Obesity Surgery

Effect of Bariatric Surgery on Cardiovascular Events and Metabolic Outcomes In Obese Patients with Insulin-treated Type 2 Diabetes: A Retrospective Cohort Study

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Abstract:	Aims To compare non-fatal cardiovascular (CV) events and metabolic outcomes, among obese patients with insulin-treated type 2 diabetes who underwent bariatric surgery compared to a propensity matched non-bariatric cohort. Methods A retrospective cohort study was conducted among 11,125 active patients with type 2 diabetes from The Health Improvement Network (THIN) database. Propensity score matching (1:6 ratio) was used to identify patients who underwent bariatric surgery (N=131) with a non-bariatric cohort (N=579). Follow-up was undertaken for 10 years (9,686 person-years) to compare differences in metabolic outcomes and CV risk events that included: Acute Myocardial Infarction (AMI), stroke, Coronary Heart Disease (CHD), Heart Failure (HF) and Peripheral Artery Disease (PAD). Cox proportional regression was used to compute the outcomes between groups. Results Mean age was 52±13 years (60% female); baseline weight and BMI were 116±25kg and 41±9kg/m2, respectively. Significant reductions in weight and BMI were observed in bariatric and non-bariatric cohorts during 10 years of follow-up. Bariatric surgery had a significant cardio-protective effect by reducing the risk of non-fatal CHD (adjusted hazard ratio [aHR]: 0.29, 95%CI:0.16–0.52, p<0.001) and PAD events (aHR: 0.31; 95%CI:0.11–0.89; p=0.03). However, surgery had no significant effect on AMI (aHR:0.98, p=0.95), stroke (HR:0.87, p=0.76) and HF (HR:0.89, p=0.73) risks. Bariatric surgery had favourable effects on insulin-independence, HbA1c and BP.

	Conclusion Among obese insulin-treated patients with type 2 diabetes, bariatric surgery is associated with significant reductions in non-fatal CHD and PAD events, lower body weight, BP, and a greater likelihood of insulin independence during 10 years of follow-up.

Title

Effect of Bariatric Surgery on Cardiovascular Events and Metabolic Outcomes In Obese Patients with Insulin-treated Type 2 Diabetes: A Retrospective Cohort Study

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Conflicts of interest: None

Abstract

Aims: To compare non-fatal cardiovascular (CV) events and metabolic outcomes, among obese patients with insulin-treated type 2 diabetes who underwent bariatric surgery compared to a propensity matched non-bariatric cohort.

Methods: A retrospective cohort study was conducted among 11,125 active patients with type 2 diabetes from The Health Improvement Network (THIN) database. Propensity score matching (1:6 ratio) was used to identify patients who underwent bariatric surgery (N=131) with a non-bariatric cohort (N=579). Follow-up was undertaken for 10 years (9,686 person-years) to compare differences in metabolic outcomes and CV risk events that included: Acute Myocardial Infarction (AMI), stroke, Coronary Heart Disease (CHD), Heart Failure (HF) and Peripheral Artery Disease (PAD). Cox proportional regression was used to compute the outcomes between groups.

Results: Mean age was 52±13 years (60% female); baseline weight and BMI were 116±25kg and 41±9kg/m^2, respectively. Significant reductions in weight and BMI were observed in bariatric and non-bariatric cohorts during 10 years of follow-up. Bariatric surgery had a significant cardio-protective effect by reducing the risk of non-fatal CHD (adjusted hazard ratio [aHR]: 0.29, 95%CI:0.16–0.52, p<0.001) and PAD events (aHR: 0.31; 95%CI:0.11–0.89; p=0.03). However, surgery had no significant effect on AMI (aHR:0.98, p=0.95), stroke (HR:0.87, p=0.76) and HF (HR:0.89, p=0.73) risks. Bariatric surgery had favourable effects on insulin-independence, HbA1c and BP.

Conclusion: Among obese insulin-treated patients with type 2 diabetes, bariatric surgery is associated with significant reductions in non-fatal CHD and PAD events, lower body weight, BP, and a greater likelihood of insulin independence during 10 years of follow-up.

What is already known about this subject?

- Obesity and type 2 diabetes are associated with high risk of cardiovascular events
- Obesity is causally associated with peripheral artery disease
- Insulin –treated type 2 diabetes is associated with additional excess risk of cardiovascular events
- Bariatric surgery in people with or without diabetes reduces cardiovascular events

What does this study add?

- This study focuses on insulin treated type 2 diabetes – recently recognised to be associated with higher risks of cardiovascular events
- Among insulin treated type 2 diabetes, bariatric surgery is associated with significant reduction in non-fatal coronary heart disease and peripheral artery disease
- Among insulin treated type 2 diabetes, bariatric surgery is associated with significant reduction and maintenance of weight loss, significant reduction in HbA1c, with relapse of HbA1c levels after 6 years of follow up and significant increase of insulin independence
-

How might this impact on clinical practice?

- Bariatric surgery should be considered as a genuine therapeutic option for the management of obese insulin treated type 2 diabetes to reduce coronary heart disease, peripheral artery disease events, reduce HbA1c levels and potentially reduce long-term risk of microvascular complications of diabetes as well as inducing insulin indepence.

Background

Obesity and Type 2 diabetes (T2D) are major global health problems that are intrinsically linked with adverse cardiovascular (CV) outcomes[1,2]. Obesity-associated coronary artery disease and myocardial dysfunction have been shown to be a direct consequence of excess dysfunctional adipose tissue, driven by increased pro-inflammatory state, insulin resistance, endothelial dysfunction and the development of myocardial hypertrophy[3]. Consequently, weight loss by any means has been shown to improve CV outcomes[4]. Although diet and exercise play a crucial role in obesity management, lifestyle alone may not achieve durable weight loss in the majority of patients[5]. Bariatric surgery therefore has emerged as the most effective and durable strategy for long-term weight loss in morbidly obese individuals[6]. The two most commonly performed bariatric surgical procedures are the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). Indeed, previous studies have shown beneficial effects of these bariatric surgical procedures on CV outcomes[7-9].

Many patients with T2D will require insulin treatment to manage hyperglycaemia, to reduce the risk of long-term vascular complications[10]. However, insulin therapy is known to induce ~4-9 kg weight gain in the first year of treatment, while escalation of insulin treatment doses are associated with greater weight gain[11] and excess CV risk[12]. Furthermore, evidence from randomized controlled trial and observational studies have implicated insulin therapy in patients with T2D with increased CV risk and mortality[13-16], possibly due to weight gain, recurrent hypoglycaemia and iatrogenic hyperinsulinemia[17,18]. Thus, a cohort of insulin-treated patients with T2D, represent a complex heterogenous, challenging group of patients, many of whom have significant comorbidities and high CV disease risk. No studies have assessed the effect bariatric surgery on cardiovascular outcomes among insulin-treated patients with T2D in routine clinical care.

Methods

Study design, data sources and study population

This was a retrospective cohort study that used The Health Improvement Network (THIN), an anonymised health care records derived from over 600 UK general practices, containing details on demographics, lifestyle characteristics, major medical and surgical conditions, drug utilisation, and health outcomes of over 17 million patients, 3.1 million of which are active patients[19]. Our dataset contains all adult patients (age >18 years) with T2D and have been prescribed with any form of insulin therapy up to September 2017 (N=11,125). Patients' index date was either the day of bariatric surgery (RYGB or SG) or, in case they have not received bariatric surgery, first intensification of insulin therapy. We excluded patients with type 1 diabetes or non- insulin-treated T2D. Ethics approval was provided by the NHS South East Multi-centre Research Ethics Committee (MREC).

Exposure and outcomes

Exposure of interest is bariatric surgery (RYGB or SG). Patients were censored throughout 10 years of follow-up – following the development of primary outcome, transferred out, loss to follow-up or at the end of the study. Primary outcome was patients' survivability against non-fatal CV events with further stratification to include CV events into divisions of time to the risk of Acute Myocardial Infarction (AMI), stroke, Coronary Heart Disease (CHD), Heart Failure (HF) and Peripheral Artery Disease (PAD). Secondary outcomes included health covariates such as body weight, calculated BMI, HbA1c, total cholesterol, systolic/diastolic blood pressure and insulin independence.

Covariates and follow-up strategy

We followed-up the treatment group whom underwent bariatric surgery and compared with their propensity-matched (PS) matched non-bariatric surgery from their first insulin prescription date up to the endpoint of 10-year of follow-up. Patients with CV events prior to the designated baseline point were excluded from the primary survival estimation on each stratified CV element. Baseline clinical parameters (average values from multiple entries) were measured at the same time window according to patient's treatment category, i.e. 90

days up to one day before the surgery date or first intensification of insulin therapy. Covariates were, then, recalculated at 6-month, and at each year point up to 10 years of follow-up; with 90 days window on every concurring point of time.

Statistical analysis

Primary analysis was time to the risk of stratified non-fatal CV events that included AMI, stroke, CHD, HF and PAD in a PS-matched groups. The PS model was estimated by using logistic regression model to adjust for baseline characteristics, thus, minimising allocation bias between groups. The balance assessment was made between bariatric (treated) and non-bariatric (untreated) groups by measuring standardised differences before and after the matching procedure. The mean form continuous covariates and proportion of categorical variables between groups were examined and summarised. Each treatment subject was matched to six reference subjects at the nearest distance measured by the estimated PS, based on the estimated treatment probabilities[20]. We employed caliper width=0.05 of the standard deviation of the logit of the PS to minimise distance within matched sets which may improve match quality but would limit excessive number of matched subjects[21]. A caliper width of <0.2 has been shown to result in optimal estimation compared to higher choices of caliper use[22]. PS was included in all Cox proportional hazards regression modelling as it was considered a prognostic covariate. Stratified log-rank test, with Kaplan-Meier survival curves respectively was used to compare the equality between the PS-matched groups. The absolute reduction in the probability of an event occurring within 10-year follow-up was calculated. Marginal hazard ratios were estimated to quantify the adjusted hazard of an event occurred in the bariatric group compared to the matched non-bariatric group. Proportional hazards assumptions were confirmed through Schoenfeld residuals test. Point estimates with 95% Confidence Intervals (CIs) at the conventional statistical significance level of 0.05 were used in the regression models. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure; no violations were observed.

Missing data among covariates were managed through multiple imputations using the predictive means matching for continuous covariates with accounting to exposure (i.e. bariatric), age, gender, diabetes duration, Townsend deprivation status, marital status,

smoking and alcohol use[23]. To test the adequacy of our multiple imputation approach in addressing the impact of some missing data, we conducted a sensitivity analysis wherein the primary endpoints in the imputed dataset and were compared with the dataset with missing values and found to be similar, thereby affirming the robustness of the imputation method employed before PS matching procedure was performed[24].

We used Student's t-test to estimate the mean changes in continuous variables (e.g. body weight & HbA1c) in both PS matched groups throughout 10-year of follow-up compared to their baseline measurements; and Pearson X^2 to test on the likelihood of being off insulin at 5 and 10 years from the baseline. Statistical significance was put at a p level of 0.05. To avoid the probability of type II error, the study was powered to 0.8 and the matched sample size of 710 was found to detect a true difference of less than 0.1 between the two groups at 5% significance level. The study fulfilled the STROBE criteria for reporting observational studies. Throughout, we used SAS Software version 9.4 in the initial dataset management (SAS Institute, Cary, NC); Stata Statistical Software version 15.1 in all carried analysis (StataCorp., College Station, TX); and GraphPad/Prism version 8.0 for visualisation (La Jolla, CA).

Results

Patients' characteristics and total follow-up

From 11,125 patients with insulin-treated T2D, we identified 155 patients who have had bariatric surgical operation. The PS matching procedure allowed 131 bariatric patients to be matched with up to six control subjects. This yielded a total number of 710 PS-matched participants. The median treatment duration was 10.07 years (interquartile range (IQR): 6.11–14.31 years). The median follow-up was 8.42 years (IQR: 2.92–14.58 years) representing a total follow-up period of 9,686 person-years.

In the matched cohort, the overall mean of age was 51.7 (SD 12.5) years; 59.6% were females. The mean body weight, BMI and HbA1c level were 115.7 (SD 25.4) kg, 40.7 (SD 9.2) kg/m^2 and 71.2 (SD 18.1) mmol/mol, respectively. The baseline characteristics in both bariatric and non-bariatric groups were compared between the full and matched cohort with their standardised differences shown in ***Table 1***.

Cardiovascular event rates

The probability of survival for non-fatal CHD was significantly different between matched bariatric and non-bariatric groups at 1-year (98.0% vs 89.6%), 5-year (92.2% vs 67.6%) and 10-year (88.2% vs 51.6%) of follow-up (log-rank test $p < 0.001$) (**Fig. 1c**). A total of 277 (18 vs 259) events were reported with a crude event rate of 52.4 (21.4 vs 58.2) per 1000 person-years (95% CI 46.6–58.9). The probability of survival for non-fatal PAD was also significantly different at 5-year (90.5% vs 78.8%) and 10-year (84.0% vs 53.1%) of follow-up (log-rank test $p = 0.007$) (**Fig. 1e**). A total of 59 (6 vs 53) events were observed with a crude event rate of 62.1 (25.9 vs 73.8) per 1000 person-year (95% CI 48.1–80.2). The probabilities of survival for non-fatal AMI, stroke and HF were with little or no statistical significance between the matched groups throughout 10 years of follow-up (log-rank test $p > 0.5$) (**Fig. 1a, 1b & 1d**). **Table 2** shows a summary of the events for each of the stratified CV components with absolute event rates.

Risk of cardiovascular disease

Bariatric surgery was protective against all analysed CV elements in the matched cohort. The risk of non-fatal CHD and PAD in the bariatric group were significantly lower (by 71% & 69%, respectively) compared to the matched non-bariatric group (CHD aHR: 0.29, 95%CI 0.16–0.52, p < 0.001; PAD aHR: 0.31, 95%CI 0.11–0.89, p = 0.03) adjusted for age, HbA1c level, diabetes duration, oral antidiabetic drug use, diuretics use, antihypertensive drug use, Townsend deprivation status, alcohol use and smoking status. Despite protective tendency against non-fatal AMI, stroke and HF, none of which was found with statistical significance (AMI aHR: 0.98, 95%CI 0.54–1.77, p = 0.94; stroke aHR: 0.87, 95%CI 0.36–2.10, p = 0.75; HF aHR: 0.89, 95%CI 0.47–1.70, p = 0.73) (**Table 2**).

Changes in metabolic outcomes

Significant reductions in the matched cohort (i.e. p < 0.001) favouring the bariatric group vs non-bariatric was observed in terms of body weight and BMI throughout all 10 years of follow-up compared to baseline. Body weight and BMI for bariatric vs non-bariatric were: at 1-year point (97.5±24.2 vs 109.8±18.6 kg; 34.2±9.0 vs 38.8±7.4 kg/m^2, respectively), at 5-year point (98.9±23.3 vs 107.1±18.2 kg; 34.8±9.2 vs 37.8±7.3 kg/m^2, respectively), and at 10-year point (94.1±20.1 vs 107.6±17.3 kg; 32.9±7.7 vs 38.0±7.1 kg/m^2, respectively) of follow-up (**Fig. 2a & 2b**). The reduction in HbA1c was statistically significant up to six years of follow-up. At the first year the level of HbA1c in the bariatric vs non-bariatric (60.3±18.2 vs 72.0±17.9 mmol/mol), at 3-year point (66.1±16.8 vs 71.3±17.8 mmol/mol) and at 6-year point (68.1±16.9 vs 72.8±18.8 mmol/mol). No statistical difference was observed beyond the seventh year in the HbA1c level between the matched groups (**Fig. 2c**). Total cholesterol was significantly reduced during the first six months of follow-up (4.12±0.99 vs 4.50±1.14 mmol/L, p = 0.008) (**Fig. 2d**). Blood pressure was also significantly reduced early following the bariatric surgery. The systolic blood pressure at 6-month point (130±18 vs 137±16 mmHg, p < 0.001) and at 1-year point (133±17 vs 137±15 mmHg, p = 0.07) (**Fig. 2e**). The diastolic blood pressure was significantly reduced in the bariatric vs non-bariatric (p < 0.05) up to two years of follow-up (6-month: 76±10 vs 79±9; 1-year: 77±9 vs 79±9; 2-year: 76±10 vs 79±10 mmHg) (**Fig. 2f**). **Figure 2** represents reduction in the matched cohort of the analysed outcome variables during 10 years of follow-up in comparison to their baseline measurements with 95% confidence intervals.

The analysis of the matched groups also revealed that, at one year of follow-up, 6.4% of whom underwent bariatric surgery were insulin independent compared to 7.9% non-bariatric with little or no statistical significance of a difference (X^2=0.35, p = 0.55). At three years, 31.2% of bariatric patients were independent from insulin use compared to 17.6% non-bariatric (X^2=10.59, p = 0.001). At six years, 41.5% of bariatric patients were independent from using insulin compared to 22.2% non-bariatric (X^2=11.47, p = 0.001). At 10 years, 77.5% of bariatric patients were independent from using insulin compared to 33.7% non-bariatric (X^2=28.71, p < 0.0001).

Discussion

This study showed that, among morbidly obese patients with insulin-treated T2D in routine clinical practice, bariatric surgery was associated with a significant 71% risk reduction in non-fatal CHD and 69% reduction in PAD events, as well as significant reductions in weight, HbA1c, insulin independence and blood pressure. However, no significant reductions was observed with AMI, stroke and heart failure.

Our findings were similar in pattern with previous observational studies on bariatric surgery with regards to cardiovascular and metabolic benefits[7-9]. Our study however focuses on patients with Insulin-treated T2D – known to be associated with higher risks of cardiovascular events[13-16]. Indeed, a previous study have shown that while bariatric surgery reduces cardiovascular events and mortality, the mortality risk in people with diabetes after bariatric surgery remains 35% higher than that of the general population.[25] Our study therefore extends evidence of cardiovascular benefit of bariatric surgery in this patient cohort whose residual CV risk are likely to be higher. Interestingly, a previous study in patients with diabetes reported a reduction in myocardial infarction but no effect was observed on stroke incidence[8]. However, a factor–treatment interaction analysis showed that the effect of bariatric surgery on AMI was greater in participants with higher total cholesterol and triglyceride levels, implying that those with dyslipidemia were the ones who are likely to gain the most benefit. Since our PS-matched cohort have optimal mean LDL-cholesterol and triglyceride levels (~2.4 and 2.3 mmol/L), respectively due to high use of statin therapy, this may explain the lack of significant reduction

of AMI in our cohort while highlighting the importance of statin therapy in this patient cohort. Our observation of significant reduction in PAD events within this patient cohort is novel and have major clinical significant. A recent study have concluded that obesity is causally associated with PAD after controlling for potential confounders like hypertension, dyslipidemia and hyperglycemia[26].

Insulin therapy is known to induce weight gain[11]. Our data showed a major reduction in weight following bariatric surgery, which persisted at 10 years of follow up. While greater significant reduction in weight following bariatric surgery compared with control is anticipated, it is interesting to note that weight loss was also observed in our PS-matched control cohort. This is likely due to concurrent use of GLP-1 analogue in our patient cohort. Evidence of weight loss with GLP-1 as adjunct to insulin treatment has been shown in randomized controlled trials.[27,28] In addition, we have also reported significant weight loss after 12 months of adding a GLP-1 to insulin therapy in routine clinical practice[29]. Of note, weight loss was not observed in our non- PS-matched control cohort, indicating robust PS matching protocol used in this study analysis (Supplement). The addition of GLP-1 therapy, in combination with use of other novel weight loss antidiabetic regimens like sodium glucose co-tranporter-2 (SGLT-2) inhibitor, as well as significant calorie restriction may also explain the smaller but appreciable percentage of patients who were insulin independence in the PS-matched control cohort, compared with those who underwent bariatric surgery. Interestingly, in contrast to the observed weight loss which persisted over 10 years of follow-up, the reduction in HbA1c was statistically significance only up to six years of follow-up post-surgery, with a rise in HbA1c during further follow-up. Previous studies comparing bariatric surgery outcomes with medical/lifestyle intervention have mainly reported HbA1c reduction up to five years post surgery[30-32], albeit in patients with T2D irrespective of treatment regimen. The discordance between long-term weight and HbA1c outcomes suggested that the observed relapse in HbA1c level was independent of weight regain. Nonetheless, any beneficial effects of bariatric surgery on weight, HbA1c reduction and insulin independence will have significant impact on the long-term risk of vascular complications of diabetes and will likely confer cost savings to the UK National Health Service in the long-term.

The main strength of our study derives from the inclusion of a relatively large cohort of insulin-treated T2D in a real-world population which can be generalized to the UK or similar population. This implies that our findings will be generalizable to various population with similar demographics. The cohort of patients studied here provides adequate statistical power and also contains information on other time-varying covariates to adjust for possible confounders. We adjusted for a large set of factors that could have differed at the baseline through a robust PS-matching protocol. This is crucial since the decision to have bariatric surgery in routine clinical practice is often based on multiple factors, not confided to UK NICE guidelines. Nevertheless, some residual confounding in our study could persists due to our inability to measure and adjust for the dosage of the insulin therapy as well as the reliability of diabetes duration due to the ongoing issue of identifying incident versus prevalent diabetes. Also, the classification of exposure into two broad types of bariatric surgery could have possibly masked the effects of individual types of bariatric surgery and could have driven our study away or closer to the null hypothesis. Nonetheless, previous high profile studies on cardiovascular benefits of bariatric surgery have not looked at individual types of surgery.

In summary, this study suggests that bariatric surgery in morbidly obese patients with insulin-treated T2D is associated with a significant reduction in a non-fatal CHD and PAD events, as well as significant reduction in weight, HbA1c and insulin independence compared with matched control. The mechanism for this cardio-protective effects remained speculative but further study is required to confirm this observation.

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Table 1. Baseline characteristics

	Cohort					
	Full population [N = 11,125]			Propensity matched [N = 710]		
Baseline variable	**Bariatric** [n = 155]	**Non-bariatric** [n = 10,970]	**Std. diff***	**Bariatric** [n = 131]	**Non-bariatric** [n = 579]	**Std. diff†**
Demographics						
Age (yrs), mean (SD)	50.01 (11.1)	57.71 (13.3)	-0.694	50.74 (11.0)	51.96 (12.8)	-0.110
Gender, no (%)						
Female	89 (57.4)	5068 (46.2)	0.224	73 (55.4)	351 (60.6)	-0.107
Townsend deprivation, %						
Least deprived	14.0	21.7	-0.204	15.7	17.3	-0.044
Less	24.3	20.7	0.086	24.0	18.1	0.145
Average	17.6	21.4	-0.094	16.5	20.2	-0.094
More	20.6	20.9	-0.008	21.5	27.7	-0.144
Most deprived	23.5	15.3	0.209	22.3	16.8	0.14
Type 2 diabetes (yrs) , mean (SD)						
Diabetes duration	14.15 (7.7)	15.12 (8.4)	-0.125	13.97 (7.8)	14.89 (7.6)	-0.117
Insulin duration	7.36 (4.9)	8.01 (5.5)	-0.130	7.3 (4.8)	8.68 (5.5)	-0.287
Clinical parameters, mean (SD)						
Weight (kg)	127.3 (30.3)	90.79 (20.6)	1.204	123.22 (28.3)	114.88 (24.5)	0.294
Height (m)	1.7 (0.1)	1.68 (0.1)	0.201	1.7 (0.1)	1.69 (0.1)	0.102
BMI (kg/m^2)	43.87 (10.0)	32.37 (7.5)	1.150	42.77 (9.6)	40.6 (9.0)	0.226
HbA1c (mmol/mol)	72.34 (19.3)	70.03 (17.2)	0.119	72.41 (18.6)	70.91 (17.9)	0.080
Fasting glucose (mmol/L)	9.83 (4.3)	9.93 (3.9)	-0.023	9.84 (4.3)	9.82 (3.9)	0.004
Blood glucose (mmol/L)	12.22 (8.8)	11.69 (5.3)	0.071	12.04 (9.1)	11.92 (5.3)	0.016
SBP (mmHg)	134.64 (14.6)	138.89 (16.5)	-0.271	135.06 (14.5)	136.4 (16.0)	-0.088
DBP (mmHg)	78.66 (8.4)	78.94 (9.6)	-0.031	79.3 (8.5)	78.77 (9.3)	0.058
Albumin (g/dL)	3.96 (0.4)	4.15 (0.5)	-0.368	3.96 (0.4)	3.96 (0.4)	-0.005
Alkaline Phosphatase (IU/L)	98.31 (47.1)	91.62 (43.0)	0.146	98.79 (48.8)	96.88 (51.5)	0.038
Serum creatinine (µmol/L)	91.74 (78.4)	92.68 (52.6)	-0.014	92.29 (84.0)	88.17 (57.7)	0.056
C-reactive protein (mg/L)	10.02 (11.4)	14.23 (25.9)	-0.208	10.15 (11.7)	10.07 (16.3)	0.006
Globulin serum (g/L)	30.98 (5.4)	29.93 (4.6)	0.206	30.87 (5.3)	30.73 (4.8)	0.027
Packed Cell Volume (L/L)	0.39 (0.04)	0.4 (0.05)	-0.142	0.39 (0.04)	0.39 (0.06)	0.003
Platelets count (10^9/L)	252.88 (99.4)	233.21 (101.2)	0.197	250.29 (100.3)	243.03 (111.5)	0.069
Triglyceride (mmol/L)	2.33 (1.5)	2.03 (1.3)	0.2	2.34 (1.6)	2.26 (1.4)	0.049
Total cholesterol (mmol/L)	4.47 (1.2)	4.49 (1.1)	-0.019	4.52 (1.2)	4.52 (1.2)	0.002
Low density lipoprotein (mmol/L)	2.39 (0.9)	2.39 (0.9)	0.001	2.39 (0.9)	2.44 (1.0)	-0.05
High density lipoprotein (mmol/L)	1.07 (0.3)	1.22 (0.4)	-0.439	1.07 (0.3)	1.1 (0.3)	-0.091
Alcohol status, %						
Unknown	3.7	3.1	0.03	3.3	3.0	0.017
Ex-drinker	11.8	7.0	0.162	11.6	11.5	0.003
Never	33.1	31.3	0.039	33.1	33.1	-0.002
Current	51.5	58.5	-0.143	52.1	52.4	-0.006

Smoking status, %						
Ex-smoker	33.1	37.1	-0.085	31.4	36.9	-0.116
Never	52.9	49.7	0.064	52.9	52.2	0.015
Current	14.0	13.1	0.025	15.7	10.9	0.141
Comorbidities, %						
AMI	24.3	20.3	0.095	23.1	20.2	0.073
Stroke	11.0	12.9	-0.059	12.4	7.7	0.156
CHD	77.9	75.6	0.055	78.5	72.9	0.132
HF	18.4	17.8	0.016	17.4	18.5	-0.029
PAD	18.4	14.6	0.101	18.2	11.3	0.195

Diabetes duration is time from first diagnosis of diabetes to date of intensification with insulin drug (index date).
* Standardised differences are the absolute difference in means or percentages divided by the SD of the treated group. Resulting standardised difference after 1:6 matching based on average treatment effect on treated propensity score technique and robust variance estimation.
† Mean of standardized difference after matching (0.081), i.e. at 8% difference measured between the matched groups.

Table 2. Non-fatal cardiovascular events, crude incidence rates and hazard ratios of events in the matched groups.

	Non-bariatric (N = 579)	Bariatric (N = 131)
AMI		
No of events/person-years	95/1084	13/153
Absolute rates[a] (95% CI)	87.6 (71.6–107.1)	84.9 (49.0–146.2)
HR[b] (95% CI)	1 (reference)	1.03 (0.57–1.86)
aHR[c] (95% CI)	1 (reference)	0.98 (0.54–1.77)
Stroke		
No of events/person-years	40/547	8/137
Absolute rates (95% CI)	73.0 (53.5–99.6)	58.2 (29.1–116.4)
HR (95% CI)	1 (reference)	0.77 (0.34–1.72)
aHR (95% CI)	1 (reference)	0.87 (0.36–2.10)
CHD		
No of events/person-years	259/4446	18/840
Absolute rates (95% CI)	58.2 (51.6–65.8)	21.4 (13.5–34.0)
HR (95% CI)	1 (reference)	0.31 (0.19–0.52)
aHR (95% CI)	1 (reference)	0.29 (0.16–0.52)
HF		
No of events/person-years	91/1327	13/205
Absolute rates (95% CI)	68.6 (55.8–84.2)	63 (36.9–109.5)
HR (95% CI)	1 (reference)	0.81 (0.44–1.49)
aHR (95% CI)	1 (reference)	0.89 (0.47–1.70)
PAD		
No of events/person-years	53/718	6/231
Absolute rates (95% CI)	73.9 (56.4–96.7)	25.9 (11.6–57.6)
HR (95% CI)	1 (reference)	0.27 (0.09–0.74)
aHR (95% CI)	1 (reference)	0.31 (0.11–0.89)

[a] Absolute rate at 1000 person-years.

[b] HR (unadjusted hazard ratio)

[c] aHR (adjusted hazard ration). Adjusted for age, diabetes duration, oral antidiabetic drug use, diuretics use, antihypertensive drug use, Townsend deprivation status, alcohol & smoking status and HbA1c level.

Figure 1. Cardiovascular Kaplan-Meier survival analysis plot for the matched cohort throughout 10 years of follow-up.

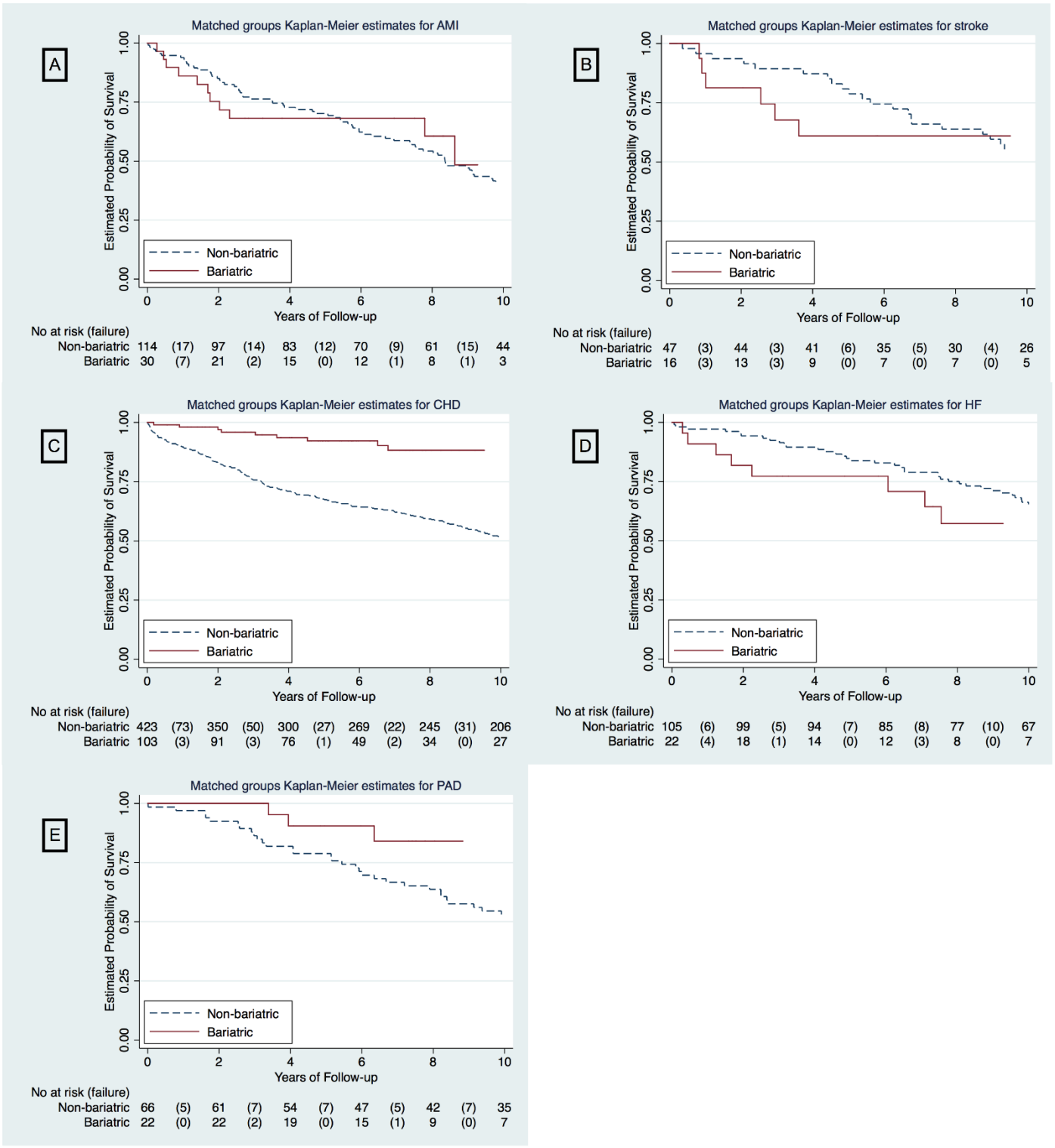
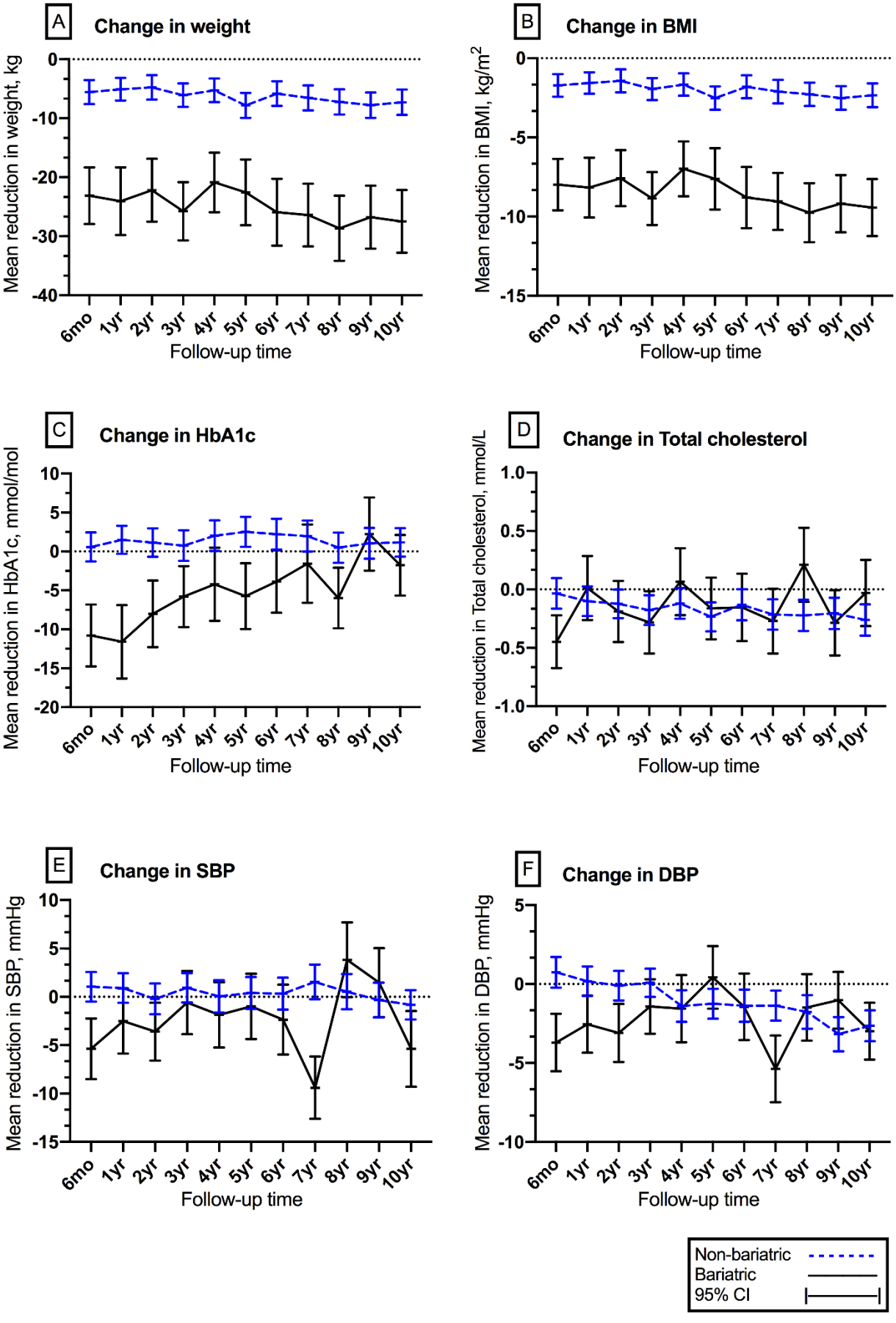


Figure 2. Mean difference in reduction in weight and health outcome variables between the matched groups throughout 10 years of follow-up compared to baseline.



Title

Effect of Bariatric Surgery on Cardiovascular Events and Metabolic Outcomes In Obese Patients with Insulin-treated Type 2 Diabetes: A Retrospective Cohort Study

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Conflicts of interest: None

Abstract

Aims: To compare non-fatal cardiovascular (CV) events and metabolic outcomes, among obese patients with insulin-treated type 2 diabetes who underwent bariatric surgery compared to a propensity matched non-bariatric cohort.

Methods: A retrospective cohort study was conducted among 11,125 active patients with type 2 diabetes from The Health Improvement Network (THIN) database. Propensity score matching (1:6 ratio) was used to identify patients who underwent bariatric surgery (N=131) with a non-bariatric cohort (N=579). Follow-up was undertaken for 10 years (9,686 person-years) to compare differences in metabolic outcomes and CV risk events that included: Acute Myocardial Infarction (AMI), stroke, Coronary Heart Disease (CHD), Heart Failure (HF) and Peripheral Artery Disease (PAD). Cox proportional regression was used to compute the outcomes between groups.

Results: Mean age was 52±13 years (60% female); baseline weight and BMI were 116±25kg and 41±9kg/m^2, respectively. Significant reductions in weight and BMI were observed in bariatric and non-bariatric cohorts during 10 years of follow-up. Bariatric surgery had a significant cardio-protective effect by reducing the risk of non-fatal CHD (adjusted hazard ratio [aHR]: 0.29, 95%CI:0.16–0.52, p<0.001) and PAD events (aHR: 0.31; 95%CI:0.11–0.89; p=0.03). However, surgery had no significant effect on AMI (aHR:0.98, p=0.95), stroke (HR:0.87, p=0.76) and HF (HR:0.89, p=0.73) risks. Bariatric surgery had favourable effects on insulin-independence, HbA1c and BP.

Conclusion: Among obese insulin-treated patients with type 2 diabetes, bariatric surgery is associated with significant reductions in non-fatal CHD and PAD events, lower body weight, BP, and a greater likelihood of insulin independence during 10 years of follow-up.

What is already known about this subject?

- Obesity and type 2 diabetes are associated with high risk of cardiovascular events
- Obesity is causally associated with peripheral artery disease
- Insulin –treated type 2 diabetes is associated with additional excess risk of cardiovascular events
- Bariatric surgery in people with or without diabetes reduces cardiovascular events

What does this study add?

- This study focuses on insulin treated type 2 diabetes – recently recognised to be associated with higher risks of cardiovascular events
- Among insulin treated type 2 diabetes, bariatric surgery is associated with significant reduction in non-fatal coronary heart disease and peripheral artery disease
- Among insulin treated type 2 diabetes, bariatric surgery is associated with significant reduction and maintenance of weight loss, significant reduction in HbA1c, with relapse of HbA1c levels after 6 years of follow up and significant increase of insulin independence
-

How might this impact on clinical practice?

- Bariatric surgery should be considered as a genuine therapeutic option for the management of obese insulin treated type 2 diabetes to reduce coronary heart disease, peripheral artery disease events, reduce HbA1c levels and potentially reduce long-term risk of microvascular complications of diabetes as well as inducing insulin indepence.

Background

Obesity and Type 2 diabetes (T2D) are major global health problems that are intrinsically linked with adverse cardiovascular (CV) outcomes[1,2]. Obesity-associated coronary artery disease and myocardial dysfunction have been shown to be a direct consequence of excess dysfunctional adipose tissue, driven by increased pro-inflammatory state, insulin resistance, endothelial dysfunction and the development of myocardial hypertrophy[3]. Consequently, weight loss by any means has been shown to improve CV outcomes[4]. Although diet and exercise play a crucial role in obesity management, lifestyle alone may not achieve durable weight loss in the majority of patients[5]. Bariatric surgery therefore has emerged as the most effective and durable strategy for long-term weight loss in morbidly obese individuals[6]. The two most commonly performed bariatric surgical procedures are the Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). Indeed, previous studies have shown beneficial effects of these bariatric surgical procedures on CV outcomes[7-9].

Many patients with T2D will require insulin treatment to manage hyperglycaemia, to reduce the risk of long-term vascular complications[10]. However, insulin therapy is known to induce ~4-9 kg weight gain in the first year of treatment, while escalation of insulin treatment doses are associated with greater weight gain[11] and excess CV risk[12]. Furthermore, evidence from randomized controlled trial and observational studies have implicated insulin therapy in patients with T2D with increased CV risk and mortality[13-16], possibly due to weight gain, recurrent hypoglycaemia and iatrogenic hyperinsulinemia[17,18]. Thus, a cohort of insulin-treated patients with T2D, represent a complex heterogenous, challenging group of patients, many of whom have significant comorbidities and high CV disease risk. No studies have assessed the effect bariatric surgery on cardiovascular outcomes among insulin-treated patients with T2D in routine clinical care.

Methods

Study design, data sources and study population

This was a retrospective cohort study that used The Health Improvement Network (THIN), an anonymised health care records derived from over 600 UK general practices, containing details on demographics, lifestyle characteristics, major medical and surgical conditions, drug utilisation, and health outcomes of over 17 million patients, 3.1 million of which are active patients[19]. Our dataset contains all adult patients (age >18 years) with T2D and have been prescribed with any form of insulin therapy up to September 2017 (N=11,125). Patients' index date was either the day of bariatric surgery (RYGB or SG) or, in case they have not received bariatric surgery, first intensification of insulin therapy. We excluded patients with type 1 diabetes or non- insulin-treated T2D. Ethics approval was provided by the NHS South East Multi-centre Research Ethics Committee (MREC).

Exposure and outcomes

Exposure of interest is bariatric surgery (RYGB or SG). Patients were censored throughout 10 years of follow-up – following the development of primary outcome, transferred out, loss to follow-up or at the end of the study. Primary outcome was patients' survivability against non-fatal CV events with further stratification to include CV events into divisions of time to the risk of Acute Myocardial Infarction (AMI), stroke, Coronary Heart Disease (CHD), Heart Failure (HF) and Peripheral Artery Disease (PAD). Secondary outcomes included health covariates such as body weight, calculated BMI, HbA1c, total cholesterol, systolic/diastolic blood pressure and insulin independence.

Covariates and follow-up strategy

We followed-up the treatment group whom underwent bariatric surgery and compared with their propensity-matched (PS) matched non-bariatric surgery from their first insulin prescription date up to the endpoint of 10-year of follow-up. Patients with CV events prior to the designated baseline point were excluded from the primary survival estimation on each stratified CV element. Baseline clinical parameters (average values from multiple entries) were measured at the same time window according to patient's treatment category, i.e. 90

days up to one day before the surgery date or first intensification of insulin therapy. Covariates were, then, recalculated at 6-month, and at each year point up to 10 years of follow-up; with 90 days window on every concurring point of time.

Statistical analysis

Primary analysis was time to the risk of stratified non-fatal CV events that included AMI, stroke, CHD, HF and PAD in a PS-matched groups. The PS model was estimated by using logistic regression model to adjust for baseline characteristics, thus, minimising allocation bias between groups. The balance assessment was made between bariatric (treated) and non-bariatric (untreated) groups by measuring standardised differences before and after the matching procedure. The mean form continuous covariates and proportion of categorical variables between groups were examined and summarised. Each treatment subject was matched to six reference subjects at the nearest distance measured by the estimated PS, based on the estimated treatment probabilities[20]. We employed caliper width=0.05 of the standard deviation of the logit of the PS to minimise distance within matched sets which may improve match quality but would limit excessive number of matched subjects[21]. A caliper width of <0.2 has been shown to result in optimal estimation compared to higher choices of caliper use[22]. PS was included in all Cox proportional hazards regression modelling as it was considered a prognostic covariate. Stratified log-rank test, with Kaplan-Meier survival curves respectively was used to compare the equality between the PS-matched groups. The absolute reduction in the probability of an event occurring within 10-year follow-up was calculated. Marginal hazard ratios were estimated to quantify the adjusted hazard of an event occurred in the bariatric group compared to the matched non-bariatric group. Proportional hazards assumptions were confirmed through Schoenfeld residuals test. Point estimates with 95% Confidence Intervals (CIs) at the conventional statistical significance level of 0.05 were used in the regression models. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure; no violations were observed.

Missing data among covariates were managed through multiple imputations using the predictive means matching for continuous covariates with accounting to exposure (i.e. bariatric), age, gender, diabetes duration, Townsend deprivation status, marital status,

smoking and alcohol use[23]. To test the adequacy of our multiple imputation approach in addressing the impact of some missing data, we conducted a sensitivity analysis wherein the primary endpoints in the imputed dataset and were compared with the dataset with missing values and found to be similar, thereby affirming the robustness of the imputation method employed before PS matching procedure was performed[24].

We used Student's t-test to estimate the mean changes in continuous variables (e.g. body weight & HbA1c) in both PS matched groups throughout 10-year of follow-up compared to their baseline measurements; and Pearson X^2 to test on the likelihood of being off insulin at 5 and 10 years from the baseline. Statistical significance was put at a p level of 0.05. To avoid the probability of type II error, the study was powered to 0.8 and the matched sample size of 710 was found to detect a true difference of less than 0.1 between the two groups at 5% significance level. The study fulfilled the STROBE criteria for reporting observational studies. Throughout, we used SAS Software version 9.4 in the initial dataset management (SAS Institute, Cary, NC); Stata Statistical Software version 15.1 in all carried analysis (StataCorp., College Station, TX); and GraphPad/Prism version 8.0 for visualisation (La Jolla, CA).

Results

Patients' characteristics and total follow-up

From 11,125 patients with insulin-treated T2D, we identified 155 patients who have had bariatric surgical operation. The PS matching procedure allowed 131 bariatric patients to be matched with up to six control subjects. This yielded a total number of 710 PS-matched participants. The median treatment duration was 10.07 years (interquartile range (IQR): 6.11–14.31 years). The median follow-up was 8.42 years (IQR: 2.92–14.58 years) representing a total follow-up period of 9,686 person-years.

In the matched cohort, the overall mean of age was 51.7 (SD 12.5) years; 59.6% were females. The mean body weight, BMI and HbA1c level were 115.7 (SD 25.4) kg, 40.7 (SD 9.2) kg/m^2 and 71.2 (SD 18.1) mmol/mol, respectively. The baseline characteristics in both bariatric and non-bariatric groups were compared between the full and matched cohort with their standardised differences shown in ***Table 1***.

Cardiovascular event rates

The probability of survival for non-fatal CHD was significantly different between matched bariatric and non-bariatric groups at 1-year (98.0% vs 89.6%), 5-year (92.2% vs 67.6%) and 10-year (88.2% vs 51.6%) of follow-up (log-rank test $p < 0.001$) (**Fig. 1c**). A total of 277 (18 vs 259) events were reported with a crude event rate of 52.4 (21.4 vs 58.2) per 1000 person-years (95% CI 46.6–58.9). The probability of survival for non-fatal PAD was also significantly different at 5-year (90.5% vs 78.8%) and 10-year (84.0% vs 53.1%) of follow-up (log-rank test $p = 0.007$) (**Fig. 1e**). A total of 59 (6 vs 53) events were observed with a crude event rate of 62.1 (25.9 vs 73.8) per 1000 person-year (95% CI 48.1–80.2). The probabilities of survival for non-fatal AMI, stroke and HF were with little or no statistical significance between the matched groups throughout 10 years of follow-up (log-rank test $p > 0.5$) (**Fig. 1a, 1b & 1d**). **Table 2** shows a summary of the events for each of the stratified CV components with absolute event rates.

Risk of cardiovascular disease

Bariatric surgery was protective against all analysed CV elements in the matched cohort. The risk of non-fatal CHD and PAD in the bariatric group were significantly lower (by 71% & 69%, respectively) compared to the matched non-bariatric group (CHD aHR: 0.29, 95%CI 0.16–0.52, p < 0.001; PAD aHR: 0.31, 95%CI 0.11–0.89, p = 0.03) adjusted for age, HbA1c level, diabetes duration, oral antidiabetic drug use, diuretics use, antihypertensive drug use, Townsend deprivation status, alcohol use and smoking status. Despite protective tendency against non-fatal AMI, stroke and HF, none of which was found with statistical significance (AMI aHR: 0.98, 95%CI 0.54–1.77, p = 0.94; stroke aHR: 0.87, 95%CI 0.36–2.10, p = 0.75; HF aHR: 0.89, 95%CI 0.47–1.70, p = 0.73) (**Table 2**).

Changes in metabolic outcomes

Significant reductions in the matched cohort (i.e. p < 0.001) favouring the bariatric group vs non-bariatric was observed in terms of body weight and BMI throughout all 10 years of follow-up compared to baseline. Body weight and BMI for bariatric vs non-bariatric were: at 1-year point (97.5±24.2 vs 109.8±18.6 kg; 34.2±9.0 vs 38.8±7.4 kg/m^2, respectively), at 5-year point (98.9±23.3 vs 107.1±18.2 kg; 34.8±9.2 vs 37.8±7.3 kg/m^2, respectively), and at 10-year point (94.1±20.1 vs 107.6±17.3 kg; 32.9±7.7 vs 38.0±7.1 kg/m^2, respectively) of follow-up (**Fig. 2a & 2b**). The reduction in HbA1c was statistically significant up to six years of follow-up. At the first year the level of HbA1c in the bariatric vs non-bariatric (60.3±18.2 vs 72.0±17.9 mmol/mol), at 3-year point (66.1±16.8 vs 71.3±17.8 mmol/mol) and at 6-year point (68.1±16.9 vs 72.8±18.8 mmol/mol). No statistical difference was observed beyond the seventh year in the HbA1c level between the matched groups (**Fig. 2c**). Total cholesterol was significantly reduced during the first six months of follow-up (4.12±0.99 vs 4.50±1.14 mmol/L, p = 0.008) (**Fig. 2d**). Blood pressure was also significantly reduced early following the bariatric surgery. The systolic blood pressure at 6-month point (130±18 vs 137±16 mmHg, p < 0.001) and at 1-year point (133±17 vs 137±15 mmHg, p = 0.07) (**Fig. 2e**). The diastolic blood pressure was significantly reduced in the bariatric vs non-bariatric (p < 0.05) up to two years of follow-up (6-month: 76±10 vs 79±9; 1-year: 77±9 vs 79±9; 2-year: 76±10 vs 79±10 mmHg) (**Fig. 2f**). **Figure 2** represents reduction in the matched cohort of the analysed outcome variables during 10 years of follow-up in comparison to their baseline measurements with 95% confidence intervals.

The analysis of the matched groups also revealed that, at one year of follow-up, 6.4% of whom underwent bariatric surgery were insulin independent compared to 7.9% non-bariatric with little or no statistical significance of a difference (X^2=0.35, p = 0.55). At three years, 31.2% of bariatric patients were independent from insulin use compared to 17.6% non-bariatric (X^2=10.59, p = 0.001). At six years, 41.5% of bariatric patients were independent from using insulin compared to 22.2% non-bariatric (X^2=11.47, p = 0.001). At 10 years, 77.5% of bariatric patients were independent from using insulin compared to 33.7% non-bariatric (X^2=28.71, p < 0.0001).

Discussion

This study showed that, among morbidly obese patients with insulin-treated T2D in routine clinical practice, bariatric surgery was associated with a significant 71% risk reduction in non-fatal CHD and 69% reduction in PAD events, as well as significant reductions in weight, HbA1c, insulin independence and blood pressure. However, no significant reductions was observed with AMI, stroke and heart failure.

Our findings were similar in pattern with previous observational studies on bariatric surgery with regards to cardiovascular and metabolic benefits[7-9]. Our study however focuses on patients with Insulin-treated T2D – known to be associated with higher risks of cardiovascular events[13-16]. Indeed, a previous study have shown that while bariatric surgery reduces cardiovascular events and mortality, the mortality risk in people with diabetes after bariatric surgery remains 35% higher than that of the general population.[25] Our study therefore extends evidence of cardiovascular benefit of bariatric surgery in this patient cohort whose residual CV risk are likely to be higher. Interestingly, a previous study in patients with diabetes reported a reduction in myocardial infarction but no effect was observed on stroke incidence[8]. However, a factor–treatment interaction analysis showed that the effect of bariatric surgery on AMI was greater in participants with higher total cholesterol and triglyceride levels, implying that those with dyslipidemia were the ones who are likely to gain the most benefit. Since our PS-matched cohort have optimal mean LDL-cholesterol and triglyceride levels (~2.4 and 2.3 mmol/L), respectively due to high use of statin therapy, this may explain the lack of significant reduction

of AMI in our cohort while highlighting the importance of statin therapy in this patient cohort. Our observation of significant reduction in PAD events within this patient cohort is novel and have major clinical significant. A recent study have concluded that obesity is causally associated with PAD after controlling for potential confounders like hypertension, dyslipidemia and hyperglycemia[26].

Insulin therapy is known to induce weight gain[11]. Our data showed a major reduction in weight following bariatric surgery, which persisted at 10 years of follow up. While greater significant reduction in weight following bariatric surgery compared with control is anticipated, it is interesting to note that weight loss was also observed in our PS-matched control cohort. This is likely due to concurrent use of GLP-1 analogue in our patient cohort. Evidence of weight loss with GLP-1 as adjunct to insulin treatment has been shown in randomized controlled trials.[27,28] In addition, we have also reported significant weight loss after 12 months of adding a GLP-1 to insulin therapy in routine clinical practice[29]. Of note, weight loss was not observed in our non- PS-matched control cohort, indicating robust PS matching protocol used in this study analysis (Supplement). The addition of GLP-1 therapy, in combination with use of other novel weight loss antidiabetic regimens like sodium glucose co-tranporter-2 (SGLT-2) inhibitor, as well as significant calorie restriction may also explain the smaller but appreciable percentage of patients who were insulin independence in the PS-matched control cohort, compared with those who underwent bariatric surgery. Interestingly, in contrast to the observed weight loss which persisted over 10 years of follow-up, the reduction in HbA1c was statistically significance only up to six years of follow-up post-surgery, with a rise in HbA1c during further follow-up. Previous studies comparing bariatric surgery outcomes with medical/lifestyle intervention have mainly reported HbA1c reduction up to five years post surgery[30-32], albeit in patients with T2D irrespective of treatment regimen. The discordance between long-term weight and HbA1c outcomes suggested that the observed relapse in HbA1c level was independent of weight regain. Nonetheless, any beneficial effects of bariatric surgery on weight, HbA1c reduction and insulin independence will have significant impact on the long-term risk of vascular complications of diabetes and will likely confer cost savings to the UK National Health Service in the long-term.

The main strength of our study derives from the inclusion of a relatively large cohort of insulin-treated T2D in a real-world population which can be generalized to the UK or similar population. This implies that our findings will be generalizable to various population with similar demographics. The cohort of patients studied here provides adequate statistical power and also contains information on other time-varying covariates to adjust for possible confounders. We adjusted for a large set of factors that could have differed at the baseline through a robust PS-matching protocol. This is crucial since the decision to have bariatric surgery in routine clinical practice is often based on multiple factors, not confided to UK NICE guidelines. Nevertheless, some residual confounding in our study could persists due to our inability to measure and adjust for the dosage of the insulin therapy as well as the reliability of diabetes duration due to the ongoing issue of identifying incident versus prevalent diabetes. Also, the classification of exposure into two broad types of bariatric surgery could have possibly masked the effects of individual types of bariatric surgery and could have driven our study away or closer to the null hypothesis. Nonetheless, previous high profile studies on cardiovascular benefits of bariatric surgery have not looked at individual types of surgery.

In summary, this study suggests that bariatric surgery in morbidly obese patients with insulin-treated T2D is associated with a significant reduction in a non-fatal CHD and PAD events, as well as significant reduction in weight, HbA1c and insulin independence compared with matched control. The mechanism for this cardio-protective effects remained speculative but further study is required to confirm this observation.

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Table 1. Baseline characteristics

	Cohort					
	Full population [N = 11,125]			Propensity matched [N = 710]		
Baseline variable	**Bariatric** [n = 155]	**Non-bariatric** [n = 10,970]	**Std. diff***	**Bariatric** [n = 131]	**Non-bariatric** [n = 579]	**Std. diff†**
Demographics						
Age (yrs), mean (SD)	50.01 (11.1)	57.71 (13.3)	-0.694	50.74 (11.0)	51.96 (12.8)	-0.110
Gender, no (%)						
Female	89 (57.4)	5068 (46.2)	0.224	73 (55.4)	351 (60.6)	-0.107
Townsend deprivation, %						
Least deprived	14.0	21.7	-0.204	15.7	17.3	-0.044
Less	24.3	20.7	0.086	24.0	18.1	0.145
Average	17.6	21.4	-0.094	16.5	20.2	-0.094
More	20.6	20.9	-0.008	21.5	27.7	-0.144
Most deprived	23.5	15.3	0.209	22.3	16.8	0.14
Type 2 diabetes (yrs) , mean (SD)						
Diabetes duration	14.15 (7.7)	15.12 (8.4)	-0.125	13.97 (7.8)	14.89 (7.6)	-0.117
Insulin duration	7.36 (4.9)	8.01 (5.5)	-0.130	7.3 (4.8)	8.68 (5.5)	-0.287
Clinical parameters, mean (SD)						
Weight (kg)	127.3 (30.3)	90.79 (20.6)	1.204	123.22 (28.3)	114.88 (24.5)	0.294
Height (m)	1.7 (0.1)	1.68 (0.1)	0.201	1.7 (0.1)	1.69 (0.1)	0.102
BMI (kg/m^2)	43.87 (10.0)	32.37 (7.5)	1.150	42.77 (9.6)	40.6 (9.0)	0.226
HbA1c (mmol/mol)	72.34 (19.3)	70.03 (17.2)	0.119	72.41 (18.6)	70.91 (17.9)	0.080
Fasting glucose (mmol/L)	9.83 (4.3)	9.93 (3.9)	-0.023	9.84 (4.3)	9.82 (3.9)	0.004
Blood glucose (mmol/L)	12.22 (8.8)	11.69 (5.3)	0.071	12.04 (9.1)	11.92 (5.3)	0.016
SBP (mmHg)	134.64 (14.6)	138.89 (16.5)	-0.271	135.06 (14.5)	136.4 (16.0)	-0.088
DBP (mmHg)	78.66 (8.4)	78.94 (9.6)	-0.031	79.3 (8.5)	78.77 (9.3)	0.058
Albumin (g/dL)	3.96 (0.4)	4.15 (0.5)	-0.368	3.96 (0.4)	3.96 (0.4)	-0.005
Alkaline Phosphatase (IU/L)	98.31 (47.1)	91.62 (43.0)	0.146	98.79 (48.8)	96.88 (51.5)	0.038
Serum creatinine (µmol/L)	91.74 (78.4)	92.68 (52.6)	-0.014	92.29 (84.0)	88.17 (57.7)	0.056
C-reactive protein (mg/L)	10.02 (11.4)	14.23 (25.9)	-0.208	10.15 (11.7)	10.07 (16.3)	0.006
Globulin serum (g/L)	30.98 (5.4)	29.93 (4.6)	0.206	30.87 (5.3)	30.73 (4.8)	0.027
Packed Cell Volume (L/L)	0.39 (0.04)	0.4 (0.05)	-0.142	0.39 (0.04)	0.39 (0.06)	0.003
Platelets count (10^9/L)	252.88 (99.4)	233.21 (101.2)	0.197	250.29 (100.3)	243.03 (111.5)	0.069
Triglyceride (mmol/L)	2.33 (1.5)	2.03 (1.3)	0.2	2.34 (1.6)	2.26 (1.4)	0.049
Total cholesterol (mmol/L)	4.47 (1.2)	4.49 (1.1)	-0.019	4.52 (1.2)	4.52 (1.2)	0.002
Low density lipoprotein (mmol/L)	2.39 (0.9)	2.39 (0.9)	0.001	2.39 (0.9)	2.44 (1.0)	-0.05
High density lipoprotein (mmol/L)	1.07 (0.3)	1.22 (0.4)	-0.439	1.07 (0.3)	1.1 (0.3)	-0.091
Alcohol status, %						
Unknown	3.7	3.1	0.03	3.3	3.0	0.017
Ex-drinker	11.8	7.0	0.162	11.6	11.5	0.003
Never	33.1	31.3	0.039	33.1	33.1	-0.002
Current	51.5	58.5	-0.143	52.1	52.4	-0.006

Smoking status, %						
Ex-smoker	33.1	37.1	-0.085	31.4	36.9	-0.116
Never	52.9	49.7	0.064	52.9	52.2	0.015
Current	14.0	13.1	0.025	15.7	10.9	0.141
Comorbidities, %						
AMI	24.3	20.3	0.095	23.1	20.2	0.073
Stroke	11.0	12.9	-0.059	12.4	7.7	0.156
CHD	77.9	75.6	0.055	78.5	72.9	0.132
HF	18.4	17.8	0.016	17.4	18.5	-0.029
PAD	18.4	14.6	0.101	18.2	11.3	0.195

Diabetes duration is time from first diagnosis of diabetes to date of intensification with insulin drug (index date).
* Standardised differences are the absolute difference in means or percentages divided by the SD of the treated group. Resulting standardised difference after 1:6 matching based on average treatment effect on treated propensity score technique and robust variance estimation.
† Mean of standardized difference after matching (0.081), i.e. at 8% difference measured between the matched groups.

Table 2. Non-fatal cardiovascular events, crude incidence rates and hazard ratios of events in the matched groups.

	Non-bariatric (N = 579)	Bariatric (N = 131)
AMI		
No of events/person-years	95/1084	13/153
Absolute rates[a] (95% CI)	87.6 (71.6–107.1)	84.9 (49.0–146.2)
HR[b] (95% CI)	1 (reference)	1.03 (0.57–1.86)
aHR[c] (95% CI)	1 (reference)	0.98 (0.54–1.77)
Stroke		
No of events/person-years	40/547	8/137
Absolute rates (95% CI)	73.0 (53.5–99.6)	58.2 (29.1–116.4)
HR (95% CI)	1 (reference)	0.77 (0.34–1.72)
aHR (95% CI)	1 (reference)	0.87 (0.36–2.10)
CHD		
No of events/person-years	259/4446	18/840
Absolute rates (95% CI)	58.2 (51.6–65.8)	21.4 (13.5–34.0)
HR (95% CI)	1 (reference)	0.31 (0.19–0.52)
aHR (95% CI)	1 (reference)	0.29 (0.16–0.52)
HF		
No of events/person-years	91/1327	13/205
Absolute rates (95% CI)	68.6 (55.8–84.2)	63 (36.9–109.5)
HR (95% CI)	1 (reference)	0.81 (0.44–1.49)
aHR (95% CI)	1 (reference)	0.89 (0.47–1.70)
PAD		
No of events/person-years	53/718	6/231
Absolute rates (95% CI)	73.9 (56.4–96.7)	25.9 (11.6–57.6)
HR (95% CI)	1 (reference)	0.27 (0.09–0.74)
aHR (95% CI)	1 (reference)	0.31 (0.11–0.89)

[a] Absolute rate at 1000 person-years.

[b] HR (unadjusted hazard ratio)

[c] aHR (adjusted hazard ration). Adjusted for age, diabetes duration, oral antidiabetic drug use, diuretics use, antihypertensive drug use, Townsend deprivation status, alcohol & smoking status and HbA1c level.

Figure 1. Cardiovascular Kaplan-Meier survival analysis plot for the matched cohort throughout 10 years of follow-up.

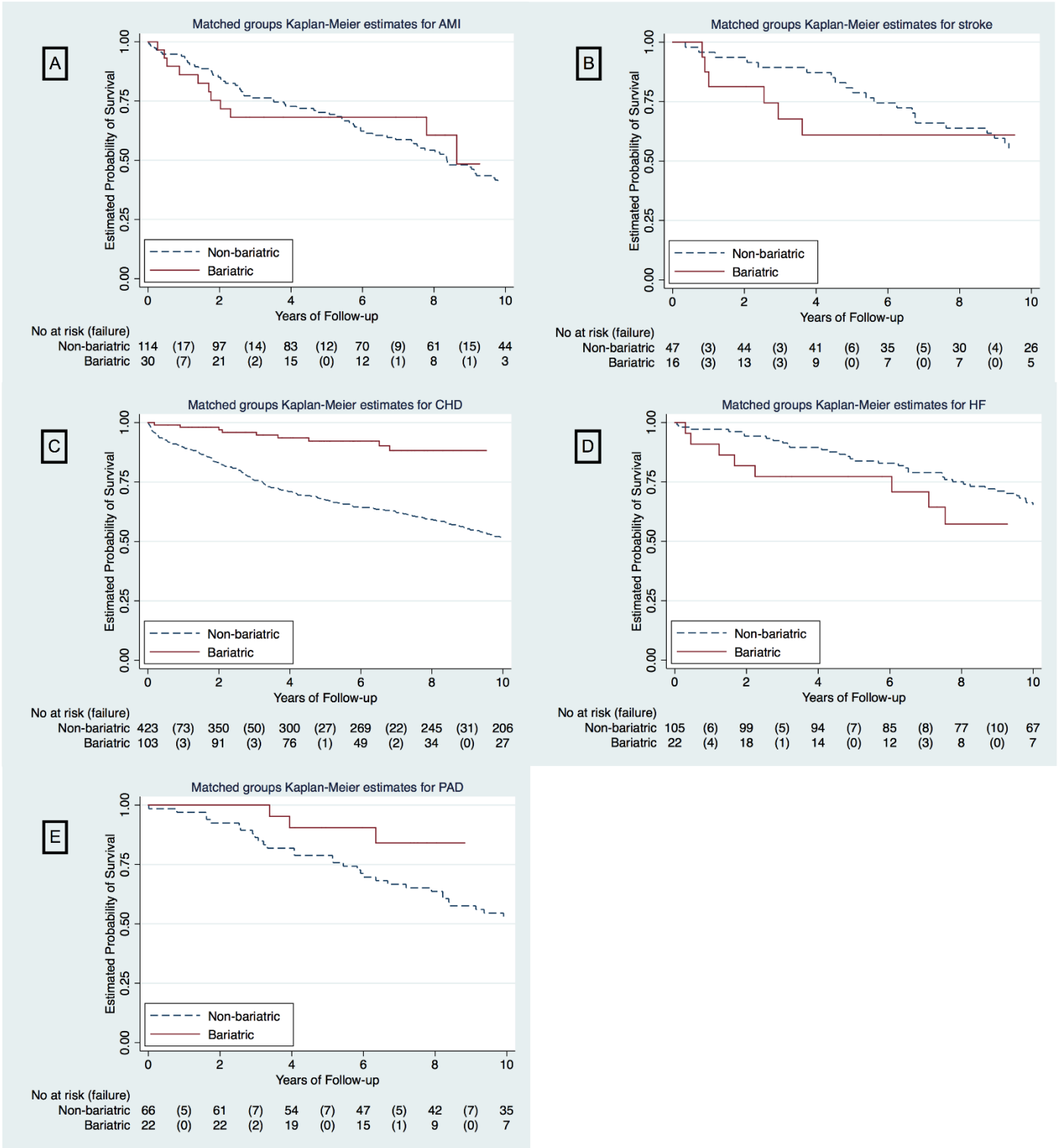


Figure 2. Mean difference in reduction in weight and health outcome variables between the matched groups throughout 10 years of follow-up compared to baseline.

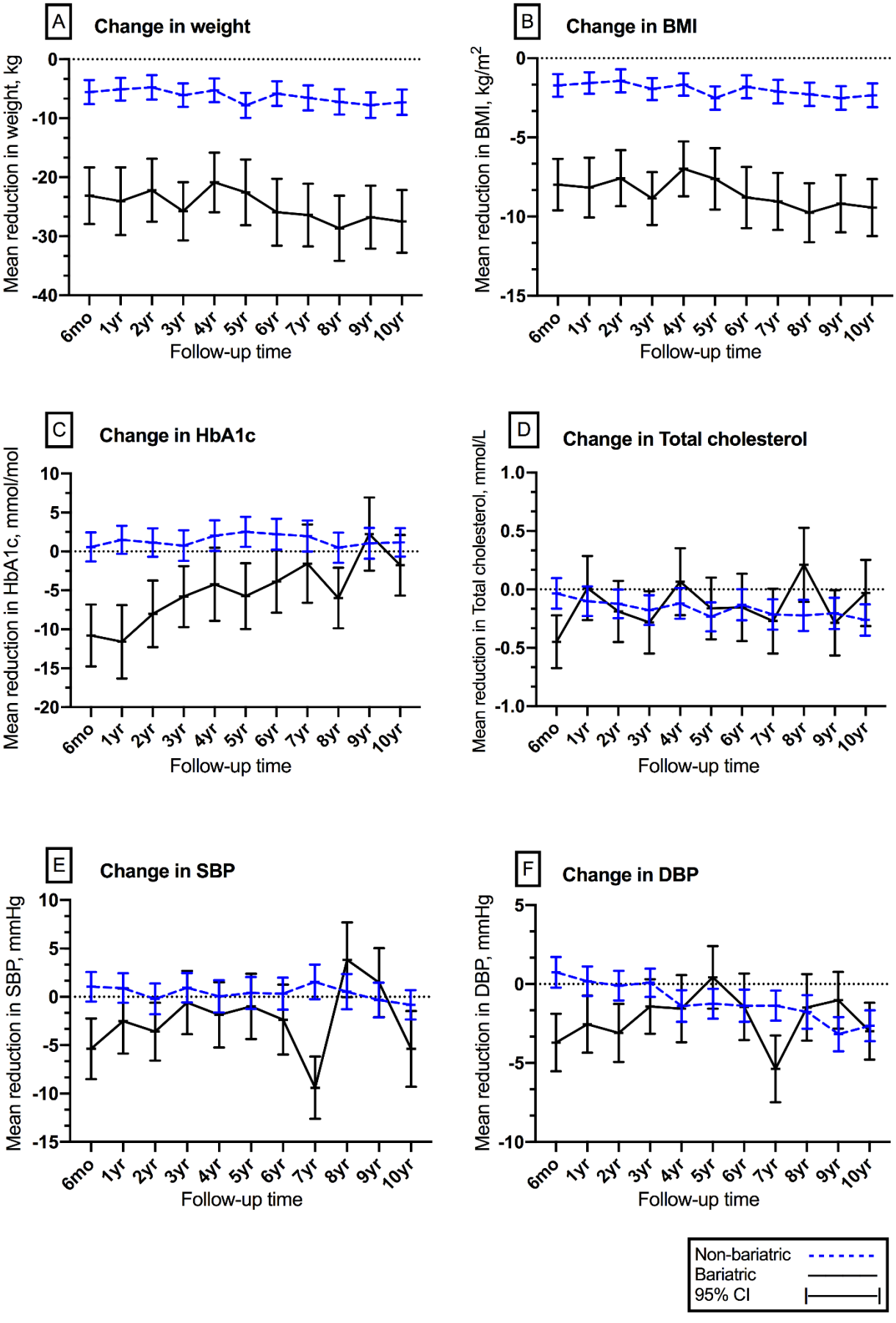
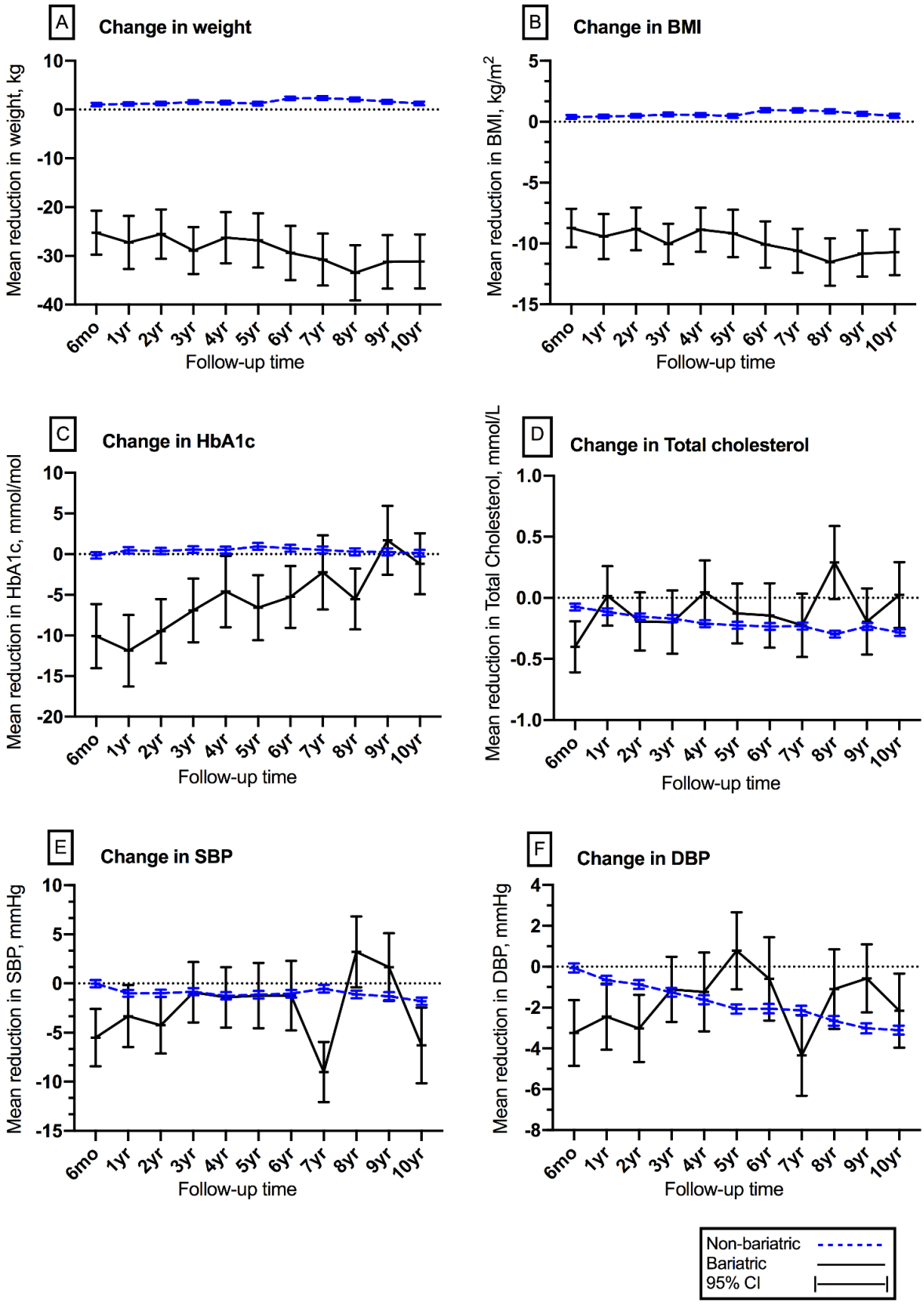


Figure S1. Mean difference in reduction in weight health outcome variables between the unmatched groups (full cohort) throughout 10 years of follow-up compared to baseline.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5,6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	6-7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	8,9 Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-10, Table 2
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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