

Effect of Bariatric Surgery on CKD Risk

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ABSTRACT

Obesity is linked to the development and progression of CKD, but whether bariatric surgery protects against CKD is poorly understood. We, therefore, examined whether bariatric surgery influences CKD risk. The study included 2144 adults who underwent bariatric surgery from March of 2006 to April of 2009 and participated in the Longitudinal Assessment of Bariatric Surgery-2 Study cohort. The primary outcome was CKD risk categories as assessed by the Kidney Disease Improving Global Outcomes (KDIGO) consortium criteria using a combination of eGFR and albuminuria. Patients were 79% women and 87% white, with a median age of 46 years old. Improvements were observed in CKD risk at 1 and 7 years after surgery in patients with moderate baseline CKD risk (63% and 53%, respectively), high baseline risk (78% and 56%, respectively), and very high baseline risk (59% and 23%, respectively). The proportion of patients whose CKD risk worsened was $\leq 10\%$; five patients developed ESRD. Sensitivity analyses using year 1 as baseline to minimize the effect of weight loss on serum creatinine and differing eGFR equations offered qualitatively similar results. Treatment with bariatric surgery associated with an improvement in CKD risk categories in a large proportion of patients for up to 7 years, especially in those with moderate and high baseline risk. These findings support consideration of CKD risk in evaluation for bariatric surgery and further study of bariatric surgery as a treatment for high-risk obese patients with CKD.

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Bariatric surgery is the most effective and sustained of all weight reduction strategies and results in improvements in a variety of disease states,

including diabetes and hypertension.^{1–5} A related but relatively understudied area involves the effect of bariatric surgery on CKD.⁶ Interest in this topic has arisen because obesity is linked either directly or through intermediate diseases, like type 2 diabetes and hypertension, with the development and progression of CKD.^{7–10} This problem is compounded by the fact that nearly one in every two individuals with CKD in the United States is obese, a proportion that continues to rise.¹¹

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However, although bariatric surgery has been shown in people with obesity and normal kidney function to lower proteinuria and reverse glomerular hyperfiltration,^{12–14} the implications of these findings on risk for CKD are unclear. The few studies of bariatric surgery in patients with existing CKD suggested benefits but were limited by small sample size, short follow-up periods, or estimations of GFR that did not use the most accurate equation.^{15–18} In addition, previous studies did not control for the possibility that observed improvements in serum creatinine and eGFR, the two most commonly used markers of kidney filtration, were because of loss of muscle mass from weight loss rather than protective effects on the kidney.

The aims of our study were to assess how bariatric surgery influences CKD risk, identify patient factors associated with higher risk, and control for the distorting effects that weight loss may have on serum creatinine. The study was performed in a large, prospective, multicenter cohort that had regular follow-up.

RESULTS

Patient Characteristics

Baseline characteristics of the 2144 study participants are shown in Table 1. Seventy-nine percent of the study cohort were women, 87% were white, and the median age was 46 years old. Roux-en-Y gastric bypass was performed in 71% of participants, and laparoscopic adjustable banding was performed in 24% of participants. CKD risk categories at baseline were the following: 83.4% low, 11.9% moderate, 3.4% high, and 1.4% very high.

Factors Associated with CKD Risk Categories at Baseline

Factors in the univariable analysis that were significantly associated with a high or very high CKD risk at baseline are shown in Supplemental Table 1. After adjustment for other variables in the model, factors significantly and independently associated with high or very high CKD risk at baseline included age (per 5-year increase; 1.44; 95% confidence interval [95% CI], 1.27 to 1.62), men (1.84; 95% CI, 1.15 to 2.94), body mass index (BMI; per 5-kg/m² increase; 1.24; 95% CI, 1.08 to 1.43), and hemoglobin A1c (HbA1c; per percentage; 1.79; 95% CI, 1.56 to 2.05).

Effect of Bariatric Surgery on CKD Risk Categories over Time

Participants with accessible information on their CKD risk category at baseline and at least one follow-up visit and who underwent laparoscopic adjustable banding gastric bypass or Roux-en-Y gastric bypass were included in the longitudinal analysis ($n=1807$) (Supplemental Figure 1). Study participants were followed for up to 7 years after bariatric surgery. Among the 2144 participants for whom CKD risk category data were

Significance Statement

Obesity is linked to the development and progression of CKD, but whether bariatric surgery protects against CKD is not known. In this observational study of a bariatric surgery cohort, CKD risk was determined using KDIGO categories at baseline, yearly for 5 years, and in a subset for 7 years. In a high proportion of the patients with moderate or high baseline risk, bariatric surgery was associated with an improvement in the assigned CKD risk category. These findings support consideration of CKD risk in evaluation for bariatric surgery and further study of bariatric surgery as a treatment for high-risk patients with CKD.

available at baseline, 1449 participants had such data available at year 1, 1236 participants had data available at year 2, 1247 participants had data available at year 3, 1216 participants had data available at year 4, 1243 participants had data available at year 5, and 824 participants had data available at year 7. Figure 1 shows trends in CKD risk categories over time categorized by level of baseline risk. In patients with low CKD risk at baseline, the risk worsened on average in a relatively small proportion (4%–9%) of patients (*i.e.*, moved to a higher-risk category) between baseline and years 1–7. No patients in the low-risk group improved their risk because they were already in the lowest-risk category. In the moderate baseline CKD risk group, a large proportion of individuals improved over time. Over the first year, approximately 63% improved their risk category (*i.e.*, from moderate to low risk), and by 7 years, 53% of patients reduced their risk category compared with a much smaller proportion that worsened (approximately 5%–8% over 7 years). In the high CKD risk group at baseline, similar patterns were observed, with 78% improving their risk category by year 1 and 56% improving their risk category by year 7, with approximately 3%–10% worsening during the same time. In the very high CKD risk group at baseline, 59% improved their risk category by year 1, and 23% had improvement by year 7. No persons in the very high CKD risk category worsened their risk profile because they were already in the highest-risk category. Five patients developed ESRD during the follow-up period and were included in the very high–risk category. In a sensitivity analysis, these results did not qualitatively change after creatinine-based eGFR (eGFR_{cr}) or cystatin C–based eGFR (eGFR_{cys}) was substituted for creatinine- and cystatin C–based eGFR (eGFR_{cr-cys}) to estimate risk^{19,20} (Supplemental Figures 2 and 3). Separate median and mean data for eGFR_{cr-cys} and albumin-to-creatinine (ACR) are shown in Table 2, Table 3, Table 4, and Table 5 (with slopes in Supplemental Figures 4 and 5). Median eGFR using eGFR_{cr-cys} peaked by year 2 and slowly declined thereafter in the overall cohort and each CKD risk subgroup. ACR levels remained stable in the low-risk group, dropped dramatically in the moderate- and high-risk groups, and ultimately worsened in the very high–risk group. Supplemental Tables 2–5 show mean and median eGFR changes using eGFR_{cr} or eGFR_{cys}.

Table 1. Baseline characteristics by CKD risk category

Variables	Low Risk	Moderate Risk	High Risk	Very High Risk
No. (%)	1788 (83.4)	254 (11.9)	73 (3.4)	29 (1.4)
Renal parameters				
eGFR _{cr-cys} , ml/min per 1.73 m ² , median (IQR)	100 (87–111)	92 (66–107)	63 (43–98)	36 (27–41)
eGFR _{cr} , ml/min per 1.73 m ² , median (IQR)	105 (93–115)	99 (78–113)	74 (50–102)	38 (31–48)
eGFR _{cys} , ml/min per 1.73 m ² , median (IQR)	96 (81–109)	84 (58–106)	58 (40–88)	31 (26–41)
ACR, mg/g, median (IQR)	6.0 (4.2–9.6)	48.0 (32.1–96.7)	325.5 (14.2–495.5)	345.4 (13.4–1185.7)
Serum creatinine, mg/dl, median (IQR)	0.71 (0.63–0.82)	0.80 (0.67–0.95)	1.01 (0.72–1.28)	1.78 (1.37–2.07)
Serum cystatin C, mg/L, median (IQR)	0.86 (0.76–0.97)	0.95 (0.79–1.22)	1.24 (0.89–1.61)	1.89 (1.62–2.22)
Demographic characteristics				
Age, yr, median (IQR)	45 (36–53)	48 (39–56)	54 (43–60)	57 (52–63)
Sex, no. (%)				
Men	326 (18.2)	85 (33.5)	24 (32.9)	13 (44.8)
Women	1462 (81.8)	169 (66.5)	49 (67.1)	16 (55.2)
Race, no. (%)				
White	1552 (86.8)	221 (87.0)	61 (83.6)	26 (89.7)
Black	185 (10.3)	25 (9.8)	5 (6.8)	2 (6.9)
Other	51 (2.9)	8 (3.1)	7 (9.6)	1 (3.4)
Annual household income, no. (%)				
<\$25,000	271 (16.6)	50 (21.5)	15 (23.1)	4 (15.4)
\$25,000–\$49,999	439 (26.9)	51 (21.9)	15 (23.1)	9 (34.6)
\$50,000–\$74,999	400 (24.5)	58 (24.9)	14 (21.5)	5 (19.2)
\$75,000–\$99,999	262 (16.1)	35 (15.0)	13 (20.0)	4 (15.4)
≥\$100,000	260 (15.9)	39 (16.7)	8 (12.3)	4 (15.4)
Education, no. (%)				
High school or less	378 (22.6)	49 (20.7)	19 (27.5)	6 (21.4)
Some college	692 (41.4)	98 (41.4)	29 (42.0)	12 (42.9)
College degree or higher	602 (36.0)	90 (38.0)	21 (30.4)	10 (35.7)
Medical insurance type, no. (%)				
No insurance	19 (1.1)	2 (0.8)	0 (0)	0 (0)
Medicaid	146 (8.7)	33 (13.9)	7 (10.1)	1 (3.6)
Medicare	159 (9.5)	39 (16.5)	16 (23.2)	6 (21.4)
Tricare	44 (2.6)	9 (3.8)	5 (7.2)	3 (10.7)
Private	1148 (68.7)	129 (54.4)	38 (55.1)	17 (60.7)
Other/unknown insurance type	154 (9.2)	25 (10.5)	3 (4.3)	1 (3.6)
Anthropometric measures				
BMI, kg/m ² , median (IQR)	45.6 (41.6–51.0)	46.8 (42.7–52.8)	46.0 (42.1–52.6)	48.1 (41.6–51.9)
Weight, kg, median (IQR)	128 (114–145)	136 (117–156)	133 (115–155)	135 (119–152)
Waist circumference, cm				
n	1695	239	69	26
Median (IQR)	130 (120–141)	137 (126–148)	138 (127–149)	140 (129–148)
Percentage body fat				
n	1507	213	60	21
Median (IQR)	51.3 (48.5–53.8)	50.8 (46.8–54)	50.7 (46.3–53.3)	48.9 (38.3–53.9)
Glycemic/insulin data				
Diabetes				
n	1752	249	72	29
No. (%)	486 (27.7)	128 (51.4)	53 (73.6)	24 (82.8)
Insulin, μIU/ml				
n	1523	222	65	26
Median (IQR)	18.7 (12.7–28.9)	21.9 (16–33.2)	24.3 (16.4–39.7)	19.2 (12–38.7)
Fasting glucose, mg/dl				
n	1516	221	65	26
Median (IQR)	97 (89–110)	106 (94–137)	114 (100–158)	112 (89–186)
HOMA_IR ^a				
n	1515	221	65	26
Median (IQR)	4.6 (2.9–7.6)	6.3 (4.2–10.7)	8.0 (4.9–14.6)	7.2 (3.8–10.4)

Table 1. Continued

Variables	Low Risk	Moderate Risk	High Risk	Very High Risk
HbA1c, %				
<i>n</i>	1777	252	73	29
Median (IQR)	5.5 (5.2–6.1)	6 (5.5–7.3)	6.8 (5.9–8.4)	6.6 (5.7–7.9)
BP				
Hypertension				
<i>n</i>	1730	247	71	29
No. (%)	1112 (64.3)	194 (78.5)	61 (85.9)	28 (96.6)
SBP				
<i>n</i>	1750	251	72	29
Median (IQR)	128 (120–139)	132 (120–142)	130 (119–140)	131 (121–147)
DBP				
<i>n</i>	1750	251	72	29
Median (IQR)	80 (73–85)	80 (71–86)	72 (65–81)	77 (68–81)
Habits				
Smoking, no. (%)				
Never	1011 (56.5)	142 (55.9)	33 (45.2)	15 (51.7)
Current	80 (4.5)	9 (3.5)	4 (5.5)	1 (3.4)
Former	697 (39.0)	103 (40.6)	36 (49.3)	13 (44.8)
Use of ACE inhibitor or ARB medications, no. (%)	566 (31.7)	124 (48.8)	44 (60.3)	19 (65.5)
Bariatric surgery type, no. (%)				
Roux-en-Y gastric bypass	1287 (72.0)	170 (66.9)	53 (72.6)	20 (69)
Laparoscopic adjustable band	435 (24.3)	68 (26.8)	14 (19.2)	6 (20.7)
Sleeve gastrectomy	34 (1.9)	12 (4.7)	4 (5.5)	2 (6.9)
BPDS	15 (0.8)	2 (0.8)	0 (0)	0 (0)
Banded gastric bypass	17 (1)	2 (0.8)	2 (2.7)	1 (3.4)

SI conversion factors are as follows. To convert serum creatinine to micromoles per liter, multiply by 76.26. To convert insulin to picomoles per liter, multiply by 6.945. To convert glucose to millimoles per liter, multiply by 0.0555. To convert HbA1c to proportion of total Hb, multiply by 0.01. ACE inhibitor can indicate ACE inhibitor, ACE inhibitor/calcium channel blocker combination, or ACE inhibitor/thiazide combination. ARB can indicate angiotensin II receptor antagonist or angiotensin II receptor antagonist/thiazide combination. IQR, interquartile range; HOMA_{IR}, insulin resistance by homeostatic model assessment; SBP, systolic BP; DBP, diastolic BP; BPDS, biliopancreatic diversion with duodenal switch.

^aHOMA_{IR} was calculated as [insulin (microunits per milliliter) × glucose (milligrams per deciliter)]/405.

Because weight loss after bariatric surgery leads to loss of muscle in addition to fat²¹ and because muscle is the major source of endogenous creatinine,²² we performed a sensitivity analysis in which the baseline was redefined as year 1, which was when weight loss in most patients plateaued⁵ (Figure 2). This was done to minimize the likelihood that any observed improvement in CKD risk categories could be related to muscle loss. Only 5% of individuals with low CKD risk at baseline went on to develop higher risk in year 2, and only 10% had higher risk in year 7. A substantial proportion of persons improved their CKD risk in the moderate (51% in year 2 and 35% by year 7) and high (58% in year 2 and 36% by year 7) baseline risk groups, with only a modest proportion developing higher CKD risk (moderate baseline risk group: 10% at year 2 and 19% at year 7; high baseline risk: 8% in year 2 and 20% in year 7). Patients with very high baseline CKD risk had a lower proportion of individuals whose risk improved over time (30% in year 2 and 36% by year 7). Results were not qualitatively different using eGFR_{cr} or eGFR_{cys} (Supplemental Figures 6 and 7).

In univariable analysis, baseline characteristics significantly associated with developing moderate, high, or very high CKD

risk during the follow-up period are shown in Supplemental Table 6. Of note, CKD risk over time was dependent on age (age and visit interaction $P < 0.001$) (Supplemental Figure 8, Supplemental Table 7). For example, a 38-year old participant had a 52% lower risk of having moderate, high, or very high CKD risk at year 3 compared with baseline (relative risk [RR], 0.51; 95% CI, 0.37 to 0.69) compared with only a 28% lower risk (RR, 0.72; 95% CI, 0.63 to 0.81) for a 55-year-old participant.

In the multivariable model (Table 6), variables significantly associated with a high or very high CKD risk included baseline BMI (RR, 1.12; 95% CI, 1.06 to 1.20 per 5-kg/m² increase), HbA1c (1.25; 95% CI, 1.19 to 1.31 per 1% increase), use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs; 1.38; 95% CI, 1.13 to 1.68), men (RR, 1.34; 95% CI, 1.10 to 1.63), lack of private medical insurance (1.34; 95% CI, 1.11 to 1.61), and less weight lost (1.05; 95% CI, 1.01 to 1.09 per 5% lower). Similar to the unadjusted model, CKD risk categories over time were age dependent (Supplemental Table 8). Replacing HbA1c in the model with presence of diabetes (RR, 1.85; 95% CI, 1.52 to 2.25) or percentage weight loss from baseline with reduction in waist

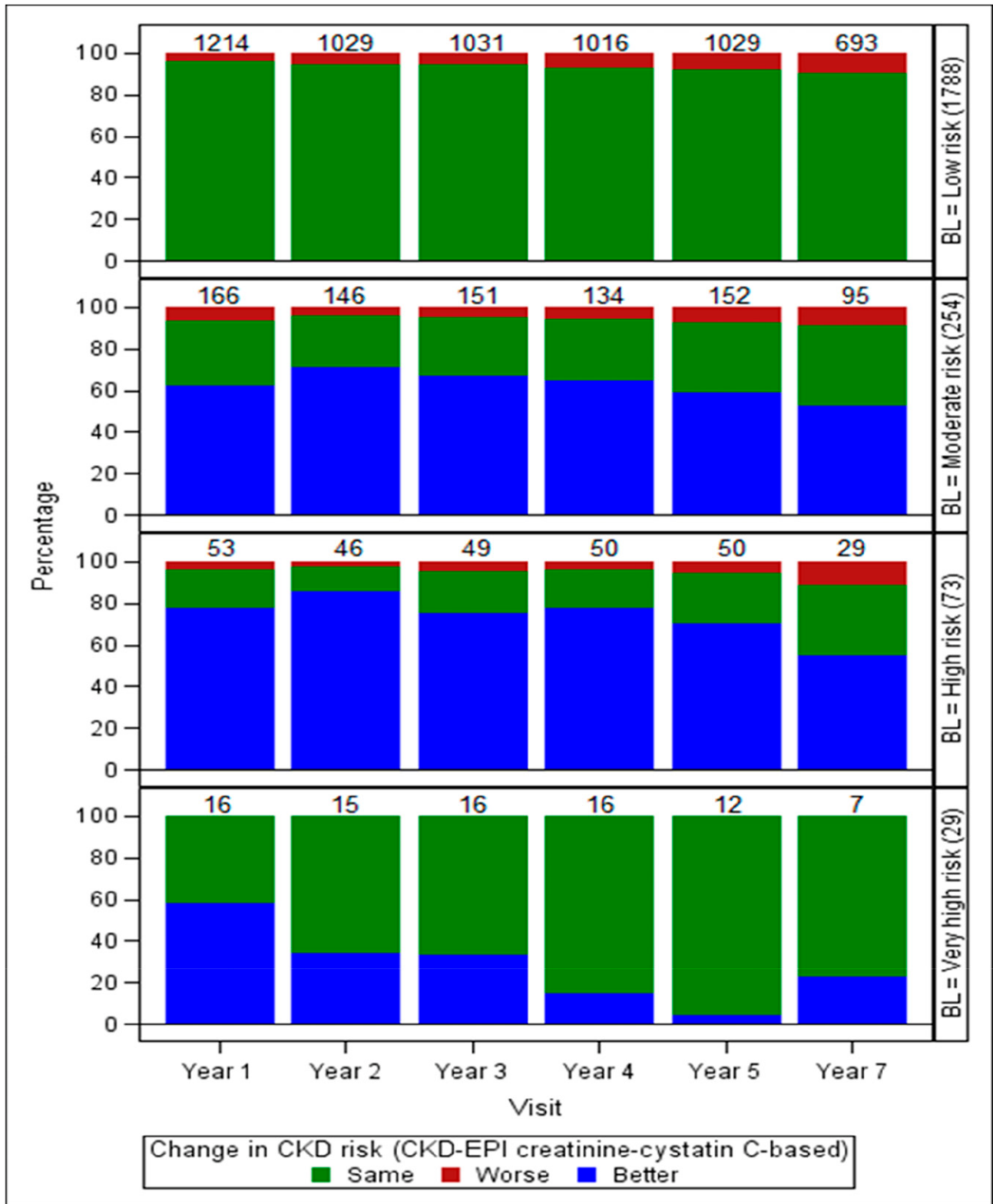


Figure 1. Trend of overall improvement in CKD risk categories over 7-year period after bariatric surgery. Predicted proportions are obtained from generalized linear mixed models stratified by baseline prognostic CKD risk category and include visit and missing related baseline variables, age, race, and smoking status. The numbers above each bar represent the total numbers of participants with accessible data at each time point. The total number at baseline is shown on the far right of each row. BL, baseline.

Table 2. Median eGFR_{cr-cys}^a over a 7-year follow-up period by baseline CKD risk category

Visit (N) ^b	Overall		Low Risk		Moderate Risk		High Risk		Very High Risk	
	N ^c	Median (IQR)	N ^d	Median (IQR)	N ^d	Median (IQR)	N ^d	Median (IQR)	N ^d	Median (IQR)
Baseline (2453)	2330	98 (84–110)	1788	100 (87–111)	254	92 (66–107)	73	63 (43–98)	29	36 (27–41)
12 mo (2397)	1696	103 (89–114)	1260	105 (93–115)	178	96 (74–110)	57	75 (59–101)	17	43 (39–60)
24 mo (2360)	1453	104 (90–115)	1076	106 (95–117)	159	98 (78–111)	51	77 (61–103)	17	48 (37–58)
36 mo (2372)	1434	103 (89–114)	1067	105 (93–115)	156	98 (80–113)	50	73 (62–105)	16	45 (29–56)
48 mo (2373)	1394	101 (85–111)	1045	103 (90–113)	141	96 (76–108)	52	69 (59–93)	16	36 (17–50)
60 mo (2378)	1455	98 (81–110)	1070	100 (86–111)	161	86 (66–105)	55	68 (59–93)	13	38 (13–44)
84 mo (2360)	937	91 (78–105)	716	94 (82–106)	100	81 (64–104)	31	69 (52–90)	8	25 (10–44)

The difference between the N values in the first and second columns is the number of participants who do not have data to calculate eGFR_{cr-cys}, whereas the difference between the N in the second column and the sum of the N values in columns 3–6 is the number of participants who were missing a CKD risk category because of missing ACR data. IQR, interquartile range.

^aMilliliters per minute per 1.73 m².

^bTotal number of available participants at each time point.

^cNumber of participants with sufficient data to calculate eGFR_{cr-cys}.

^dNumber of participants with sufficient data to assess CKD risk category using eGFR_{cr-cys} and ACR.

circumference from baseline (RR, 1.05; 95% CI, 1.02 to 1.08 per 5-cm decrease) did not qualitatively change results. Importantly, presence of hypertension, baseline systolic BP, and type of bariatric surgery were not significantly associated with CKD risk categories during follow-up.

DISCUSSION

The study’s major finding was that bariatric surgery resulted in lower CKD risk in a substantial proportion of patients throughout the 7-year follow-up period. Reduction in risk was most pronounced in persons with high baseline risk. However, improvements were also observed in patients with moderate and to a lesser extent, very high baseline risk.

We identified several variables that conferred higher CKD risk after bariatric surgery in addition to traditional risk factors, like men, greater adiposity, and diabetes. The higher risk associated with ACE inhibitors/ARBs may reflect the fact that their use was reserved for sicker patients in light of reports

suggesting that they offer renoprotection in people with obesity.²³ Similarly, the protective association with private medical insurance could be indicative of better access to health care. What is notable is that greater weight loss and not the mechanism through which weight loss was achieved (*i.e.*, type of bariatric surgery) was an independent predictor of reduced CKD risk. This important and novel finding is consistent with reports in rats in which equivalent weight loss from surgical or medical interventions led to similar histologic improvements in the kidney.²⁴

In comparison with the previous literature,^{15–18,25} our study offers several important strengths, including a prospective multicenter design, large size, and long follow-up period. Additionally, we estimated GFR using eGFR_{cr-cys}, which we previously identified as the most accurate in the bariatric surgery population¹² and that incorporates the two major and complementary endogenous filtration markers serum creatinine and cystatin C.²⁰ Because both eGFR and albuminuria were available at regular time points, we were also able to assess CKD risk using the Kidney Disease Improving Global

Table 3. Mean eGFR_{cr-cys}^a over a 7-year follow-up period by baseline CKD risk category

Visit (N) ^b	Overall		Low Risk		Moderate Risk		High Risk		Very High Risk	
	N ^c	Mean (SD)	N ^d	Mean (SD)	N ^d	Mean (SD)	N ^d	Mean (SD)	N ^d	Mean (SD)
Baseline (2453)	2330	96 (21.4)	1788	99 (16.9)	254	88 (24.6)	73	71 (29.1)	29	34 (12.3)
12 mo (2397)	1696	100 (21.3)	1260	104 (17.9)	178	92 (23.7)	57	78 (25.5)	17	48 (17.7)
24 mo (2360)	1453	102 (20.9)	1076	105 (17.2)	159	94 (21.7)	51	80 (26.4)	17	50 (21.8)
36 mo (2372)	1434	100 (21.2)	1067	104 (17.6)	156	94 (24.2)	50	79 (26.3)	16	45 (21.6)
48 mo (2373)	1394	97 (22.1)	1045	101 (18.6)	141	92 (22.6)	52	74 (24.4)	16	36 (20.2)
60 mo (2378)	1455	95 (22.1)	1070	98 (18.6)	161	86 (24.6)	55	74 (24.8)	13	33 (17.6)
84 mo (2360)	937	90 (21.8)	716	93 (18.8)	100	82 (24.6)	31	73 (24.0)	8	31 (25.1)

The difference between the N values in the first and second columns is the number of participants who do not have data to calculate eGFR_{cr-cys}, whereas the difference between the N in the second column and the sum of the N values in columns 3–6 is the number of participants who were missing a CKD risk category because of missing ACR data.

^aMilliliters per minute per 1.73 m².

^bTotal number of available participants at each time point.

^cNumber of participants with sufficient data to calculate eGFR_{cr-cys}.

^dNumber of participants with sufficient data to assess CKD risk category using eGFR_{cr-cys} and ACR.

Table 4. Median ACR^a over a 7-year follow-up period by baseline CKD risk category

Visit (N) ^b	Overall		Low Risk		Moderate Risk		High Risk		Very High Risk	
	N ^c	Median (IQR)	N ^d	Median (IQR)	N ^d	Median (IQR)	N ^d	Median (IQR)	N ^d	Median (IQR)
Baseline (2453)	2192	6.8 (4.5–13.3)	1788	6.0 (4.2–9.6)	254	48.0 (32.1–96.7)	73	325.6 (14.2–495.5)	29	245.4 (13.4–1185.8)
12 mo (2397)	1618	6.5 (4.4–10.7)	1217	5.9 (4.3–9.1)	167	11.9 (6.2–32.0)	53	21.2 (8.1–73.8)	16	237.7 (13.9–1316.6)
24 mo (2360)	1386	6.4 (4.3–11.3)	1036	5.9 (4.1–9.3)	148	12.1 (5.9–26.4)	46	15.4 (6.9–52.8)	15	761.3 (81.6–1472.4)
36 mo (2372)	1414	6.5 (4.4–11.9)	1053	5.8 (4.2–9.6)	151	12.1 (6.6–33.6)	49	25.1 (12.3–69.9)	16	484.2 (118.9–905.6)
48 mo (2373)	1383	6.4 (4.3–11.8)	1035	5.9 (4.1–9.9)	138	12.3 (5.1–34.8)	50	18.4 (6.4–85.5)	17	385.5 (157.1–1056.5)
60 mo (2378)	1424	6.6 (4.4–12.6)	1050	6.0 (4.1–10.1)	153	12.8 (5.9–32.5)	50	28.2 (10.8–89.7)	12	273.2 (74.4–1618.4)
84 mo (2360)	931	6.9 (4.2–12.0)	706	6.1 (4.0–10.1)	101	13.5 (5.9–30.4)	29	25.7 (6.9–79.5)	9	722.2 (424.3–1014.5)

The difference between the *N* values in the first and second columns is the number of participants who do not have data to calculate eGFR_{cr-cys}, whereas the difference between the *N* in the second column and the sum of the *N* values in columns 3–6 is the number of participants who were missing a CKD risk category because of missing ACR data. IQR, interquartile range.

^aMg albumin/g creatinine.

^bTotal number of available participants at each time point.

^cNumber of participants with sufficient data to calculate eGFR_{cr-cys}.

^dNumber of participants with sufficient data to assess CKD risk category using eGFR_{cr-cys} and ACR.

Outcomes (KDIGO) criteria, which was validated in over 1.5 million persons and offers more clinical information than the traditional CKD staging system on the basis of eGFR alone.²⁶ Substituting eGFR_{cr} and eGFR_{cys} for eGFR_{cr-cys} gave similar results. To account for the fact that weight loss might lower serum creatinine (and thereby, spuriously raise eGFR and improve the CKD risk profile), we performed an additional analysis using year 1 as baseline. Although a lower proportion of patients had improvement in CKD risk after surgery, results were qualitatively similar to the main analysis. This suggests that, although weight reduction–related changes in muscle mass influence eGFR to a certain extent, bariatric surgery in fact has salutary effects on kidney health.

We also found that patients in higher baseline CKD risk categories benefited from bariatric surgery. This is an important observation not only because these individuals are most likely to have progression of CKD to ESRD but also, because they are at higher surgical risk.²⁷ In fact, it is possible that our findings may have underestimated the benefits of bariatric surgery if some of the patients whose risk status remained

unchanged after surgery would have naturally progressed without weight loss. Similarly, the relatively lower protective effect noted in older patients should not necessarily be interpreted as indicating that bariatric surgery is not beneficial in such patients, because their CKD risk could have been higher had surgery not been performed. Of note, although a small proportion of patients increased their CKD risk during follow-up, this could simply have reflected progression of their original disease. Alternatively, these patients could have suffered from complications of AKI, kidney stones, or even oxalate nephropathy, all of which have been reported after bariatric surgery.⁶ Clarification of these issues requires a control group, which our study lacked.

Our study findings reinforce previous interest in bariatric surgery as a potential treatment option for CKD.⁶ Although bariatric surgery is a costly intervention with real risks, few effective treatments are currently available to slow or stop the progression of CKD, which is associated with rates of hospitalization, rehospitalization, and death that are several times higher than those in patients without CKD.²⁸ The risks of

Table 5. Mean ACR^a over a 7-year follow-up period by baseline CKD risk category

Visit (N) ^b	Overall		Low Risk		Moderate Risk		High Risk		Very High Risk	
	N ^c	Mean (SD)	N ^d	Mean (SD)	N ^d	Mean (SD)	N ^d	Mean (SD)	N ^d	Mean (SD)
Baseline (2453)	2192	44.4 (291.92)	1788	7.9 (5.52)	254	67.9 (58.40)	73	429.3 (638.55)	29	1137.2 (1963.37)
12 mo (2397)	1618	27.8 (176.96)	1217	9.7 (20.52)	167	49.3 (133.12)	53	72.2 (115.32)	16	843.2 (1108.12)
24 mo (2360)	1386	37.1 (327.39)	1036	11.2 (31.91)	148	28.0 (39.93)	46	62.0 (121.30)	15	1379.9 (2034.14)
36 mo (2372)	1414	27.6 (181.16)	1053	11.2 (30.89)	151	37.2 (106.68)	49	96.4 (164.50)	16	956.1 (1365.50)
48 mo (2373)	1383	32.5 (260.25)	1035	12.2 (57.80)	138	39.6 (75.43)	50	73.7 (121.25)	17	1223.4 (1997.80)
60 mo (2378)	1424	30.6 (221.11)	1050	11.0 (26.38)	153	46.4 (97.82)	50	116.4 (215.94)	12	1151.0 (2035.49)
84 mo (2360)	931	35.9 (333.44)	706	11.4 (42.43)	101	38.8 (68.27)	29	95.6 (161.96)	9	1944.9 (2905.37)

The difference between the *N* values in the first and second columns is the number of participants who do not have data to calculate eGFR_{cr-cys}, whereas the difference between the *N* in the second column and the sum of the *N* values in columns 3–6 is the number of participants who were missing a CKD risk category because of missing ACR data.

^aMg albumin/g creatinine.

^bTotal number of available participants at each time point.

^cNumber of participants with sufficient data to calculate eGFR_{cr-cys}.

^dNumber of participants with sufficient data to assess CKD risk category using eGFR_{cr-cys} and ACR.

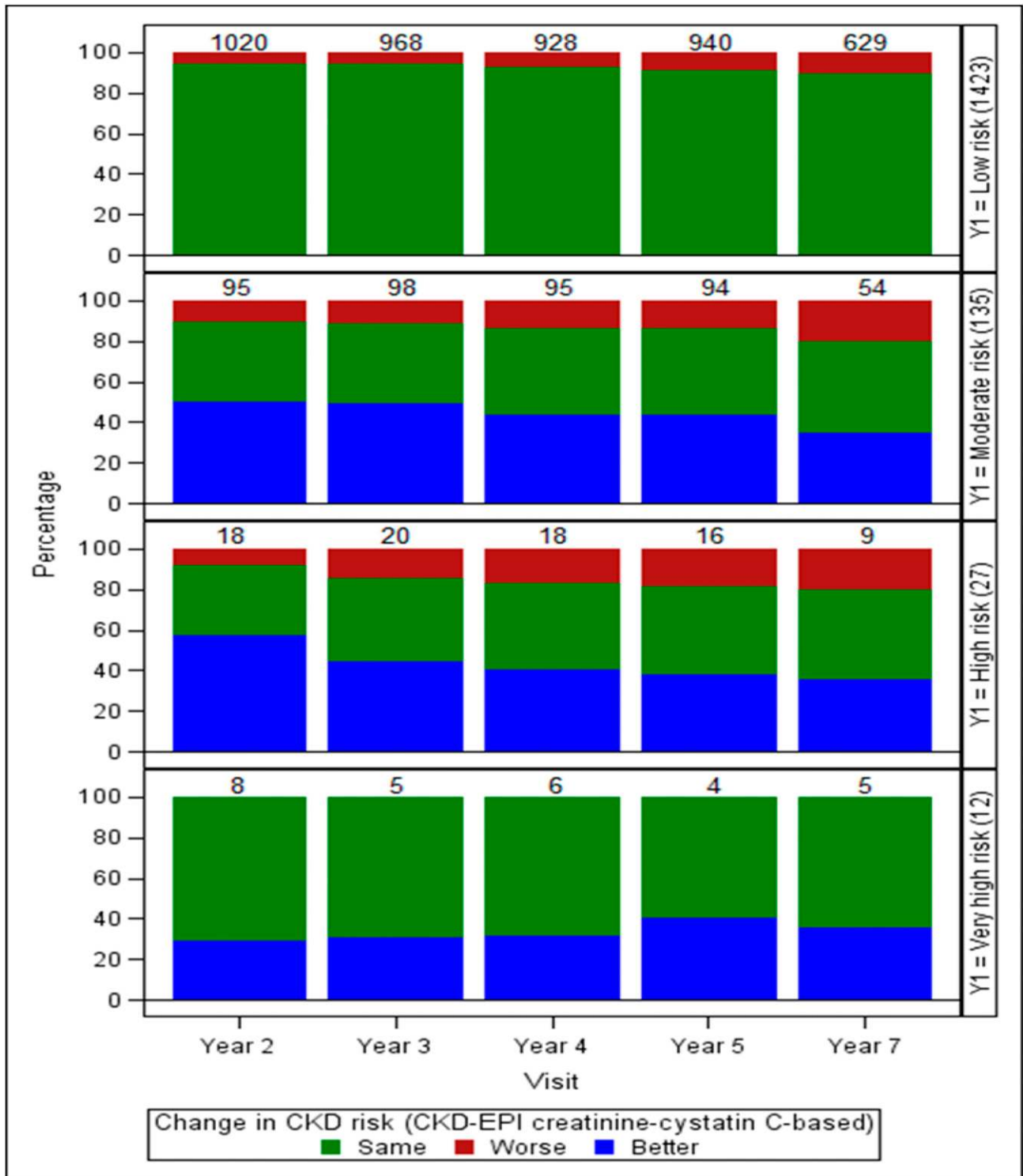


Figure 2. Trend of overall improvement in CKD risk categories after bariatric surgery using year 1 post-surgery as baseline. Predicted proportions are obtained from generalized linear mixed models stratified by baseline CKD risk category and include visit and missing related baseline variables, age, race, and smoking status. The numbers above each bar represent the total numbers of participants with accessible data at each time point. The total number at year 1 is shown on the far right of each row. Y1, year 1.

Table 6. Variables associated with moderate, high, or very high CKD risk over time in adjusted model

Covariate ^a	RR Ratio (95% CI)	P Value
Presurgery characteristics		
Age (per 5-yr increase)		<0.001
Baseline	1.13 (1.07 to 1.20)	<0.001
Year 1	1.12 (1.04 to 1.20)	0.003
Year 2	1.20 (1.11 to 1.30)	<0.001
Year 3	1.25 (1.15 to 1.36)	<0.001
Year 4	1.27 (1.17 to 1.38)	<0.001
Year 5	1.27 (1.18 to 1.36)	<0.001
Year 7	1.31 (1.21 to 1.42)	<0.001
Men	1.32 (1.09 to 1.59)	0.004
BMI, kg/m ² , per 5-kg/m ² increase	1.10 (1.04 to 1.17)	0.001
HbA1c, %, per 1% increase	1.24 (1.18 to 1.30)	<0.001
SBP, mm Hg, per 5-mm Hg increase	1.02 (0.99 to 1.05)	0.12
Use of ACE inhibitor or ARB medications	1.37 (1.13 to 1.65)	0.001
No private medical insurance	1.38 (1.15 to 1.66)	0.001
Postsurgery characteristics		
Weight loss from baseline, %, per 5% decrease	1.05 (1.01 to 1.08)	0.02
Surgery type		
LAGB versus RYGB	1.17 (0.96 to 1.44)	0.13
Visit ^b		
Year 1 versus baseline	0.88 (0.69 to 1.13)	0.31
Year 2 versus baseline	0.83 (0.63 to 1.10)	0.19
Year 3 versus baseline	0.77 (0.59 to 1.02)	0.07
Year 4 versus baseline	0.82 (0.63 to 1.07)	0.14
Year 5 versus baseline	1.00 (0.78 to 1.27)	0.95
Year 7 versus baseline	1.15 (0.89 to 1.50)	0.29

SBP, systolic BP; LAGB, laparoscopic adjustable banding gastric bypass; RYGB, Roux-en-Y gastric bypass.

^aA generalized linear mixed model was used to test the associations of covariates with moderate or higher prognostic risk for CKD. Independent variables with *P* values <0.40 in the univariable analyses (*i.e.*, age, sex, BMI, HbA1c, systolic BP, use of ACE inhibitor or ARB, no private medical insurance, education, annual household income, surgery type, and percentage weight loss from baseline) were considered and retained if the *P* value was <0.20 adjusted for baseline variables related to missing follow-up assessment of prognostic risk for CKD (*i.e.*, race, smoking status, and site; *n*=1623).

^bCalculated at median age of 47 years old.

morbidity and death rise further with progression to ESRD, when average annual costs can reach nearly \$100,000.²⁸ Therefore, bariatric surgery may be a reasonable therapeutic option for select patients.

In addition to its strengths, the study has limitations, the most important of which is a lack of comparator or control groups, making it challenging to ascertain the relative kidney-related benefits and risks of bariatric surgery. An additional limitation was the modest proportion of patients with existing CKD, which explained why so few participants progressed to ESRD. These limitations can be overcome by designing weight loss trials that include controls and enroll patients with established CKD. Missing data were another limitation, and they were related to patients either missing follow-up appointments or refusing blood draws. However, many of the missing visits in year 7 occurred as a result of the study being closed before the 7-year anniversary date; therefore, these can be regarded as missing completely at random and less likely to introduce bias into our analyses. Other missing visits were treated as missing at

random and were appropriately accounted for by including predictors of missing data into the regression models. In addition, the analysis that used year 1 as baseline further reduced concerns about missing data, because there was 1 less year of potential missing data. Another limitation involved an abrupt and modest drift in cystatin C measurements early on in the study that was related to the manufacturer's calibrator method. However, the robustness of our results is shown by the fact that eGFR_{cr} (using rigorous calibration) did not qualitatively change our findings. Finally, although it is reasonable to assume that the predominant causes of CKD were diabetic kidney disease (because about one third of the population had diabetes) or obesity-related glomerulopathy, the lack of kidney biopsy data prevents confirmation.

In conclusion, treatment of severe obesity with bariatric surgery was associated with improvements in CKD risk categories for up to 7 years in a large proportion of patients, especially those with moderate to high baseline risk. These findings support consideration of CKD risk in evaluation for bariatric surgery and further study of bariatric surgery as a treatment for high-risk obese patients with CKD.

CONCISE METHODS

Study Population

The study was made up of participants in the Longitudinal Assessment of Bariatric Surgery-2 (LABS-2) Study, a National Institutes of Health–sponsored, prospective, longitudinal, multicenter trial designed to study the long-term safety and efficacy of bariatric surgery and its effects on a variety of health-related parameters (trial registration: NCT00465829).²⁹ The LABS-2 Study participants were at least 18 years old and underwent first-time bariatric procedures between March of 2006 and April of 2009.

Measures

Kidney disease was a prespecified end point of the LABS-2 trial, so serum creatinine, serum cystatin C, and the urine ACR were routinely measured. The study assessed CKD risk using the nomenclature system developed by the KDIGO consortium, which is the most recent internationally accepted criteria established for CKD.²⁶ The classification offers four CKD risk categories on the basis of a combination of eGFR_{cr-cys} and ACR: (1) low risk: an eGFR_{cr-cys} ≥ 60 ml/min per 1.73 m² and an ACR < 30 mg/g (this category includes patients without CKD);

(2) moderate risk: an $eGFR_{cr-cys}$ between 45 and 59 ml/min per 1.73 m^2 and an $ACR < 30\text{ mg/g}$ or an $eGFR_{cr-cys} \geq 60\text{ ml/min per } 1.73\text{ m}^2$ and an ACR between 30 and 300 mg/g; (3) high risk: an $eGFR_{cr-cys}$ between 30 and 44 ml/min per 1.73 m^2 and an $ACR < 30\text{ mg/g}$, an $eGFR_{cr-cys}$ between 45 and 59 ml/min per 1.73 m^2 and an ACR between 30 and 300 mg/g, or an $eGFR \geq 60\text{ ml/min per } 1.73\text{ m}^2$ and an $ACR > 300\text{ mg/g}$; and (4) very high risk: $eGFR_{cr-cys} < 30\text{ ml/min per } 1.73\text{ m}^2$ and an $ACR < 30\text{ mg/g}$, an $eGFR_{cr-cys} < 45\text{ ml/min per } 1.73\text{ m}^2$ and an ACR between 30 and 300 mg/g, or an $eGFR_{cr-cys} < 60\text{ ml/min per } 1.73\text{ m}^2$ and an $ACR > 300\text{ mg/g}$. These categories predict the likelihood of having progressive CKD, AKI, or kidney failure and also closely correlate with cardiovascular and all-cause mortality risk.²⁶ The classification used the serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation¹⁹ to estimate GFR and describes the kidney abnormalities as lasting at least 3 months. Our study used an updated version of the CKD-EPI equation²⁰ and did not verify chronicity.

Details on data collection, measurements, and definitions of diseases in the LABS-2 Study have previously been published (Supplemental Material).^{29–31}

Statistical Analyses

Baseline characteristics were summarized by CKD risk categories (low, moderate, high, and very high) among patients with complete information for baseline CKD risk ($n=2144$). Categorical data were summarized with frequencies and percentages, and continuous data were summarized with medians and interquartile ranges. Changes of CKD risk from baseline and year 1 were categorized as improvement (moving to a lower CKD risk category), no change (staying in the same risk category), or worsening (moving to a higher CKD risk category), and they were summarized with frequencies and percentages.

Ordinal logistic regression model was fitted to assess the association of baseline covariates with baseline CKD risk categories. Because there were relatively few participants at very high prognostic risk, for this analysis we combined high- and very high-risk groups to increase statistical power. We first tested if the proportional odds assumption that the odds of having high risk compared with those of having moderate or low CKD risk were the same as those of having moderate or higher risk compared with low risk was met. If so, a single odds ratio and 95% CI were reported. Otherwise, a generalized logistic regression model was fitted with lowest risk category as the reference, and odds ratios comparing higher-risk groups with the lowest-risk group were reported. Independent covariates with <0.2 significance level in the univariable analysis (*i.e.*, age, sex, BMI, HbA1c, serum creatinine, insulin resistance by homeostatic model assessment, presence of diabetes, presence of hypertension, and use of ACE inhibitors or ARBs) were included in the multivariable model, wherein a stepwise regression with a P value cutoff of 0.10 for both entry and removal procedures was used for covariate selection. Regardless of

P value, covariates that, if removed, would significantly ($>20\%$) change the coefficients of other covariates remained in the model.

Generalized linear mixed models were used for subsequent analyses to account for repeated measures and within-subject correlations. All models were adjusted for race, site, and baseline smoking status, because these variables were associated with missing follow-up data and needed to be in the model to produce accurate estimates of the odds ratios under missing at random assumption (Supplemental Table 9). The missing at random assumption was deemed reasonable by analyzing whether there were any systematic patterns that gave rise to incomplete data in CKD risk categories during follow-up. Among the participants missing CKD risk categories during follow-up versus not missing these data, the changing pattern of predicted probability of being in moderate or higher CKD risk group was not distributed differently over other time points after controlling for missing related baseline variables (*i.e.*, race, site, and baseline smoking status) (Supplemental Table 10). This indicates that missing follow-up data were not related to outcome and should, therefore, not bias the results.

To investigate the trends in CKD risk categories over time, generalized ordinal logistic regression models stratified by baseline and year 1 risk category were used to estimate the proportions of changing status in the KDIGO risk level.

To evaluate the roles of baseline predictors for CKD risk after bariatric surgery, longitudinal analyses were performed using random intercept logistic regression models with risk categories as outcome (moderate or higher risk versus low risk) and visit (treated as categories), baseline covariates, follow-up weight loss, and their interaction with visit as covariates. Potential covariates and their interaction with visit were tested individually. Independent covariates with a P value <0.40 in univariable analyses (*i.e.*, age, sex, BMI, HbA1c, systolic BP, use of ACE inhibitors or ARBs, no private medical insurance, education, annual household income, surgery type, and percentage weight loss from baseline) were included in the adjusted model as well as corresponding interaction with follow-up that had P value <0.05 . Partial F values with P value <0.20 from type 3 sum of squares were used to determine whether to keep covariates in the final model. RR ratios and 95% CIs are reported in the tables.

All reported P values are two sided, and P values <0.05 were considered to be statistically significant.

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The NIDDK scientists contributed to the design and conduct of the study, which included collection and management of data. The project scientist from the NIDDK served as a member of the steering committee along with the principal investigator from each clinical site and the data coordinating center. The data coordinating center housed all data during the study and performed data analyses according to a prespecified plan developed by the data coordinating center biostatistician and approved by the steering committee and the independent data and safety monitoring board. The decision to publish was made by the LABS-2 Study steering committee, with no restrictions imposed by the sponsor. As a coauthor (P.L.K.), an NIDDK scientist contributed to the interpretation of the data and preparation, review, or approval of the manuscript.

DISCLOSURES

None.

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- See related perspective, “Bariatric Surgery and Kidney Health,” on pages 1085–1086.
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