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Microvascular Outcomes in Patients With Diabetes After Bariatric Surgery Versus Usual Care

A Matched Cohort Study

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Background: Bariatric surgery improves glycemic control in patients with type 2 diabetes mellitus (T2DM), but less is known about microvascular outcomes.

Objective: To investigate the relationship between bariatric surgery and incident microvascular complications of T2DM.

Design: Retrospective matched cohort study from 2005 to 2011 with follow-up through September 2015.

Setting: 4 integrated health systems in the United States.

Participants: Patients aged 19 to 79 years with T2DM who had bariatric surgery (n = 4024) were matched on age, sex, body mass index, hemoglobin A_{1c} level, insulin use, diabetes duration, and intensity of health care use up to 3 nonsurgical participants (n = 11 059).

Intervention: Bariatric procedures (76% gastric bypass, 17% sleeve gastrectomy, and 7% adjustable gastric banding) compared with usual care.

Measurements: Adjusted Cox regression analysis investigated time to incident microvascular disease, defined as first occurrence of diabetic retinopathy, neuropathy, or nephropathy.

Results: Median follow-up was 4.3 years for both surgical and nonsurgical patients. Bariatric surgery was associated with significantly lower risk for incident microvascular disease at 5 years (16.9% for surgical vs. 34.7% for nonsurgical patients; adjusted hazard ratio [HR], 0.41 [95% CI, 0.34 to 0.48]). Bariatric surgery was associated with lower cumulative incidence at 5 years of diabetic neuropathy (7.2% for surgical vs. 21.4% for nonsurgical patients; HR, 0.37 [CI, 0.30 to 0.47]), nephropathy (4.9% for surgical vs. 10.0% for nonsurgical patients; HR, 0.41 [CI, 0.29 to 0.58]), and retinopathy (7.2% for surgical vs. 11.2% for nonsurgical patients; HR, 0.55 [CI, 0.42 to 0.73]).

Limitation: Electronic health record databases could misclassify microvascular disease status for some patients.

Conclusion: In this large, multicenter study of adults with T2DM, bariatric surgery was associated with lower overall incidence of microvascular disease (including lower risk for neuropathy, nephropathy, and retinopathy) than usual care.

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The profound effects of bariatric surgery on glycemic control are well established in many studies, including several randomized trials that compared surgery versus intensive medical and lifestyle treatment of type 2 diabetes mellitus (T2DM) (1–7). Remission of T2DM is common after bariatric surgery, and Roux-en-Y gastric bypass (RYGB) outperforms sleeve gastrectomy (SG) in most reports (4, 8, 9).

More important than improvements in glycemic control is whether these glycemic changes reduce the incidence of major complications, such as microvascular events. In the United States, T2DM is the primary cause of nephropathy, end-stage renal disease, adult blindness, and neuropathy, which together lead to significant downstream costs and decreased quality of life (10–12). Thus, a major goal of diabetes treatment is to mitigate the risk for these long-term sequelae (13).

We have previously shown that in patients with T2DM who have bariatric surgery, risk for incident microvascular disease is reduced for every year of remission from T2DM—even if patients eventually relapse back to T2DM (indicating a legacy effect) (14). However, a detailed 2016 review of long-term microvascular outcomes of diabetes concluded that data were inadequate to support a superior effect of bariatric surgery compared with medical therapy (15).

Two recently published studies help inform this question (4, 16). The STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) trial (4) randomly assigned 150 patients with obesity and T2DM to have RYGB, SG, or an intensive medical and lifestyle intervention. After 5 years, urinary albumin–creatinine ratios had decreased in the SG group only. Retinopathy did not change in any group, and neuropathy was not examined. STAMPEDE was limited by a relatively small sample size, which made it underpowered for rare outcomes.

The prospective SOS (Swedish Obesity Subjects) matched cohort study (16) followed 2010 patients who had bariatric surgery (13% RYGB, 19% gastric banding, and 68% vertical-banded gastroplasty) and 2037

See also:

Editorial comment 1
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matched patients who received usual care. The incidence of microvascular disease after 15 years of follow-up was significantly lower in the surgery group than the control group (hazard ratio [HR], 0.56 [95% CI, 0.48 to 0.66]), including among subgroups with prediabetes (HR, 0.18 [CI, 0.11 to 0.30]), established diabetes (HR, 0.54 [CI, 0.40 to 0.72]), and normoglycemia (HR, 0.63 [CI, 0.48 to 0.81]) at baseline. The SOS study was limited by the small number of RYGB procedures and lack of SG procedures, which are now the 2 most common bariatric procedures worldwide (17).

To address these gaps in the literature, we did a matched cohort study to determine whether bariatric surgery was associated with lower incidence of microvascular disease than usual care for severe obesity and T2DM. We hypothesized that patients having bariatric surgery would have lower risk for any incident microvascular disease (composite of the first occurrence of retinopathy, neuropathy, or nephropathy). We further hypothesized that patients having bariatric surgery would have lower risk for incident retinopathy, nephropathy, and neuropathy than nonsurgical patients.

METHODS

Settings

We did a retrospective observational cohort study of adults with T2DM who had bariatric surgery between 2005 and 2011 while enrolled in 1 of 4 integrated health care systems from the Health Care Systems Research Network: Kaiser Permanente (KP) Washington in Washington state, HealthPartners in Minnesota, KP Northern California, and KP Southern California. All study procedures were reviewed and approved by the institutional review board at each site, and we were permitted to do the research without explicit consent from participants.

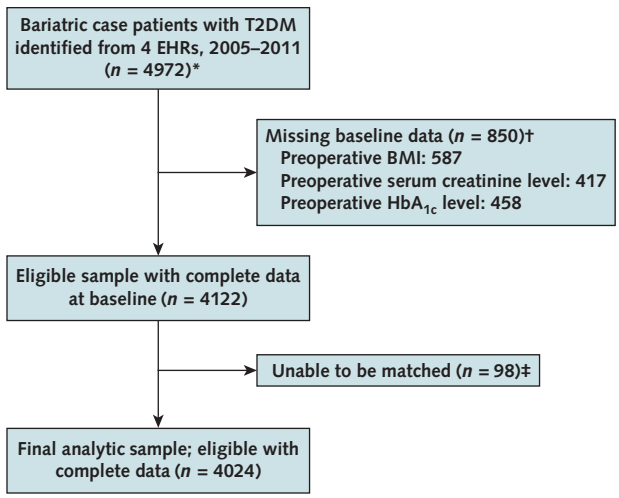
Data Sources

At each study site, staff used standardized electronic medical records, insurance claims, and other data systems (18) to extract enrollee data, including enrollment and insurance coverage; demographics; blood pressure; height; weight; laboratory values; medications dispensed; deaths; outpatient, inpatient, and emergency department use; and inpatient and outpatient diagnosis and procedure codes.

Surgical Participants

The bariatric population included adults (aged 19 to 79 years) with severe obesity (body mass index [BMI] ≥35 kg/m^2) and T2DM who had a primary (first observed) bariatric surgical procedure between 1 January 2005 and 31 December 2011. Following an approach adopted in prior studies (14, 19, 20), we used a combination of bariatric registries; review of medical records; codes from the International Classification of Diseases, Ninth Revision (ICD-9) (43.89, 44.31, 44.38, 44.39, 44.68, 44.69, and 44.95); and Current Procedural Terminology codes (43633, 43644, 43645, 43659, 43770, 43775, 43842, 43843, 43844, 43845, 43846, and 43847) to identify bariatric procedures. Patients were classified as having

Figure 1. Flow diagram for identification of eligible patients with T2DM and no history of microvascular disease who had bariatric surgery.



BMI = body mass index; EHR = electronic health record; HbA_{1c} = hemoglobin A_{1c}; T2DM = type 2 diabetes mellitus.
* Adults aged 20–79 y who had a primary (first observed) bariatric surgical procedure between 1 January 2005 and 31 December 2011. Bariatric procedures were identified using a combination of bariatric registries; review of medical records; International Classification of Diseases, Ninth Revision, codes (43.89, 44.31, 44.38, 44.39, 44.68, 44.69, and 44.95); and Current Procedural Terminology codes (43633, 43644, 43645, 43659, 43770, 43775, 43842, 43843, 43844, 43845, 43846, and 43847). We excluded patients with any of the following: <1 y of continuous enrollment; history of gastrointestinal surgery for cancer; pregnancy in the year before surgery; gestational diabetes as the sole diabetes diagnosis; preexisting neuropathy, nephropathy, or retinopathy; metformin as the sole indicator of possible T2DM (no other T2DM medications, laboratory values, or diagnoses); or maximum BMI <35 kg/m^2.
† Patients may have >1 type of missing data (BMI, creatinine concentration, or HbA_{1c} level) or have no follow-up time after surgery.
‡ 98 surgical patients could not be matched to a nonsurgical patient on site, age, BMI, insulin use, HbA_{1c} level, and sex.

T2DM if they had a hemoglobin A_{1c} (HbA_{1c}) level of at least 6.5% or fasting plasma glucose level of at least 6.99 mmol/L (126 mg/dL) at the most recent measurement within 2 years before surgery, or a current prescription for any diabetes medication.

After selecting the population, we applied the following exclusion criteria based on information in the 2 years before surgery: less than 1 full year of continuous enrollment; history of gastrointestinal surgery for cancer; pregnancy in the year before surgery; gestational diabetes as the sole diabetes diagnosis; metformin as the sole indicator of possible T2DM (that is, no other T2DM medications, laboratory values, or diagnoses); preexisting neuropathy, retinopathy, or nephropathy (defined in Outcome and Censoring Definitions); and maximum preoperative BMI less than 35 kg/m^2. This left 4972 patients. We further excluded 850 patients who were missing values for BMI, HbA_{1c} level, or serum creatinine concentration in the 2 years before surgery. Surgical patients who were missing these values differed from those who had complete data (**Appendix Table 1**, available at Annals.org). Specifically, they were

Table 1. Baseline Characteristics of Patients With Type 2 Diabetes Who Had Bariatric Surgery and Matched Nonsurgical Patients, 2005–2011*

Characteristic	Surgical Patients (n = 4024)	Matched Nonsurgical Patients (n = 11 059)
Mean age (SD), *y*	47.6 (9.7)	48.7 (9.7)
Age category, *n (%)*		
18–29 y	124 (3.1)	306 (2.8)
30–44 y	1393 (34.6)	3319 (30.0)
45–54 y	1457 (36.2)	4135 (37.4)
55–64 y	940 (23.4)	2894 (26.2)
65–79 y	110 (2.7)	405 (3.7)
Female, *n (%)*	3052 (75.8)	8266 (74.7)
Race/ethnicity, *n (%)*		
Hispanic	748 (18.6)	2008 (18.2)
Non-Hispanic black	608 (15.1)	1853 (16.8)
Non-Hispanic white	1843 (45.8)	4515 (40.8)
Other	305 (7.6)	709 (6.4)
Unknown/missing	520 (12.9)	1974 (17.8)
Health care site, *n (%)*		
HeathPartners	161 (4.0)	461 (4.2)
KP Northern California	1049 (26.1)	3035 (27.4)
KP Southern California	2555 (63.5)	6800 (61.5)
KP Washington	259 (6.4)	763 (6.9)
Insurance type, *n (%)*		
Commercial	3790 (94.2)	9946 (89.9)
Medicaid	94 (2.3)	365 (3.3)
Medicare	81 (2.0)	542 (4.9)
Other	59 (1.5)	206 (1.9)
Year of surgery/index date, *n (%)*		
2005	155 (3.9)	393 (3.6)
2006	280 (7.0)	809 (7.3)
2007	395 (9.8)	1132 (10.2)
2008	547 (13.6)	1525 (13.8)
2009	618 (15.4)	1634 (14.8)
2010	876 (21.8)	2352 (21.3)
2011	1153 (28.7)	3214 (29.1)
Mean total days of health care use in the 7–24 mo before the index date (SD), *n*	18.2 (11.7)	14.0 (8.8)
Mean BMI (SD), *kg/m²*	44.9 (6.9)	43.8 (6.7)
BMI category, *n (%)*		
35.0–39.9 kg/m²	1073 (26.7)	3746 (33.9)
40.0–49.9 kg/m²	2109 (52.4)	5487 (49.6)
≥50.0 kg/m²	842 (20.9)	1826 (16.5)
Mean serum creatinine level (SD)		
μmol/L	70 (15)	72 (36)
mg/dL	0.79 (0.17)	0.81 (0.41)
Mean eGFR (SD), *mL/min/1.73 m²*	96.6 (17.9)	94.8 (19.8)
Mean HbA_{1c} level (SD), %	7.10 (1.20)	7.14 (1.20)
Mean observed duration of diabetes (SD), *y*	4.63 (3.65)	4.50 (3.36)
Observed duration of diabetes, *n (%)*		
0–4 y	2458 (61.1)	6938 (62.7)
≥5 y	1566 (38.9)	4121 (37.3)
Use of oral diabetes medication, *n (%)*	2731 (67.9)	7467 (67.5)
Use of insulin, *n (%)*	674 (16.7)	1883 (17.0)

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Table 1–Continued

Characteristic	Surgical Patients (n = 4024)	Matched Nonsurgical Patients (n = 11 059)
Dyslipidemia, *n (%)*		
Triglyceride level ≥1.7 mmol/L (≥150 mg/dL)	1909 (47.4)	5042 (45.6)
Missing triglyceride level	19 (0.5)	442 (4.0)
Dyslipidemia diagnosis†	3126 (77.7)	8607 (77.8)
Use of a statin	1998 (49.7)	5703 (51.6)
Use of other lipid-lowering medications	222 (5.5)	651 (5.9)
Hypertension, *n (%)*		
Uncontrolled hypertension	286 (7.1)	1061 (9.6)
Missing BP measurement	180 (4.5)	91 (0.8)
Hypertension diagnosis†	2923 (72.6)	7248 (65.5)
Use of ACE inhibitors or ARBs	2118 (52.6)	6273 (56.7)
Use of other antihypertensive medications	1644 (40.9)	5763 (52.1)
Cardiovascular disease, *n (%)*		
≥1 cardiac event†	60 (1.5)	267 (2.4)
≥1 cerebrovascular event†	40 (1.0)	173 (1.6)
Use of a platelet inhibitor	43 (1.1)	353 (3.2)
Self-reported smoking status, *n (%)*		
Current	389 (9.7)	1517 (13.7)
Former	1208 (30.0)	2652 (24.0)
Never	2209 (54.9)	6374 (57.6)
Missing	218 (5.4)	516 (4.7)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; KP = Kaiser Permanente.
* Values represent characteristics at the time of bariatric surgery for surgical patients (or an equivalent index date for nonsurgical patients) unless otherwise indicated.
† Values represent this characteristic during the 2-y period before surgery.

more likely to be non-Hispanic white, to be from the HealthPartners site, to have had their procedure in the first year of our study (2005), and to have had a shorter observed duration of T2DM at the time of surgery. Of the remaining 4122 patients, 4024 could be matched to at least 1 nonsurgical patient (**Figure 1**).

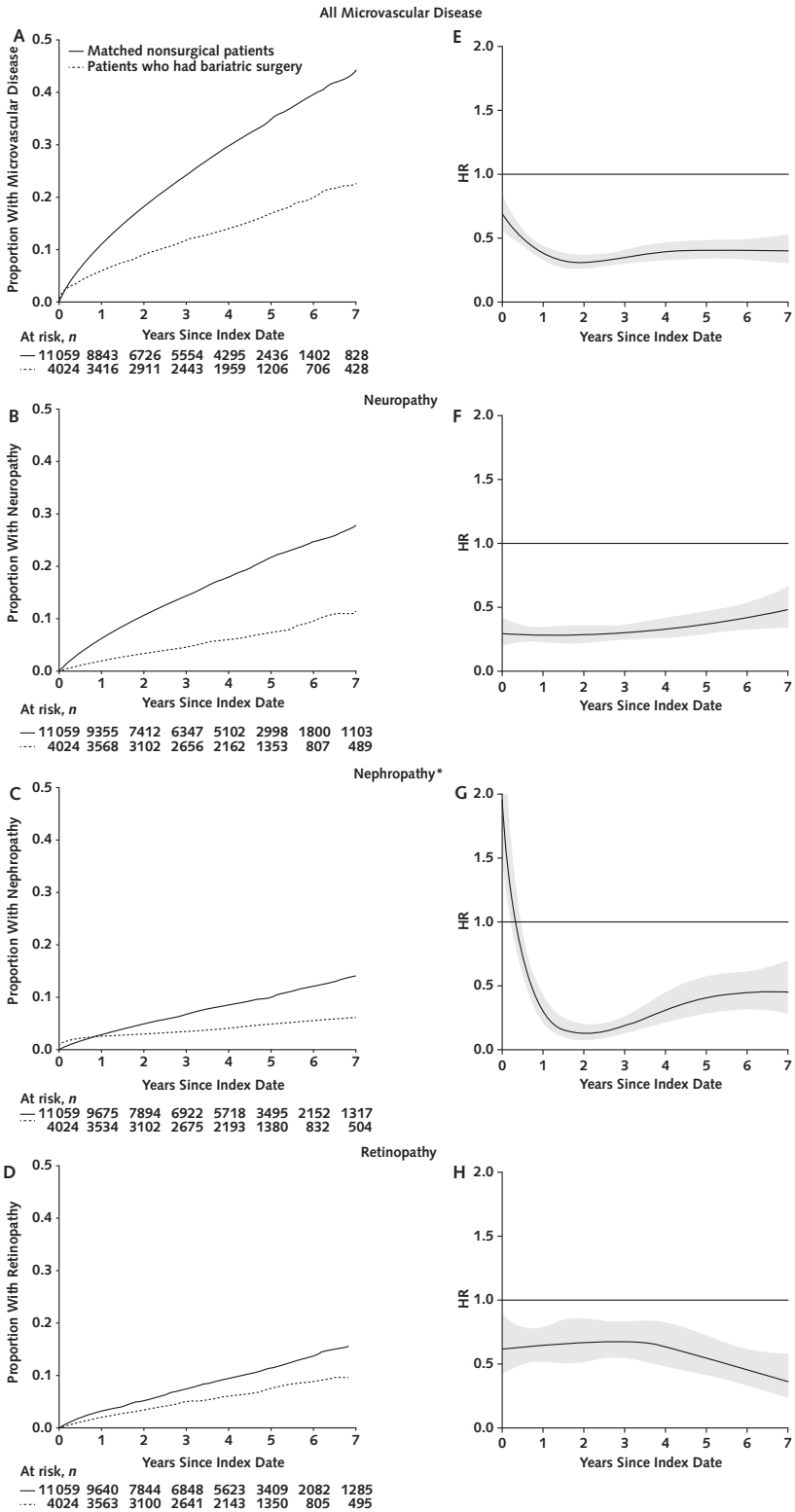
Matched Nonsurgical Participants

For each surgical patient, we identified up to 3 matched nonsurgical control participants via a 2-step process. First, among all patients with diabetes and at least 1 BMI measurement of 35 kg/m^2 or greater who did not have bariatric surgery during the study (n = 320 345), we identified a pool of potential control participants who were enrolled at the time of the surgery; satisfied the study inclusion criteria; and matched the surgical patient on the basis of study site, sex, age (± 10 years), BMI (± 5 kg/m^2), HbA_{1c} level (± 1.5 percentage points), and insulin use. Second, for each control participant in the pool, we calculated Mahalanobis distance from the surgical patient on the basis of age, BMI, HbA_{1c} level, diabetes duration, and total days of health care use in the 7 to 24 months before the date of surgery (21). Finally, up to 3 control participants were selected on the basis of the shortest Mahalanobis distance. Throughout, nonsurgical patients could be used as a control for only 1 surgical patient (matching without replacement). The **Appendix** (available at Annals.org) gives additional details on the process we used to establish the matched cohort.

Outcome and Censoring Definitions

The primary outcome measure was time to incident microvascular disease (composite of the first occurrence of retinopathy, neuropathy, or nephropathy). Retinopathy was defined by the first appearance of either ICD-9 code 362.0x (diabetic retinopathy) or both a retinal surgical procedure code or other retinopathic code (**Appendix Table 2**, available at Annals.org) and ICD-9 code 250.5x (diabetes with ophthalmic manifestations). Neuropathy was identified on the basis of the first occurrence of ICD-9 code 250.6 (diabetes with neurologic manifestations) or 357.2 (polyneuropathy in diabetes). Finally, nephropathy was defined by at least 2 measures of estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 separated by at least 90 days without any intervening values of 60 mL/min/1.73 m^2 or greater. We approximated estimated glomerular filtration rate using serum creatinine values and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation (22). We chose not to use urine protein measures to define incident nephropathy because nearly 25% of our cohort had no baseline measurements of urine protein. Patients were censored at first incidence of cancer (excluding nonmelanoma skin cancer), disenrollment, death, study end (31 September 2015), or a period of 13 months with no measurement of weight or blood pressure (**Appendix Table 3**, available at Annals.org). In secondary analyses, we considered each of the 3 component microvascular outcomes separately.

Figure 2. Kaplan–Meier–derived estimates of the cumulative incidence of microvascular disease (*A–D*) and time-varying HR comparing the risk for incident microvascular disease (*E–H*).



Separate estimates for neuropathy (*B, F*), nephropathy (*C, G*), and retinopathy (*D, H*) are shown, as well as a composite estimate for incident microvascular disease due to any of the 3 (*A, E*). Shaded areas represent 95% CIs. HR = hazard ratio.
* Defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 on two separate measures separated by 90 days with no interim measures 60 mL/min/1.73 m^2 or greater.

Table 2. Cumulative Incidence Rates and 95% CIs for Microvascular Disease Outcomes in Surgical and Matched Nonsurgical Patients*

Outcome	Cumulative Incidence Rate (95% CI), %							
	1 Year		3 Years		5 Years		7 Years	
	Surgical Group	Nonsurgical Group	Surgical Group	Nonsurgical Group	Surgical Group	Nonsurgical Group	Surgical Group	Nonsurgical Group
Composite index of incident microvascular disease†	6.0 (5.2–6.7)	11.2 (10.6–11.8)	11.8 (10.8–12.9)	24.3 (23.4–25.2)	16.9 (15.5–18.3)	34.7 (33.6–35.8)	22.5 (20.5–24.5)	44.2 (42.7–45.7)
Incident diabetic neuropathy	1.8 (1.4–2.3)	6.0 (5.6–6.5)	4.6 (3.9–5.3)	14.1 (13.4–14.8)	7.2 (6.3–8.2)	21.4 (20.4–22.3)	11.3 (9.7–12.8)	27.6 (26.3–28.9)
Incident diabetic nephropathy	2.7 (2.2–3.2)	2.8 (2.5–3.2)	3.6 (3.0–4.2)	6.8 (6.2–7.3)	4.9 (4.2–5.7)	10.0 (9.3–10.7)	6.4 (5.3–7.6)	14.0 (13–15.1)
Incident diabetic retinopathy	1.9 (1.5–2.4)	3.0 (2.7–3.4)	4.9 (4.2–5.6)	7.3 (6.8–7.8)	7.2 (6.3–8.2)	11.2 (10.5–11.9)	9.8 (8.4–11.2)	15.9 (14.8–17.0)

* Patients were matched on age, sex, body mass index, site, insulin use, hemoglobin A_{1c} level, observed diabetes duration, and number of days of health care use in the 7–24 mo before the index date.
† Indicates the first occurrence of neuropathy, nephropathy, or retinopathy.

Statistical Analysis

Cox hazards regression models were used to investigate the association between bariatric surgery (versus usual care in nonsurgical control participants) and incident microvascular disease. Patients were followed from the index date (date of surgery or, for nonsurgical patients, date of surgery for their matched case patient) until the first occurrence of incident microvascular disease or a censoring event. On the basis of preliminary analyses, the proportional hazards assumption was assessed not to hold for bariatric surgery versus usual care ($P < 0.001$ for an interaction with log time in the Cox model). We therefore fitted a flexible time-varying HR association as a function of time since surgery, using restricted cubic splines with knots at the 5th, 35th, 65th, and 95th percentiles of the observed follow-up time scale (23).

Potential confounders of the association between bariatric surgery and microvascular disease were identified a priori. Our 2-part matching strategy was designed to ensure balance between surgical and nonsurgical patients for many factors (see Matched Nonsurgical Participants), and we achieved an exact balance for select matching covariates (such as sex and insulin use). We also fitted the Cox models for the primary and secondary outcomes, adjusting for the following covariates: age, race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, or non-Hispanic other), year of surgery, BMI, smoking status (current, former, or never), duration of observed diabetes before surgery (defined as first observed diagnosis, laboratory value, or prescription indicating T2DM), insulin use, oral diabetes medication use, uncontrolled blood pressure (defined as either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at 2 consecutive measures on different days), use of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker medications, use of any other antihypertensive medication, insurance type (commercial, Medicare, Medicaid, or other), triglyceride level of 2.82 mmol/L (250 mg/dL) or greater, use of cholesterol-lowering medication (statin or other), use of aspirin or another platelet inhibitor, and history of a cardiac or cerebrovascular event before surgery (defined on the basis of ICD-9 codes). Because of potential variation in care between health systems, we adjusted for study site (HealthPartners, KP Southern California, KP Northern California, and KP Washington) via stratification of the baseline hazard function. Of note, by including variables used in matching or Mahalanobis distance calculation in the Cox models, our analyses provide 2 (parallel) adjustments for potential confounding effects.

Some data were missing at baseline for race/ethnicity, smoking status, blood pressure, and triglyceride levels. We did multiple imputation via chained equations, using unordered categorical variables and multinomial logistic regression for imputation of race/ethnicity and smoking status and logistic regression for elevated blood pressure and triglyceride levels (24). We generated 10 imputed data sets and combined the results using Rubin rules. The **Appendix** provides more details.

We did 3 sensitivity analyses to examine the effect of not adjusting for potential confounders excluded from the matching process (vs. adjusting for those confounders in our main analysis), the effect of using 1:1 and 10:1 matching, and the effect of assessing robustness of the 5-year results to unmeasured confounding using the E-value method of VanderWeele and Ding (25). Throughout, we used SAS, version 9.4 (SAS Institute), for data manipulation; Stata, version 15.1 (StataCorp), for multiple imputation and analysis; and R for visualization.

Role of the Funding Source

The National Institute of Diabetes and Digestive and Kidney Diseases had no role in the design or conduct of the study or reporting of the results.

RESULTS

Participants

The final analytic sample comprised 4024 surgical patients and 11 059 nonsurgical matches (**Table 1**). Median follow-up was 4.3 years in both groups, and retention rates at 1, 3, and 5 years were similar for nonsurgical (90%, 67%, and 56%) and surgical (90%, 69%, and

56%) patients. Table 1 shows that most surgical patients were middle aged women with commercial insurance and that more than 40% were racial/ethnic minorities. In 2005 to 2011, 76% of surgical patients had RYGB, 17% had SG, and 7% had adjustable gastric banding. At the index date, half of patients had a BMI of 40 to 49.9 kg/m^2, 38% had had T2DM for 5 years or more before baseline, and the mean HbA_{1c} level was 7.1%. More nonsurgical patients had been current smokers in the 2 years before surgery (13.7% vs. 9.7%), and more nonsurgical patients had been using medications to control hypertension.

Effect of Bariatric Surgery Versus Usual Care on Risk for Incident Microvascular Disease

Figure 2 (*A-D*) and Table 2 show estimates of the cumulative probability of incident microvascular disease over time after bariatric surgery and nonsurgical care (for matched control participants), as well as the cumulative probability of each of the indicators of microvascular disease (nephropathy, neuropathy, and retinopathy). Rates of incident microvascular disease at 1, 3, 5, and 7 years were 6.0%, 11.8%, 16.9%, and 22.5%, respectively, after bariatric surgery and 11.2%, 24.3%, 34.7%, and 44.2% after usual care. The difference was primarily driven by the incidence of neuropathy, which was lower for surgical than nonsurgical participants. Rates of retinopathy were also lower in surgical patients. Cumulative incidence rates of nephropathy were similar among surgical and nonsurgical patients (2.7% and 2.8%) in the first year after surgery; however, rates of nephropathy were lower among surgical patients at all time points after 1 year.

Figure 2 (*E-H*) shows the change in adjusted HR over time for each outcome. The HR for all microvascular events decreased after the index date (favoring surgery) and remained relatively stable after 1 year. Bariatric surgery was associated with a stable decrease in risk for neuropathy over time. Risk for nephropathy was initially higher among surgical patients but decreased rapidly and remained lower among surgical patients in years 1 through 7. The HR for retinopathy followed a trajectory similar to that of the composite index of all microvascular events, aside from a slight strengthening of the association starting 4 years after surgery.

Table 3 shows the key results from the multivariable adjusted Cox models investigating the association between bariatric surgery (vs. usual care) and incident microvascular disease 1, 3, and 5 years after the index date. At 5 years, risk for incident microvascular disease was significantly lower in surgical patients than matched nonsurgical patients (HR, 0.41 [CI, 0.34 to 0.48]). Bariatric surgery was associated with a lower 5-year risk for diabetic neuropathy (HR, 0.37 [CI, 0.30 to 0.47]), nephropathy (HR, 0.41 [CI, 0.29 to 0.58]), and retinopathy (HR, 0.55 [CI, 0.42 to 0.73]). Appendix Table 4 (available at Annals.org) shows the full Cox models.

Sensitivity Analyses

Appendix Figures 1 and 2 (available at Annals.org) provide results of the sensitivity analyses. A matched, unadjusted analysis of our primary outcome was not significantly different from the fully adjusted model (Appendix Figure 1). Our primary outcome results using 3:1 matching were qualitatively similar to those using 1:1 and 10:1 matching (Appendix Figure 2). For the 5-year results reported in Table 3, the E-values for the point estimate and upper confidence bound for incident microvascular disease were 3.09 and 2.70, respectively; the corresponding E-values for incident retinopathy were 3.04 and 2.08. We also found no differences in the frequency of microvascular disease surveillance across surgical and nonsurgical groups over 5 years of follow-up (Appendix Table 5, available at Annals.org).

DISCUSSION

Prior studies have shown that most patients who have bariatric procedures experience a remission of their T2DM (20, 26). However, less is known about whether bariatric surgery reduces risk for incident microvascular disease (15). In the current study, bariatric surgery was associated with half the incidence of microvascular disease at 5 years compared with usual medical care. A lower rate of neuropathy primarily drove this finding, but we also saw lower incidence of nephropathy and retinopathy through 5 years of follow-up.

Only 3 other studies of microvascular outcomes after bariatric surgery have included a nonsurgical popu-

Table 3. Results of Matched, Fully Adjusted Cox Proportional Hazards Model Comparing Risk for Incident Microvascular Disease Outcomes in Surgical Versus Matched Nonsurgical Patients*

Outcome	Hazard Ratio (95% CI)			
	1 Year	3 Years	5 Years	7 Years
Composite index of incident microvascular disease†	0.38 (0.33–0.44)	0.35 (0.30–0.41)	0.41 (0.34–0.48)	0.40 (0.30–0.53)
Incident diabetic neuropathy	0.28 (0.23–0.35)	0.30 (0.25–0.37)	0.37 (0.30–0.47)	0.48 (0.34–0.67)
Incident diabetic nephropathy	0.29 (0.21–0.42)	0.19 (0.14–0.27)	0.41 (0.29–0.58)	0.45 (0.29–0.71)
Incident diabetic retinopathy	0.64 (0.52–0.79)	0.68 (0.55–0.84)	0.55 (0.42–0.73)	0.37 (0.24–0.58)

* Patients were matched on age, sex, body mass index, site, insulin use, hemoglobin A_{1c} level, observed diabetes duration, and number of days of health care use in the 7–24 mo before the index date. Values were adjusted for all matching variables plus race/ethnicity; insurance type; diabetes duration; hypertension diagnosis; baseline blood pressure; use of oral diabetes medication, an angiotensin-converting enzyme inhibitor, an angiotensin-receptor blocker, other antihypertensive medications, a statin, or other lipid-lowering agents; dyslipidemia diagnosis; coronary heart disease; cerebrovascular disease; and smoking status.
† Indicates the first occurrence of neuropathy, nephropathy, or retinopathy.

lation as a comparator. These are the STAMPEDE randomized trial (4), which reported changes in microalbuminuria and retinopathy; the prospective SOS cohort study (16, 27, 28), which reported neuropathy, nephropathy, and retinopathy incidence (using ICD-9, Clinical Modification, codes; ICD, 10th Revision, codes; nationwide registries; and albuminuria measures); and a retrospective cohort study by Johnson and colleagues (29) that included 2580 surgical patients and 13 371 matched control participants and reported incident end-stage microvascular events. We place our findings in the context of these and other relevant studies.

Among types of microvascular disease after bariatric surgery, renal outcomes have been studied most frequently. Despite varying definitions of renal outcomes, prior studies suggest that the outcomes of bariatric surgery are favorable for patients with and without renal disease at baseline (28, 30–36). In our study, incidence of nephropathy was 59% lower at 5 years among patients who had bariatric surgery. Recently published data from the STAMPEDE trial's 5-year follow-up (4) showed that urinary albumin–creatinine ratios were significantly better in the SG group than the medical therapy group ($P < 0.001$), but creatinine-based measures of renal function did not differ. Johnson and colleagues (29) reported a significant reduction in end-stage renal disease in patients who had bariatric surgery compared with matched nonsurgical patients. In the most recent study of microvascular outcomes, surgical patients with chronic kidney disease stage 3 or higher had significant improvements in estimated glomerular filtration rate compared with matched control participants, and patients having RYGB saw the greatest improvements (vs. those having SG) (35).

The hazard of neuropathy at 5 years (defined by ICD-9, Clinical Modification, codes) was 63% lower at 5 years in our surgical cohort than in the usual care group. Few population-based studies have reported neuropathy independent of other microvascular outcomes (27, 29). STAMPEDE (4) found a 50% reduction in neuropathy on a patient-reported questionnaire. Miras and associates (37) did not find any improvement in peripheral nerve conduction at 12 to 18 months in a small ($n = 70$) prospective case–control study.

We also report a 45% lower hazard of incident diabetic retinopathy at 5 years (defined using diagnosis and procedure codes) in surgical versus nonsurgical patients. Strict glycemic control is an important factor in preventing progression of diabetic retinopathy (38–40), and bariatric surgery is superior to medical treatment in achieving T2DM remission (1–7). Despite this, the effects of bariatric surgery on diabetic retinopathy have been mixed: Some studies showed improvement (41), whereas others reported progression (42–45). Johnson and colleagues (29) showed fewer cases of blindness or retinal surgery in the surgical group than the nonsurgical group. Five-year data from the STAMPEDE study showed no evidence of benefit of RYGB or SG (vs. intensive lifestyle and medical treatment) on retinopathy rates (4). The SOS study did not examine retinopathy independent of other microvascular outcomes (27).

Factors are at play that may mitigate the potential benefit of improved glycemic control with bariatric surgery on the incidence of retinopathy. These include an overly rapid decrease in HbA_{1c} level (which was associated with early worsening of diabetic retinopathy in the DCCT [Diabetes Control and Complications Trial]) (46), hypoglycemia after bariatric surgery (47), discontinuation of fenofibrate and angiotensin-receptor blockers after bariatric surgery (these medications can reduce risk for retinopathy but may be discontinued after bariatric surgery in patients whose diabetes is in remission) (48, 49), pregnancy (weight loss can reduce infertility, increasing the chance of pregnancy, which may worsen retinopathy) (50), and vitamin deficiencies (particularly vitamins A, D, and B12; copper; and folate) (51–55). Despite these potential negative effects of bariatric surgery on retinal outcomes, we observed a strong association with lower retinopathy risk over time.

Several factors limit the interpretation of our results. First, the observational study design precludes causal inference, and residual unmeasured confounding by indication might be present. Second, we adjusted for health system in our models, but we could not adjust at the level of clinic or provider, which could have caused unmeasured confounding due to differences in care quality. However, our sensitivity analyses indicate that each 5-year outcome (**Table 3**) had an E-value greater than 2 for the upper bound of the CI; this suggests, for example, that the results could be explained by an unmeasured confounder that was associated with both receipt of bariatric surgery and risk for microvascular disease by a risk ratio of 2.7, beyond the measured confounders. For our study, we believe that this degree of confounding remains unmeasured is implausible and, as such, do not believe that our conclusions would change. Third, data used to define incident microvascular disease (retinopathy, nephropathy, and neuropathy) were collected as part of routine clinical care across 4 large, integrated health care systems, so that missing data (eye examinations, blood tests, and neuropathy assessments) may have resulted in misclassification of microvascular complication status for some patients. Fourth, neuropathy may be misclassified because it was not identified using an objective end point and its symptoms, such as paresthesias, are common.

Not all patients will be interested in bariatric surgery to treat their T2DM, but providers should engage all patients with T2DM and a BMI of 35 kg/m^2 or higher in a shared decision-making conversation about the benefits and risks of bariatric procedures (56). Our results add to a growing body of evidence suggesting that bariatric surgery not only improves glucose, blood pressure, and lipid control but is likely to reduce macrovascular and microvascular complications, as well as improve survival, in patients with severe obesity and T2DM (57). The findings from this study should help patients and providers to better understand the potential tradeoffs of bariatric surgery as treatment of T2DM and help them to make more informed decisions about care.

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Reproducible Research Statement: *Study protocol:* See the Appendix (available at Annals.org). *Statistical code:* Available from Dr. Arterburn (e-mail, arterburn.d@ghc.org). *Data set:* Our data access committee will review any requests for access to data and make a determination. Please contact Dr. Arterburn for details on making a request (e-mail, arterburn.d@ghc.org).

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Appendix: Statistical Methods

Here we provide additional detail and rationale for specific aspects of the design and analysis of our matched cohort study. As such, this Appendix is intended to complement the main article.

Overarching Strategy

The study used a matched cohort design with surgical case patients (that is, "exposed") matched to noncase patients (that is, "unexposed"). In identifying matched, unexposed persons, the most salient point is the need to define "time 0" for the time-to-event analyses; for surgical patients, this time is the date of surgery. Thus, at a minimum the matched design needed to match on date (that is, nonsurgical patients had to be enrolled in the health system on the date of the case patient's surgery). Beyond time matching, we believe that 2 options exist in a matched cohort design. The first is to construct a model for treatment allocation using all patients across the study period and use propensity scores as a basis for identifying matched, unexposed persons. The second approach is to match directly on a list of a priori–specified covariates that may contribute to confounding bias. We took the latter approach. The decision not to use propensity scores was based on concern among the investigative team about how information across patients and across time would be "borrowed" within a single regression model for treatment allocation. We understand that many approaches can be used to build propensity score models, but we also believed that the data were sufficiently rich to match directly on covariates. The key advantage of doing so is that it ensures exact balance between exposed and unexposed patients for at least some key confounders. For those (measured) confounders that were not included in the matching, adjustment was done via the regression modeling.

Construction of Analytic Data Sets

To construct the analytic data set, we used the following steps. 1) Identify all bariatric surgery case patients who met the study inclusion criteria (see Methods). This resulted in a sample of 4972 patients.

2) Of these, 850 were excluded because of missing values for BMI, HbA_{1c} level, or serum creatinine concentration in the 2 years before surgery, leaving 4122 patients. See Missing Data for additional detail.

3) Identify all patients with at least 1 BMI measurement of 35 kg/m^2 or greater who *did not* have bariatric surgery during the study period (n = 320 345).

4) For each bariatric surgery case patient, identify a pool of potential control participants who were enrolled at the time of the surgery and satisfied the study inclusion criteria and restrict the pool to those who matched the bariatric case patient on the basis of study site, sex, age (± 10 years), BMI (± 5 kg/m^2), HbA_{1c} level (± 1.5 percentage points) and insulin use. For each remaining control participant, calculate the Mahalanobis distance with the surgical patient on the basis of age, BMI, HbA_{1c} level, diabetes duration, and total days of health care use in the 7 to 24 months before the date of surgery. Control participants may be matched to only 1 surgical patient. When a control participant was eligible for several surgical patients, he or she was assigned to the surgical patient with fewer potential control participants (potential control numbers were capped at 20 for these calculations). If both surgical patients had the same number of control participants available, the control participant was randomly assigned to 1 of the surgical patients. Select up to 3 control participants to be

retained in the final matched cohort, using those with the smallest Mahalanobis distance.

5) Of note, 98 case patients could not be matched; that is, no nonsurgical patients matched them on the basis of site, age, BMI, insulin use, HbA_{1c} level, and sex.

When matching is done on the basis of the propensity score, it is critical to check post hoc the balance in confounder distributions between the treatment groups. Given our use of a combination of exact and Mahalanobis distance–based matching, however, we checked balance by constructing and reporting Table 1 (that is, presenting baseline characteristics by exposure status). From this, we believe that we achieved reasonable balance. Nevertheless, we took a conservative approach to the analysis and explicitly adjusted for all potential confounders, including those in the matching process. Thus, our control of confounding does not rely exclusively on the success of the balancing.

Statistical Analysis

Given that the primary outcome is a time-to-event outcome, we investigated the association between surgery or nonsurgery and incident microvascular disease via a Cox model. Patients were followed from the index date (date of bariatric surgery or, for nonsurgical patients, date of surgery for the patient to whom they had been matched) until the first occurrence of either incident microvascular disease or a censoring event. After preliminary modeling, the proportional hazards assumption was assessed not to hold for bariatric surgery versus usual care ($P < 0.001$ for an interaction with log time in the Cox model). We therefore fitted a flexible time-varying HR association, as a function of time since surgery, using restricted cubic splines with knots at the 5th, 35th, 65th, and 95th percentiles of the observed follow-up time scale. Adjusted models were fitted that included age, race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, or non-Hispanic other), year of surgery, BMI, smoking status (current, former, or never), duration of observed diabetes before surgery (defined as first observed diagnosis, laboratory value, or prescription indicating T2DM), insulin use, oral diabetes medication use, uncontrolled blood pressure (defined as either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg at 2 consecutive measures on different days), use of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker medications, use of any other antihypertensive medication, insurance type (commercial, Medicare, Medicaid, or other), triglyceride level of 2.82 mmol/L (250 mg/dL) or greater, use of cholesterol-lowering medication (statin or other), use of aspirin or another platelet inhibitor, and history of a cardiac or cerebrovascular event before surgery (defined on the basis of ICD-9 codes). Because of potential variation in care between health systems, we adjusted for study site (HealthPartners, KP Southern California, KP Northern California, and KP Washington) via stratification of the baseline hazard function. Missing data were imputed using chained equations, as detailed elsewhere in the Appendix.

Overall Approach to Confounding

Collectively, the matched cohort design and the analytic approach just described provide 2 (parallel) approaches to controlling confounding bias. Sjölander and Greenland (58) provide a detailed justification for including the covariates used in the matching process in the Cox regression models. In this sense, the extent to which confounding bias has been controlled does not rely solely on the extent to which the matching process has created perfect balance between surgical and nonsurgical patients.

Cumulative Incidence Plots

Figure 2 presents a series of plots that compare the cumulative incidence among bariatric case patients and noncase patients (for various outcome definitions). These figures are not "unadjusted" (as might typically be the case in Kaplan–Meier estimates of incidence) because they were calculated on the basis of the matched cohort. Moreover, because the matched adjusted and matched unadjusted Cox models yield nearly identical results, we believe that the cumulative incidence plots are a very reasonable approximation of the underlying rates in the 2 groups.

SE Estimation

Because all covariates used to construct the matched cohort were included in the model, no further statistical adjustment for the design was necessary to obtain valid estimates. Beyond study site (which was adjusted for via stratification of the baseline hazard function), we did not adjust for clinical center within site, mostly because it is unclear how to "assign" a clinical center for a nonexposed person at the time of surgery. This, we believe, may be an inherent limitation of the matched cohort design as applied in our setting. However, we do not believe that adjustment for correlation due to clinical center would change our conclusions. The SE that underpins the 95% CI for the composite index measure (Table 3) is at most 0.06 across each of the years presented. In order for the 95% CI at year 1 for an HR of 0.38 to cover 1.0, for example, the SE would have to increase to approximately 0.32 (a >6-fold increase). In our experience, although adjusting for correlation can affect SEs, such a large effect is implausible.

Missing Data

Missing data manifested at 2 points in the study. First, 850 of the 4972 bariatric case patients (15%) who

satisfied our inclusion criteria were missing values for BMI, HbA_{1c} level, or serum creatinine concentration in the 2 years before surgery. Second, in the final matched cohort, patients may have been missing select baseline covariates, specifically race/ethnicity, smoking status, elevated blood pressure, or elevated triglyceride levels.

Appendix Table 1 compares the characteristics of the 15% of surgical patients who were missing values for BMI, HbA_{1c} level, or serum creatinine concentration versus those who had complete preoperative data. These data show that surgical patients with missing data were similar in most characteristics. Those that did differ suggest that persons who were missing data were either new to our health care systems (that is, had not been receiving care long enough to have all of these baseline data captured in our systems) or had the procedure with a surgeon who was not in our integrated network (we are less likely to capture complete data, such as laboratory values and vital signs, on patients who receive care from surgeons outside our health systems because we receive only insurance claims for those patients). For example, patients missing data were more often from HealthPartners (35% missing vs. 4% nonmissing); were more often non-Hispanic white (57% missing vs. 46% nonmissing); more often had their procedure in the first year of our study, 2005 (26% missing vs. 5% nonmissing); more often had a shorter duration of observed diabetes (72% missing vs. 61% nonmissing); more often had missing blood pressure and triglyceride measures (40% missing vs. 0.5% nonmissing); and more often had missing information on smoking status (72% missing vs. 6% nonmissing).

Missing data were encountered at baseline for race/ethnicity, self-reported smoking status, blood pressure, and triglyceride levels. Table 1 shows the amount of missing data for each variable, stratified by surgical versus control status. To address the issue of missing data, we performed multiple imputation via chained equations using Stata's built-in mi suite (24). Race/ethnicity and smoking status were imputed using multinomial logistic regression, whereas uncontrolled blood pressure and high triglyceride levels were imputed via logistic regression. We detected no issues with perfect prediction or nonconvergence of models. The imputation used all variables involved in the 4 analytic models, including the outcome variables of time-to-event and event status. We used M = 10 imputations, with 100 iterations between saved data sets to prevent autocorrelation between imputations. Stata's "mi estimate" prefix was used to automatically combine the results of the Cox regressions using Rubin rules.

Software Used

Throughout, we used SAS, version 9.4 (SAS Institute), for data manipulation; Stata, version 15.1 (StataCorp) (59), for multiple imputation and analysis; and R, version 3.4.2 (60), for visualization.

Appendix Table 1. Comparison of Characteristics of Surgical Patients Who Were Missing Values for BMI, HbA_{1c}, or Serum Creatinine at Baseline Versus Those Who Had Complete Information on These Values at Baseline

Characteristic	Complete Data on BMI, $_{1c}$, and Creatinine at Baseline (n = 4122)	Missing BMI, HbA_{1c}, or Creatinine Measure at Baseline (n = 850)
Mean age (SD), *y*	47.4 (9.7)	48.1 (10.4)
Age category, *n (%)*		
18–29 y	133 (3.2)	41 (4.8)
30–44 y	1448 (35.1)	269 (31.6)
45–54 y	1479 (35.9)	288 (33.9)
55–64 y	952 (23.1)	218 (25.6)
65–79 y	110 (2.7)	34 (4)
Female, *n (%)*	3123 (75.8)	654 (76.9)
Race/ethnicity, *n (%)*		
Hispanic	770 (18.7)	86 (10.1)
Non-Hispanic black	628 (15.2)	95 (11.2)
Non-Hispanic white	1891 (45.9)	488 (57.4)
Other	307 (7.4)	30 (3.5)
Unknown/missing	526 (12.8)	151 (17.8)
Health care site, *n (%)*		
HealthPartners	173 (4.2)	295 (34.7)
KP Northern California	1106 (26.8)	80 (9.4)
KP Southern California	2579 (62.6)	394 (46.4)
KP Washington	264 (6.4)	81 (9.5)
Insurance type, *n (%)*		
Commercial	3878 (94.1)	780 (91.8)
Medicaid	96 (2.3)	25 (2.9)
Medicare	85 (2.1)	23 (2.7)
Other	63 (1.5)	22 (2.6)
Year of surgery/index date, *n (%)*		
2005	213 (5.2)	224 (26.4)
2006	286 (6.9)	168 (19.8)
2007	402 (9.8)	131 (15.4)
2008	551 (13.4)	78 (9.2)
2009	621 (15.1)	77 (9.1)
2010	887 (21.5)	93 (10.9)
2011	1162 (28.2)	79 (9.3)
BMI category, *n (%)*		
35.0–39.9 kg/m^2	1087 (26.4)	50 (5.9)
40.0–49.9 kg/m^2	2146 (52.1)	155 (18.2)
≥50.0 kg/m^2	889 (21.6)	58 (6.8)
Unknown/missing	0 (0)	587 (69.1)
Mean serum creatinine level (SD)		
μmol/L	69.8 (15.9)	79.6 (21.2)
mg/dL	0.79 (0.18)	0.90 (0.24)
Missing, *n (%)*	0 (0)	331 (38.9)
Mean eGFR (SD), *mL/min/1.73 m^2*	96.8 (18.0)	86.1 (24.1)
Mean HbA_{1c} level (SD), %	7.11 (1.23)	7.02 (1.34)
Missing, *n (%)*	0 (0)	417 (49.1)
Observed duration of diabetes, *n (%)*		
0-4 y	2518 (61.1)	612 (72)
≥5 y	1604 (38.9)	238 (28)
Use of oral diabetes medication, *n (%)*	2795 (67.8)	550 (64.7)
Use of insulin, *n (%)*	701 (17)	138 (16.2)

Continued on following page

Appendix Table 1–Continued

Characteristic	Complete Data on BMI, HbA_{1c}, and Creatinine at Baseline (n = 4122)	Missing BMI, HbA_{1c}, or Creatinine Measure at Baseline (n = 850)
Dyslipidemia, *n (%)*		
Triglyceride level ≥1.7 mmol/L (≥150 mg/dL)	1948 (47.3)	258 (30.4)
Missing triglyceride level	21 (0.5)	336 (39.5)
Dyslipidemia diagnosis*	3193 (77.5)	652 (76.7)
Use of a statin	2036 (49.4)	393 (46.2)
Use of other lipid-lowering medications	227 (5.5)	64 (7.5)
Hypertension, *n (%)*		
Uncontrolled hypertension	292 (7.1)	21 (2.5)
Missing BP measurement	235 (5.7)	606 (71.3)
Hypertension diagnosis*	2983 (72.4)	638 (75.1)
Use of ACE inhibitors or ARBs	2169 (52.6)	434 (51.1)
Use of other antihypertensive medications	1680 (40.8)	393 (46.2)
Cardiovascular disease, *n (%)*		
≥1 cardiac event*	61 (1.5)	15 (1.8)
≥1 cerebrovascular event*	40 (1)	8 (0.9)
Use of platelet inhibitor	46 (1.1)	8 (0.9)
Self-reported smoking status, *n (%)*		
Current	403 (9.8)	31 (3.6)
Former	1222 (29.6)	72 (8.5)
Never	2234 (54.2)	124 (14.6)
Missing	263 (6.4)	623 (73.3)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; BP = blood pressure; eGFR = estimated glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; KP = Kaiser Permanente.
* Values represent this characteristic during the 2-y period before surgery.

Appendix Table 2. Retinopathy Procedure Codes Used to Indicate Diabetic Retinopathy in Patients With ICD-9 Diagnosis Code 250.5x, "Diabetes With Ophthalmic Manifestations"

Code	Description
CPT	
67005	Vitrectomy, anterior, partial
67010	Vitrectomy, anterior, subtotal, mechanical
67015	Aspiration or release of vitreous, subretinal, or choroidal fluid, pars plana approach
67025	Injection of vitreous substitute
67027	Implantation of intravitreal drug delivery system
67028	Intravitreal injection of a pharmacological agent
67036	Vitrectomy, mechanical pars plana approach
67038	Vitrectomy, mechanical pars plana approach, with epiretinal membrane stripping
67039	Vitrectomy with focal endolaser photocoagulation
67040	PPV and PRP
67041	PPV and preretinal cellular membrane removal
67042	PPV and internal limiting membrane removal
67043	PPV and removal of subretinal membrane
67101–67112	Repair of retinal detachment
67113	Complex retinal detachment repair with PPV and epiretinal membrane removal
67141–67145	Prophylaxis of retinal detachment; cryotherapy, diathermy, photocoagulation
67208–67218	Destruction of localized lesion of retina
67220–67225	Destruction of localized lesion of choroid
67227–67228	Destruction of progressive retinopathy; cryotherapy, diathermy, photocoagulation
ICD-9-CM procedure	
14.1x–14.9	Operations on retina, choroid, vitreous, and posterior chamber Includes vitrectomy, retinal detachment repair, retinal destruction

CPT = Current Procedural Terminology; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-9-CM = ICD-9, Clinical Modification; PPV = pars plana vitrectomy; PRP = panretinal photocoagulation.

Appendix Table 3. Reasons for Censoring for Surgical and Nonsurgical Populations*

Variable	1 Year	2 Years	3 Years	4 Years	5 Years
Nonsurgical population					
Incident cancer	122 (1.1)	217 (2)	288 (2.6)	343 (3.1)	401 (3.6)
Death	46 (0.4)	80 (0.7)	117 (1.1)	144 (1.3)	165 (1.5)
No contact >13 mo	0 (0)	876 (7.9)	1150 (10.4)	1351 (12.2)	1465 (13.2)
Disenrollment	941 (8.5)	1584 (14.3)	2074 (18.8)	2410 (21.8)	2646 (23.9)
Study end	0 (0)	0 (0)	0 (0)	548 (5)	2462 (22.3)
Not censored	9950 (90)	8302 (75.1)	7430 (67.2)	6263 (56.6)	3920 (35.4)
Surgical population					
Incident cancer	31 (0.8)	56 (1.4)	86 (2.1)	106 (2.6)	122 (3)
Death	10 (0.2)	19 (0.5)	21 (0.5)	25 (0.6)	30 (0.7)
No contact >13 mo	0 (0)	111 (2.8)	298 (7.4)	440 (10.9)	511 (12.7)
Disenrollment	350 (8.7)	629 (15.6)	837 (20.8)	985 (24.5)	1074 (26.7)
Study end	0 (0)	0 (0)	0 (0)	175 (4.3)	827 (20.6)
Not censored	3633 (90.3)	3209 (79.7)	2782 (69.1)	2293 (57)	1460 (36.3)

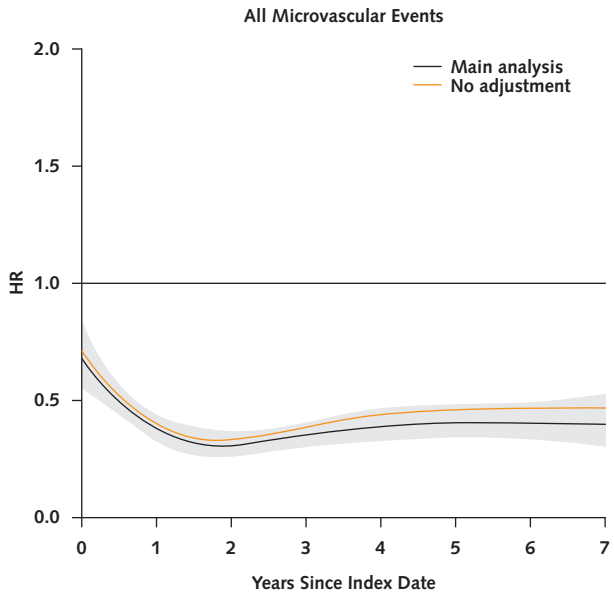
* Values are numbers (percentages).

Appendix Table 4. Fully Adjusted Cox Proportional Hazards Models of Time to Any Incident Microvascular Disease Event, as Well as Incident Retinopathy, Nephropathy, and Neuropathy Separately

Variable	All Microvascular Events		Retinopathy		Nephropathy		Neuropathy	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Surgery	0.684 (0.554–0.845)	0.000	0.616 (0.427–0.887)	0.009	1.919 (1.414–2.604)	0.000	0.296 (0.207–0.424)	0.000
Surgery*Spline[1]	0.998 (0.997–0.999)	0.000	1.000 (0.999–1.001)	0.84	0.995 (0.993–0.996)	0.000	1.000 (0.999–1.001)	0.81
Surgery*Spline[2]	1.009 (1.004–1.014)	0.001	1.000 (0.994–1.007)	1.00	1.026 (1.017–1.035)	0.000	1.001 (0.995–1.007)	0.73
Surgery*Spline[3]	0.984 (0.975–0.994)	0.002	0.999 (0.985–1.013)	0.88	0.952 (0.934–0.969)	0.000	0.998 (0.986–1.011)	0.79
Smoking (reference: never)								
Current	0.939 (0.839–1.051)	0.27	1.102 (0.906–1.340)	0.33	1.033 (0.817–1.305)	0.79	0.838 (0.731–0.962)	0.012
Former	0.912 (0.824–1.010)	0.078	1.100 (0.919–1.316)	0.30	1.071 (0.861–1.332)	0.54	0.769 (0.677–0.872)	0.000
Diabetes duration in years	1.062 (1.051–1.072)	0.000	1.146 (1.127–1.166)	0.000	1.035 (1.016–1.054)	0.000	1.029 (1.016–1.043)	0.000
Oral hypoglycemic use	1.114 (1.028–1.207)	0.008	1.190 (1.034–1.370)	0.015	0.961 (0.831–1.111)	0.59	1.180 (1.064–1.310)	0.002
Blood pressure ≥140/90 mm Hg at baseline	1.024 (0.919–1.142)	0.67	1.227 (1.030–1.460)	0.022	1.186 (0.993–1.418)	0.060	1.014 (0.884–1.163)	0.84
Hypertension diagnosis	1.065 (0.975–1.165)	0.163	0.998 (0.862–1.155)	0.98	1.153 (0.959–1.387)	0.130	1.068 (0.951–1.201)	0.27
ACE inhibitor or ARB use	0.960 (0.888–1.038)	0.31	0.919 (0.802–1.053)	0.23	1.157 (0.998–1.342)	0.054	0.919 (0.830–1.017)	0.102
Race/ethnicity (reference: white)								
Hispanic	0.844 (0.756–0.943)	0.003	0.997 (0.833–1.193)	0.97	0.734 (0.602–0.895)	0.002	0.848 (0.745–0.965)	0.012
Non-Hispanic black	0.992 (0.900–1.093)	0.87	1.189 (1.006–1.405)	0.043	0.950 (0.800–1.128)	0.56	0.951 (0.835–1.084)	0.45
Other	0.919 (0.800–1.056)	0.24	1.190 (0.965–1.467)	0.103	0.938 (0.709–1.242)	0.66	0.768 (0.637–0.924)	0.005
Insurance (reference: commercial)								
Medicaid	1.595 (1.326–1.918)	0.000	1.331 (0.948–1.868)	0.099	1.581 (1.096–2.280)	0.014	1.672 (1.336–2.093)	0.000
Medicare	1.511 (1.306–1.748)	0.000	1.441 (1.106–1.876)	0.007	1.340 (1.062–1.689)	0.013	1.505 (1.248–1.815)	0.000
Other	1.217 (0.962–1.539)	0.102	1.457 (1.003–2.116)	0.048	1.276 (0.820–1.985)	0.28	1.261 (0.946–1.681)	0.113
Use of other non-ACE/ARB antihypertensive medications	1.192 (1.104–1.286)	0.000	1.004 (0.883–1.141)	0.95	1.798 (1.541–2.097)	0.000	1.020 (0.921–1.129)	0.70
Dyslipidemia diagnosis	1.266 (1.141–1.404)	0.000	1.310 (1.098–1.563)	0.003	1.260 (1.013–1.568)	0.038	1.198 (1.047–1.370)	0.009
Statin use	1.020 (0.945–1.100)	0.62	1.005 (0.884–1.143)	0.94	1.062 (0.925–1.219)	0.39	0.988 (0.894–1.092)	0.82
Cerebrovascular disease diagnosis	1.489 (1.176–1.886)	0.001	1.572 (1.057–2.338)	0.025	1.764 (1.250–2.491)	0.001	1.327 (0.996–1.768)	0.053
Cardiovascular disease diagnosis	1.091 (0.903–1.318)	0.37	1.115 (0.812–1.530)	0.50	0.869 (0.630–1.198)	0.39	1.274 (1.019–1.593)	0.034
Triglyceride level ≥1.7 mmol/L (≥150 mg/dL)	1.069 (0.998–1.145)	0.059	0.897 (0.797–1.010)	0.072	1.202 (1.060–1.362)	0.004	1.116 (1.020–1.221)	0.017
Fibrate or niacin use	1.108 (0.982–1.251)	0.095	1.000 (0.817–1.225)	1.00	1.153 (0.932–1.426)	0.189	1.101 (0.938–1.292)	0.24
BMI category (reference: 34–39.9 kg/m^2)								
40–49.9 kg/m^2	1.143 (1.062–1.231)	0.000	1.086 (0.959–1.229)	0.192	1.174 (1.026–1.344)	0.020	1.100 (1.000–1.211)	0.049
≥50 kg/m^2	1.233 (1.113–1.365)	0.000	1.004 (0.835–1.208)	0.96	1.453 (1.197–1.762)	0.000	1.173 (1.026–1.339)	0.019
Age (reference: 18–29 y)								
30–44 y	1.630 (1.121–2.370)	0.011	1.154 (0.671–1.986)	0.60	2.174 (0.531–8.893)	0.28	2.206 (1.290–3.770)	0.004
45–54 y	2.454 (1.689–3.566)	0.000	1.418 (0.824–2.441)	0.21	6.666 (1.649–26.957)	0.008	3.042 (1.779–5.202)	0.000
55–64 y	3.475 (2.384–5.066)	0.000	1.628 (0.939–2.825)	0.083	13.567 (3.348–54.972)	0.000	3.896 (2.269–6.689)	0.000
65–79 y	4.381 (2.918–6.576)	0.000	1.471 (0.787–2.750)	0.23	24.056 (5.837–99.143)	0.000	4.499 (2.529–8.002)	0.000
Insulin use	1.525 (1.401–1.659)	0.000	1.902 (1.668–2.168)	0.000	1.434 (1.225–1.680)	0.000	1.408 (1.256–1.579)	0.000
HbA_{1c} level at baseline	1.142 (1.112–1.174)	0.000	1.275 (1.225–1.327)	0.000	0.942 (0.885–1.002)	0.059	1.127 (1.088–1.167)	0.000
Year of surgery (reference: 2011)								
2005	1.688 (1.411–2.018)	0.000	1.578 (1.166–2.137)	0.003	2.186 (1.594–2.998)	0.000	1.661 (1.323–2.086)	0.000
2006	1.671 (1.457–1.916)	0.000	1.769 (1.405–2.227)	0.000	1.729 (1.315–2.273)	0.000	1.532 (1.279–1.834)	0.000
2007	1.422 (1.258–1.607)	0.000	1.389 (1.125–1.715)	0.002	1.731 (1.383–2.165)	0.000	1.437 (1.224–1.687)	0.000
2008	1.266 (1.133–1.415)	0.000	1.276 (1.052–1.548)	0.014	1.527 (1.248–1.867)	0.000	1.340 (1.159–1.549)	0.000
2009	1.142 (1.024–1.273)	0.017	1.305 (1.081–1.575)	0.006	1.094 (0.894–1.340)	0.38	1.186 (1.027–1.369)	0.020
2010	1.019 (0.922–1.126)	0.72	1.011 (0.846–1.208)	0.90	0.995 (0.821–1.206)	0.96	1.085 (0.951–1.238)	0.23
Count of days with any health care use in 7–24 mo before baseline	1.020 (1.017–1.024)	0.000	1.004 (0.997–1.012)	0.27	1.028 (1.020–1.035)	0.000	1.018 (1.013–1.022)	0.000

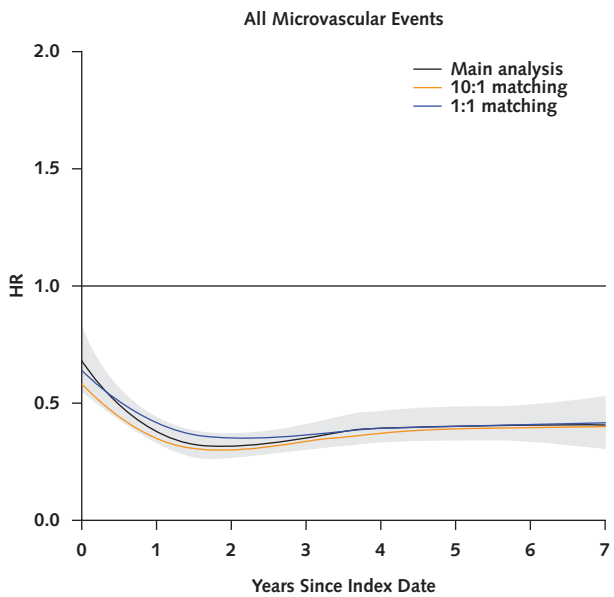
ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio.

Appendix Figure 1. Sensitivity analyses comparing the time-varying HR for all microvascular events (composite end point) in the main analysis (fully adjusted) versus a matched, unadjusted analysis.



HR = hazard ratio.

Appendix Figure 2. Sensitivity analyses comparing the time-varying HR for all microvascular events (composite end point) in the main analysis (3:1 matching) versus alternative 10:1 and 1:1 matching approaches.



HR = hazard ratio.

Appendix Table 5. Differences Between Groups in the Number of Key Measures/Contacts*

Variable	Surgical Group	Nonsurgical Group
Creatinine measures	10.2 per 5 y	9.0 per 5 y
Eye examination visits	1.44 per 5 y	1.32 per 5 y
Weight measures years 2–5 (as a proxy for visits)	11.6 per 4 y	10.1 per 4 y

* Values are numbers. We wondered if our study findings might reflect differences between the matched groups in number of contacts with health care providers or in surveillance for retinopathy or nephropathy because these are somewhat more "silent" conditions than diabetic neuropathy. Thus, we examined whether there were differences in the occurrence of visits in which a weight was recorded, eye examination visits, and laboratory measures of serum creatinine over the first 5 y after the index date for surgical and nonsurgical patients. These analyses show that numbers of creatinine measurements and eye examination visits did not differ between the surgical and nonsurgical groups over 5 y of follow-up. We also examined the occurrence of weight measurements after the index date as a proxy for the intensity of overall visits with the health care system. Standard care after bariatric surgery involves repeatedly monitoring weight in the first year. As expected, the surgical group had more weight measurements in the first year after the index date (15.5 vs 7.1 measurements). Of note, however, the number of weight measurements did not differ between the surgical and nonsurgical groups in years 2–5. Overall, this suggests that surgical and nonsurgical patients did not differ in terms of surveillance of microvascular disease.

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