Supplementary Online Content

Inge TH, Laffel LM, Jenkins TM, et al; Teen–Longitudinal Assessment of Bariatric Surgery (Teen-LABS) and Treatment Options of Type 2 Diabetes in Adolescents and Youth (TODAY) Consortia. Comparison of surgical and medical therapy for type 2 diabetes in severely obese adolescents. *JAMA Pediatr.* Published online March 12, 2018. doi:10.1001/jamapediatrics.2017.5763

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A. Definitions

Comorbidity prevalence, remission, and incidence definitions
The data bearing on presence or absence of co-morbid conditions was objectively and the following standard definitions were used. Comorbidity remission was calculated as the percentage of subjects without the condition at the 6, 12, and 24 month time points, among those with who had the condition at baseline and had evaluable data at follow-up.

<u>Diabetes mellitus (DM).</u> In the Teen LABS cohort, DM at baseline was defined as use of medications for DM, baseline HbA1c of ≥6.5%, or fasting glucose of at least 126 mg/dL, or 2hr glucose > 200mg/dL after oral glucose tolerance testing in the 6 months prior to enrollment. Participants reporting having polycystic ovarian syndrome who did not meet laboratory criteria for DM and were not taking a DM medication other than metformin were not considered to have diabetes. Participants who were on metformin at baseline for weight management or for insulin resistance, with no other indication of a prior diagnosis of DM documented and no laboratory findings consistent with the diagnosis of DM were not considered to have DM. Remission of DM was defined as no use of medication for DM, and HbA1c < 6.5%, or, if HbA1c was not available, FBG <126mg/dL.

<u>Dyslipidemia.</u> Dyslipidemia was defined for those <21 years of age as fasting triglycerides (TG) ≥130 mg/dL, or low density lipoprotein cholesterol (LDL-C) ≥130 mg/dL, or high density lipoprotein cholesterol (HDL-C) < 40mg/dL, or use of lipid lowering medications (LLM). Remission of dyslipidemia: If <21 years of age, at follow-up, remission of dyslipidemia was defined as TG <130 mg/dL, and LDL-C <130 mg/dL, and HDL-C ≥40 mg/dL, and no use of LLM. If age was ≥ 21 years, resolution of dyslipidemia was defined as TG <200 mg/dL, and LDL-C <160 mg/dL, and HDL-C ≥40 mg/dL (males) or HDL-C ≥50 mg/dL (females), and no use of LLM.

<u>Elevated blood pressure (BP).</u> Elevated BP was defined as: use of BP lowering medications or SBP ≥ 95th P or DBP ≥ 95th P (for age, sex, height) if <18 years of age; or if ≥18 years, SBP>140 mmHg or DBP > 90 mmHg. Remission of elevated BP required that absence of BP lowering medications, and SBP and DBP in the normal range for age.

<u>Abnormal Kidney Function.</u> The presence of abnormal kidney function was determined using accepted criteria for chronic kidney disease (CKD)[3] using Estimated glomerular filtration rate (eGFR) calculated using cystatin C levels per Larsson 2004[1], where eGFR=77.24 x (Cys C)$^{-1.2623}$. eGFR was considered low if <90 mL/min/1.73m^2. Elevated urinary albumin was defined as urine albumin to creatinine ratio > 0.03. No distinction was drawn between micro- and macroalbuminuria.

Adverse event definitions
In the Teen-LABS cohort, the occurrence of any procedures, abdominal operations, and hospital readmission was queried at each study visit. Any operations or inpatient admissions documented by study investigators resulted in retrieval of medical records. Records were reviewed by study staff, investigators, and by the Teen-LABS Adjudication Committee consisting of volunteer experts not otherwise participating in the study. The Adjudication Committee classified the events as related to the bariatric procedure, unrelated to the bariatric procedure, or unknown. Similarly, in TODAY, emergency room visits, hospitalizations, and severe adverse events were queried at each quarterly visit. If participants reported such events, medical records were obtained and reviewed blindly by the TODAY Safety Committee to confirm the report.

B. Laboratory Analyses

All laboratory assays for both Teen-LABS and TODAY cohorts were performed by the Northwest Lipid Metabolism and Diabetes Research Laboratories (Seattle, WA). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation except for participants whose triglycerides were ≥400 mg/dl, for whom LDL cholesterol was measured directly by beta-quantification. Analysis of fasting and stimulated glucose was performed enzymatically using Roche reagents on a Roche Module P Chemistry autoanalyzer (Roche Diagnostics Inc., Indianapolis, IN). The Roche reagent is based on the glucose hexokinase method. Measurement of the relative proportion of hemoglobin subclasses and calculation of the HbA1c levels were performed by a dedicated analyzer (TOSOH, Biosciences, Inc., South San Francisco, CA) using non-porous ion exchange high performance chromatography to achieve rapid and precise separation of stable HbA1c from other hemoglobin fractions. The immunochemical measurement of albumin in urine was performed by using Siemens reagent (Siemens Healthcare Diagnostics Inc., Newark, DE) on a Siemens BN II Nephelometer. The immunochemical measurement of Cystatin C levels was performed by the nephelometric method using Siemens reagents (Siemens Healthcare Diagnostics, Inc, Newark, DE) to estimate kidney function. Nutritional measures and parathyroid hormone were also measured at the reference laboratory.

C. Height and Weight

Height was measured using the same device for pre and postoperative measurements. At each center, a calibrated wall-mounted stadiometer was be used. For home visits, a stadiometer was shipped to the field examiner and calibrated prior to the visit. Height measurements were also made in triplicate.

Preoperative measurement of weight was obtained at the time of enrollment visit and on the same Tanita scale (Tanita model TBF-310, Tokyo, Japan) at each clinical visit. Tanita scales were shipped to the field examiner for home visits and calibrated prior to the visit. Measurements were obtained with patients in light clothing and without shoes. Weight measurements were obtained in triplicate and recorded to the nearest 100 grams.

Weight values from female participants in their second or third trimester of pregnancy and up to six months postpartum were omitted from analyses.

D. Sensitivity Analyses

We conducted sensitivity analyses for the HbA1c variable. Pattern-mixture models were performed to calculate HbA1c values, adjusting estimates from -5% through +5% of what they would be if the data were MAR. eFigure 1 below displays beta estimates and 95% confidence intervals comparing the effect of study group (Teen-LABS vs. TODAY) on follow-up HbA1c. As seen in eFigure 1 below, estimates remain consistent across the adjusted HbA1c levels suggesting the missing at random assumption is reasonable.

eTable 1. Prevalence of Select Conditions by Study Group and Timepoint*

	Baseline		6 months		1 year		2 year	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Elevated Blood Pressure								
Teen-LABS	66.7	45.3, 82.9	41.7	22.3, 64.1	30.0	14.0, 52.8	18.6	6.8, 41.6
TODAY	20.6	11.6, 34.1	28.1	17.0, 42.7	32.9	20.6, 48.0	41.9	27.7, 57.6
Dyslipidemia								
Teen-LABS	72.1	50.4, 86.8	43.0	23.0, 65.6	39.5	21.1, 61.3	42.7	21.5, 67.0
TODAY	66.7	52.1, 78.7	75.1	60.6, 85.9	66.5	50.8, 79.3	72.2	56.6, 83.8
eGFR, (LS-Mean)								
Teen-LABS	109.1	99.5, 118.6	--	--	116.1	106.5, 125.7	120.2	109.8, 130.7
TODAY	110.4	102.4, 118.4	--	--	115.2	107.1, 123.2	115.9	107.8, 124.1
Low eGFR (<90 mL/min/1.73m^2)*								
Teen-LABS	24.1	11.9, 42.8	--	--	17.9	7.6, 36.5	0.0	0.0, 1.0
TODAY	23.8	13.3, 39.0	--	--	20.5	10.6, 36.1	10.3	3.9, 24.5
Elevated Urine Albumin/Creatinine Ratio								
Teen-LABS	25.7	11.9, 46.9	--	--	3.4	0.01, 22.6	4.6	0.01, 30.0
TODAY	19.2	10.6, 32.4	--	--	24.6	13.9, 39.7	19.7	10.1, 35.0

* Modeled values.
** No significant differences by group or group*time;
*** No significant differences by group, time, or group*time;

eTable 2. Admissions and Procedures by Subject

| Subject	Timeframe	Reason for admission	Length of re-admissi	Procedure, if any	Adjudication Decision▲
1	Postop day 1	Bowel obstruction		Reoperation for bowel obstruction	Related
2	Initial hospitalizati	Bowel obstruction		Reoperation for bowel obstruction	Related
3	Postop day 9	Wound dehiscence	2 days	Negative pressure wound therapy device placement	Related
4	Postop day 11	Gastric leak	24 days	Drain placed, endoluminal stent placement	Related
5	31d to 6mo	Staphyloccus skin infection	3 days	IV antibiotics	Not Related
6	31d to 6mo	Ulcer	3 days	Upper endoscopy and dilation	Related
3	31d to 6mo	Bowel obstruction	1 day	none	Related
7	6-12mo	Bipolar disorder	12 days	none	Not Related
8	6-12mo	Pneumonia	1 day	none	Not Related
9	12-24mo	Breast abscess	4 days	Incision and drainage	Not Related
10	12-24mo	Abdominal pain, nausea,	3 days		Unknown
6	12-24mo	Bowel obstruction	3 days	Lysis of adhesions for bowel obstruction	Related
3	12-24mo	Bowel obstruction, ulcer	8 days	Lysis of adhesions, EGD, percutaneous drain	Related
3	12-24mo	Abdominal abscess	6 days	Percutaneous drain	Related
3	12-24mo	Abdominal pain	3 days	none	Related
3	12-24mo	Gallbladder disease	1 day	Cholecystectomy	Not Related
3	12-24mo	Bowel obstruction	9 days	Lysis of adhesions, internal hernia reduction	Related
3	12-24mo	Ascites, infection	36 days	Upper endoscopy, gastrostomy, drainage	Related
3	12-24mo	Colocutaneous fistula	31 days	Upper endoscopy, laparotomy, diverting ileostomy	Related
11	12-24mo	Abdominal pain	1 day	Exploratory laparotomy	Related
11	12-24mo	Abdominal pain	2 days	Cholecystectomy	Related
12	12-24mo	Pregnancy	2 days	Childbirth	Not Related

▲ relatedness of the event to the original bariatric procedure was determined after review of clinical records by experts not otherwise involved with the study.

eFigure 1. Effect of Study Group Membership on Postoperative HbA$_{1c}$ by Adjusted Level of Missing Values

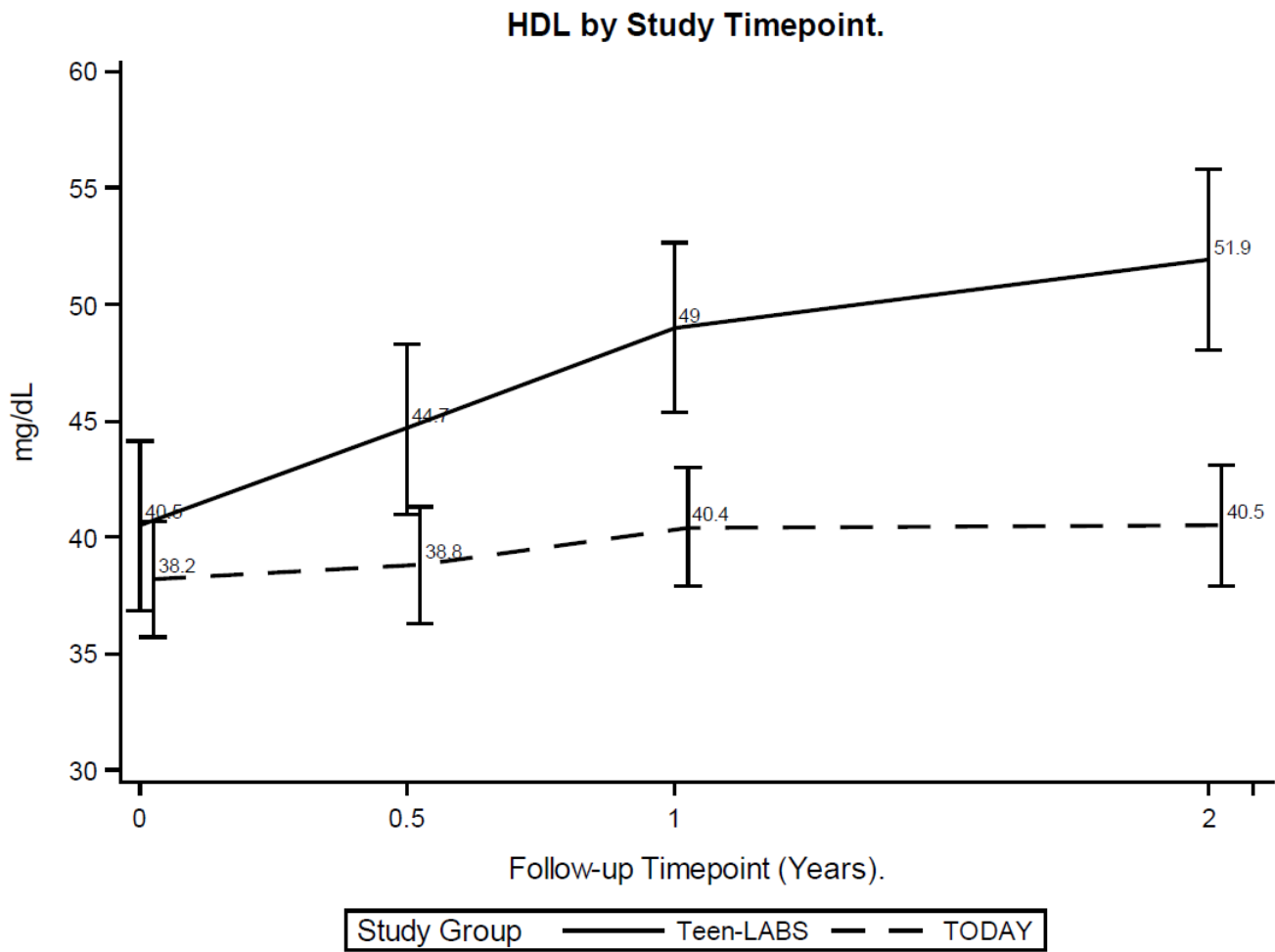**Effect of Study Group Membership on post-operative HbA1c by adjusted level of missing values.**
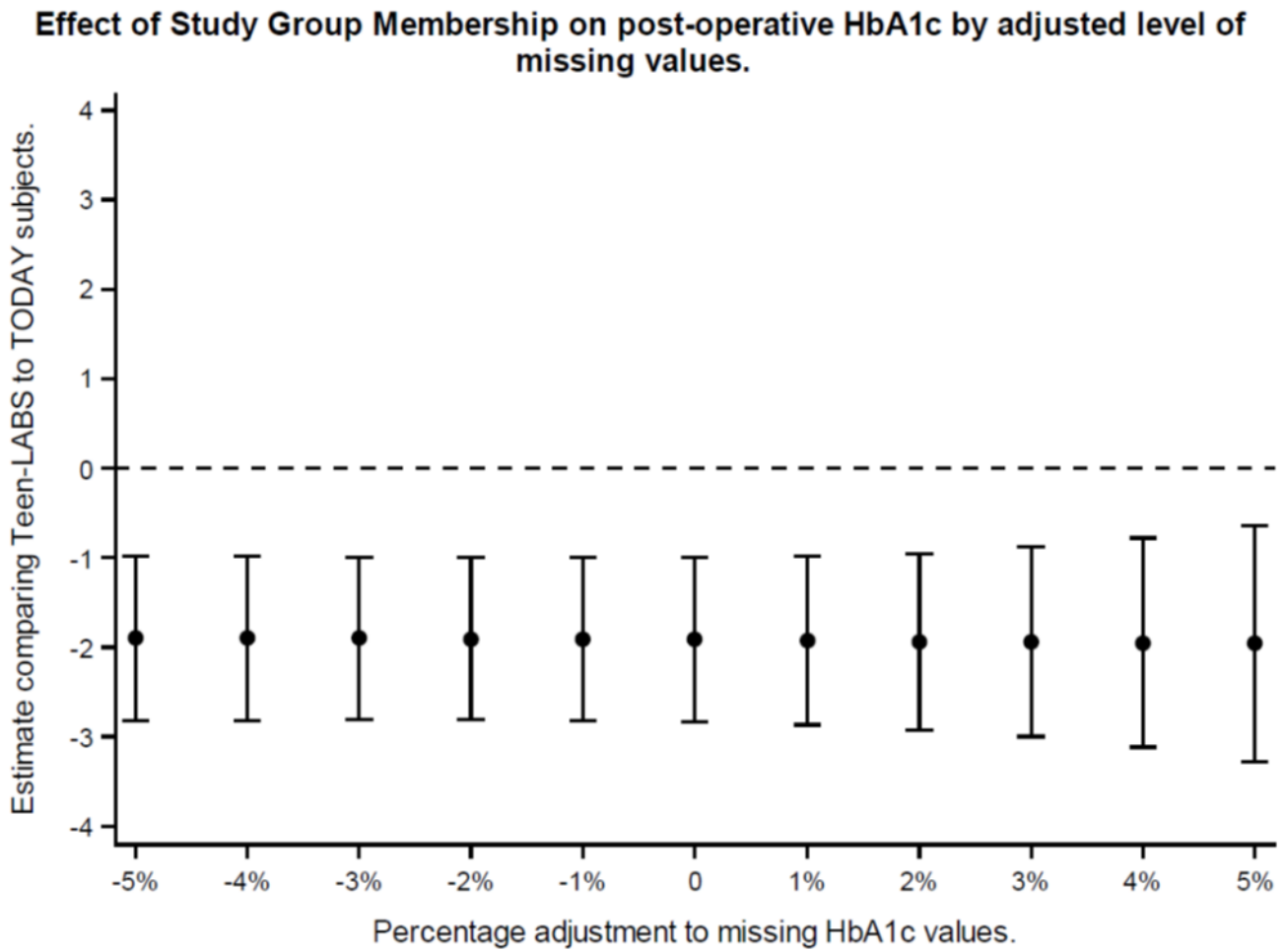
Sensitivity analysis was performed as described above in Appendix D.

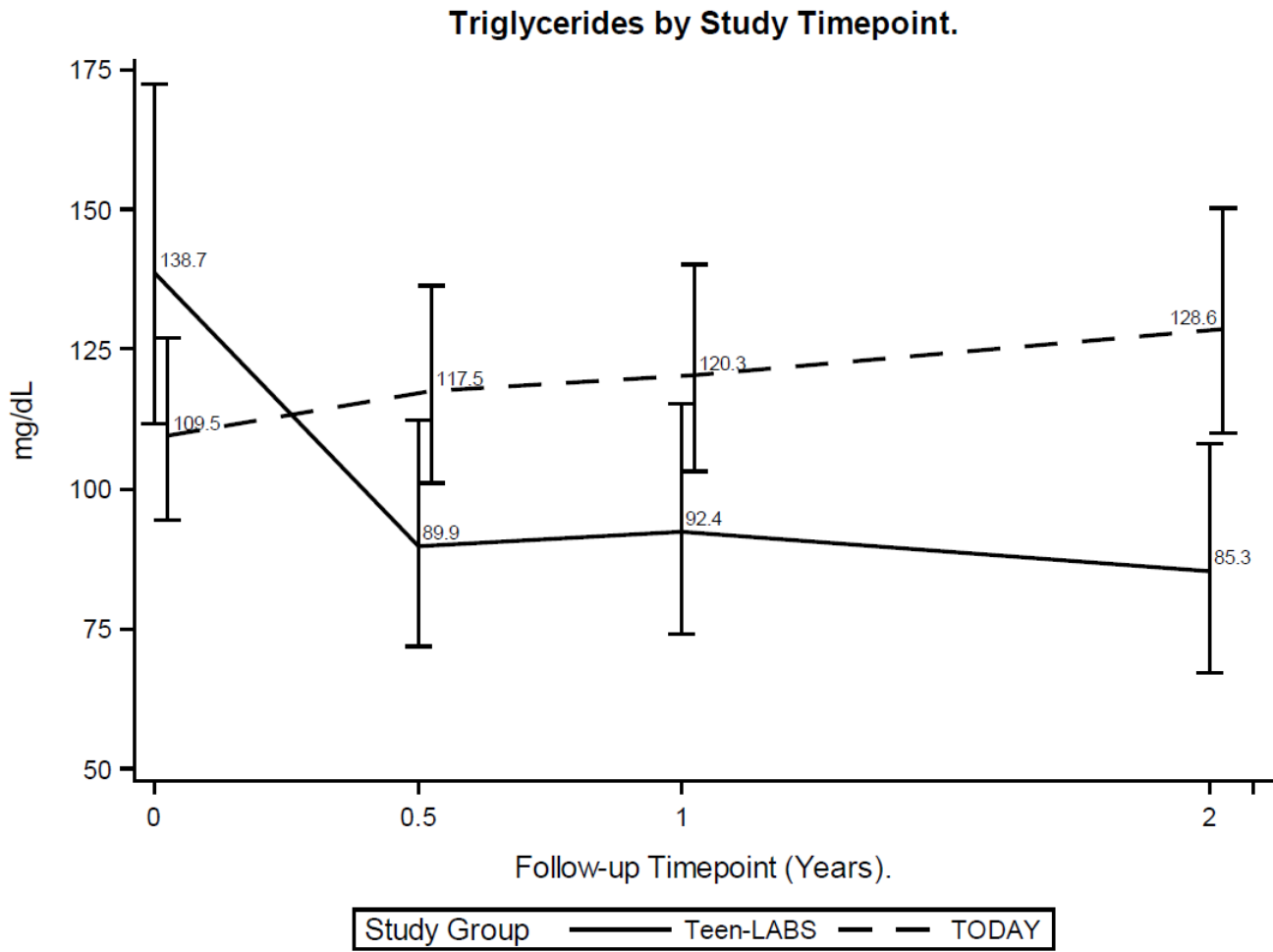**eFigure 2.** LDL By Study Timepoint
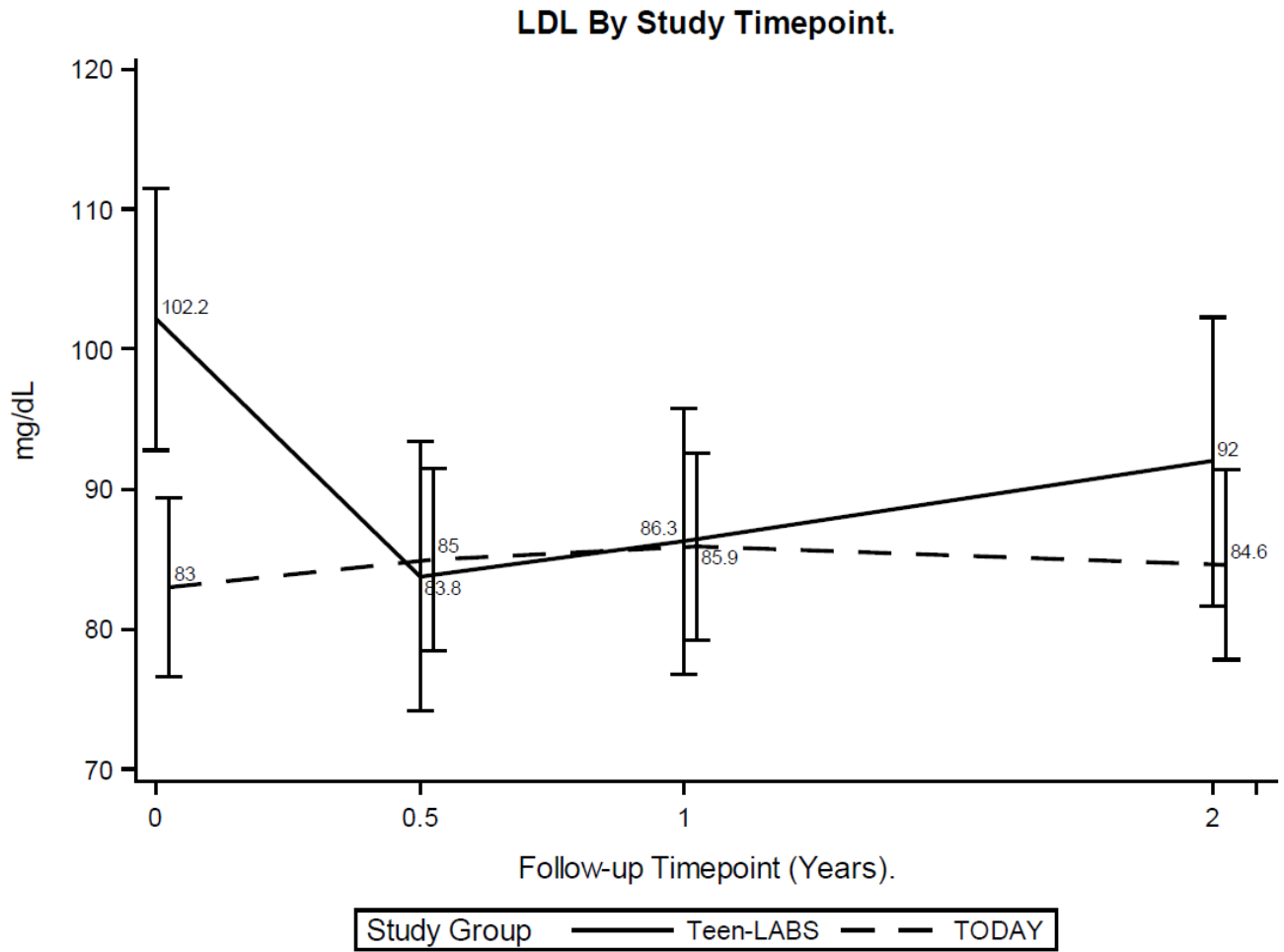
Serum concentration (median ± CI) of low density lipoprotein cholesterol was plotted for each study visit for each group

eFigure 3. HDL By Study Timepoint

HDL by Study Timepoint.

Serum concentration (median ± CI) of high density lipoprotein cholesterol was plotted for each study visit for each group

eFigure 4. Triglycerides by Study Timepoint

Serum concentration (median ± CI) of high density lipoprotein cholesterol was plotted for each study visit for each group

eReference

1. Larsson A, Malm J, Grubb A, Hansson LO. Calculation of glomerular filtration rate expressed in mL/min from plasma cystatin C values in mg/L. Scand J Clin Lab Invest 2004;64:25-30.