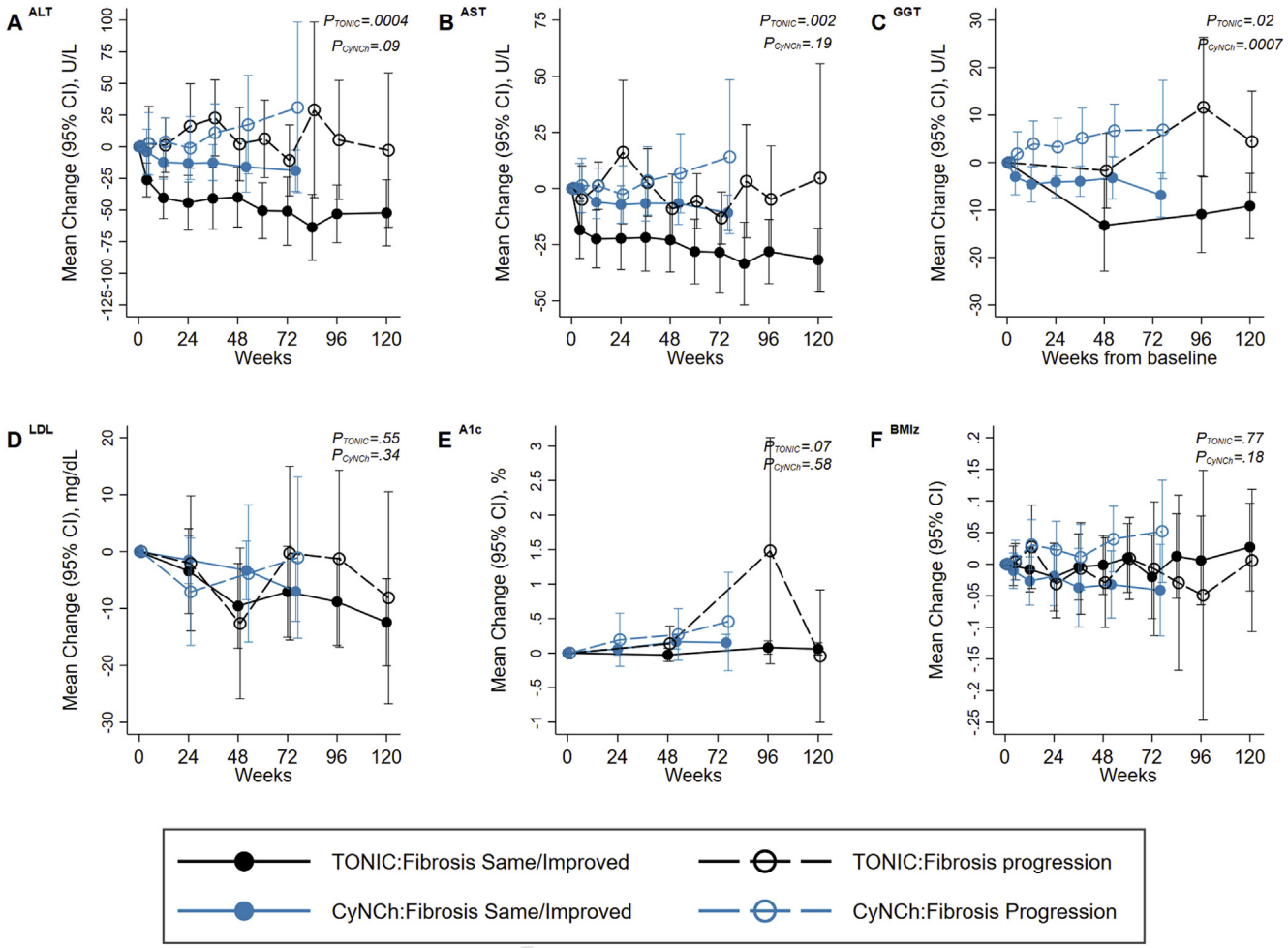


Supplementary Figure 1. CONSORT flow diagram depicting the allocation of participants to placebo arms in the TONIC and CyNCh clinical trials and the combined number with end-of-treatment biopsies available for analysis.



Supplementary Figure 2. Mean change from baseline in characteristics associated with progression vs. same/improved NASH by trial. Panels include (on y-axis): (*A*) ALT (U/L), (*B*) AST (U/L), (*C*) GGT (U/L), (*D*) LDL cholesterol (mg/dL), (*E*) hemoglobin $A1_C$ ($A1_C$) (%), and (*F*) BMI *z*-score (BMIz). The x-axis indicates weeks of observation. Same/improved NASH is denoted by black (TONIC) or blue (CyNCh) solid lines, while progression in NASH is indicated by black-dashed (TONIC) or blue-dashed (CyNCh) lines. Generalized estimating equation estimators were used to account for repeated visits for multiple regression models of the change in laboratory test or BMI *z*-score in relation to the histological outcome indicator as described in the Figure 2 legend. Each trial was analyzed separately. The longitudinal probability (2-sided) was determined by testing the histological effect and the interaction term.



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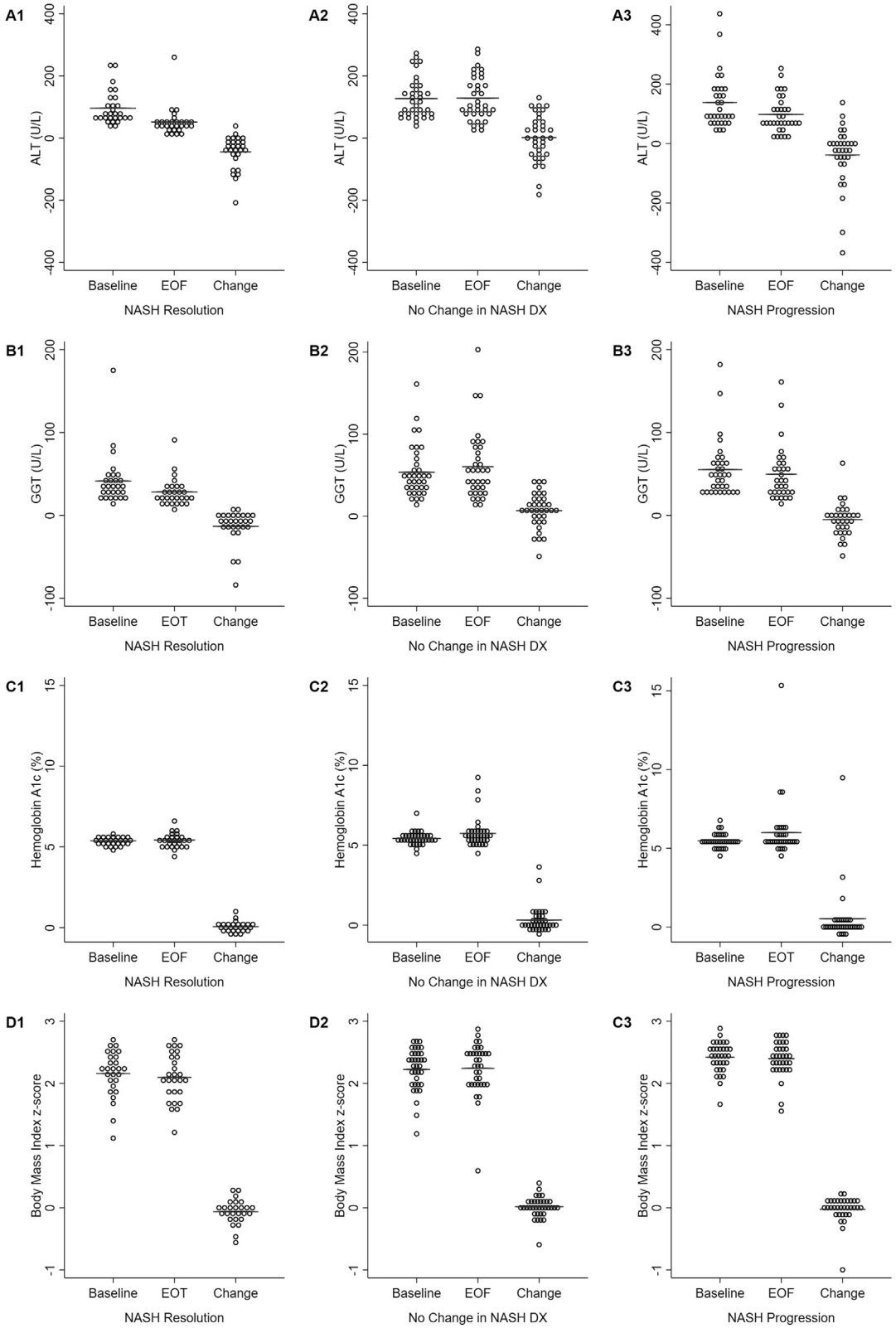
Supplementary Figure 3. Mean change from baseline in characteristics associated with progression of vs same/improved fibrosis by trial. Panels include (on y-axis): (*A*) ALT (U/L), (*B*) AST (U/L), (*C*) GGT (U/L), (*D*) LDL cholesterol (mg/dL), (*E*) hemoglobin $A1_C$ ($A1_C$) (%), and (*F*) BMI *z*-score (BMIz). The x-axis indicates weeks of observation. Fibrosis improvement is denoted by black (TONIC) or blue (CyNCh) solid lines, while fibrosis progression is indicated by black-dashed (TONIC) or blue-dashed (CyNCh) lines. Generalized estimating equation estimators were used to account for repeated visits for multiple regression models of the change in lab test or BMI *z*-score in relation to the histological outcome indicator as described in Figure 3 legend. Each trial was analyzed separately. The longitudinal probability (2-sided) was determined by testing the histological effect and the interaction term.



Supplementary Figure 4. Individual patient data are displayed (dots) for change in (*A*) ALT (U/L), (*B*) GGT (mg/dL), (*C*) hemoglobin A1C ($A1_C$), and (*D*) BMI *z*-score (BMIz) at baseline, end-of-follow-up (EOF), and change from baseline for resolution of NASH (A1, B1, C1, D1; N = 28 [29%]) compared with those with no change in NASH diagnosis (A2, B2, C2, D2; N = 35 [36%]) or with progression to NASH (A3, B3, C3, D3; N = 33 [34%]). The black horizontal line depicts mean value at each time point.

Supplementary Table 1. Histologic outcomes and changes from baseline for clinical characteristics by Study Group in children with NAFLD followed over 52 or 96 weeks

Histologic outcomes and change from baseline for clinical characteristics	TONIC (96 wk) (n = 47) n (%) or mean (SD)	CyNCh (52 weeks) (n = 75) n (%) or mean(SD)	OR (95% CI) or Adjusted mean changes	P[a]
Histologic Outcomes:				
Resolution of NASH (n = 96)	11 (28)	17 (30)	1.08 (0.44 to 2.66)	.87
Progression to definite NASH (n = 84)	6 (20)	9 (17)	0.8 (0.25 to 2.52)	.70
Combined improvement in:				
Fibrosis or NASH resolution (n = 99)	23 (56)	28 (48)	0.73 (0.33 to 1.63)	.44
Fibrosis and NASH resolution (n = 96)	7 (18)	12 (21)	1.22 (0.43 to 3.44)	.71
Combined progression in:				
Fibrosis or to definite NASH (n = 95)	14 (40)	20 (33)	0.66 (−0.16 to 2.68)	.57
Fibrosis and to definite NASH (n = 84)	4 (13)	5 (9)	0.66 (0.16 to 2.68)	.57
Fibrosis				
Patients with improvement	19 (40)	23 (31)	0.65 (0.30 to 1.40)	.27
Patients with worse fibrosis	12 (26)	16 (21)	0.70 (0.34 to 1.86)	.59
Change in score	−0.1 (1.3)	−0.1 (1.0)	−0.07 (−0.44 to 0.29)	.70
Total NAFLD activity score (NAS)				
Patients with improvement	26 (55)	40 (53)	0.92 (0.44 to 1.92)	.83
Patients with worse NAS	14 (30)	16 (21)	0.64 (0.28 to 1.47)	.29
Change in score	−0.7 (2.0)	−0.8 (1.8)	0.04 (−0.58 to 0.66)	.90
Hepatocellular ballooning				
Patients with improvement	10 (21)	21 (28)	1.44 (0.61 to 3.41)	.41
Patients with worse ballooning	12 (26)	7 (9)	0.30 (0.11 to 0.83)	**.02**
Change in score	0.1 (0.8)	−0.3 (0.8)	−0.39 (0.65 to −0.14)	**.002**
Steatosis				
Patients with improvement	19 (40)	33 (44)	1.16 (0.55 to 2.43)	.70
Patients with worse steatosis	9 (19)	10 (13)	0.65 (0.23 to 1.74)	.39
Change in score	−0.4 (1.2)	−0.4 (0.9)	0.23 (−0.12 to 0.58)	.20
Lobular inflammation				
Patients with improvement	20 (43)	17 (23)	0.40 (0.18 to 0.87)	**.02**
Patients with worse lobular inflammation	7 (15)	14 (19)	1.31 (0.49 to 3.53)	.59
Change in score	−0.3 (0.8)	−0.1 (0.8)	0.20 (−0.05 to 0.45)	.12
Portal inflammation				
Patients with improvement	7 (15)	14 (19)	1.31 (0.49 to 3.53)	.59
Patients with worse portal inflammation	10 (21)	11 (15)	0.64 (0.25 to 1.64)	.35
Change in score	0.06 (0.60)	−0.1 (0.6)	−0.09 (−0.29 to 0.12)	.40

Supplementary Table 1. Continued

Histologic outcomes and change from baseline for clinical characteristics	TONIC (96 wk) (n = 47) n (%) or mean (SD)	CyNCh (52 weeks) (n = 75) n (%) or mean(SD)	OR (95% CI) or Adjusted mean changes	*P*[a]
Change from baseline at 52 or 96 weeks for clinical characteristics:				
Change in age (y)	1.4 (0.3)	0.5 (0.3)	−0.9 (−1.0 to −0.8)	**<.001**
Diabetes type 2 incident cases:				
Incident cases over 72 or 120 wk[b]	4 (9)	2 (3)	0.29 (0.05 to 1.68)	.17
Body Mass Index (BMI, *kg/m²*)	1.8 (2.9)	1.0 (2.2)	−0.92 (−1.91 to 0.06)	.07
BMI z-score: >0 (BMI higher) vs				
≤ 0 (same or lower)	26 (57)	40 (54)	0.90 (0.43 to 1.90)	.79
Mean change	−0.01 (0.2)	−0.02 (0.2)	−0.01 (−0.10 to 0.07)	.87
Laboratory:				
Change in ALT (*U/L*)	−38 (74)	−9 (78)	11.7 (−12.4 to 35.8)	.34
Change in AST (*U/L*)	−22.1 (42.8)	−3.8 (35.9)	6.8 (−5.7 to 19.3)	.28
Change in GGT (*U/L*)	−5.0 (25.7)	0.01 (16.5)	2.1 (−5.4 to 9.6)	.58
Change in fasting glucose (*mg/dL*)	4.3 (24.9)	4.6 (27.3)	−0.3 (−10.2 to 9.6)	.95
Change in HbA1c (%)	0.4 (1.5)	0.2 (0.5)	−0.3 (−0.7 to 0.1)	.12

OR or adjusted mean changes, 95% confidence limits and *P* (2-sided) are determined from multiple linear regression of the change in continuous measure on study indicator and adjustment for the baseline value of the outcome. For binary measures, logistic regression of the outcome on study indicator was used.
[a]For each study, either unadjusted mean changes (standard deviations) or n (%) are reported.