# Cardiovascular, cancer and mortality events after bariatric surgery in people with and without pre-existing diabetes: A nationwide study

**Running Title** Bariatric surgery in diabetes

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# ABSTRACT

**Background:** Bariatric surgery reduces cardiovascular events and mortality risk in obese individuals. However, it is unclear whether diabetes modified this effect. We aimed to examine mortality, cardiovascular and cancer risk following bariatric surgery in adults with and without pre-existing diabetes and compare mortality risk to the general population.

**Methods:** Using mortality linked-Hospital Episodes Statistics (2006-2014) from England, we examined risk of death, myocardial infarction, stroke, unstable angina, heart failure, and cancer following bariatric surgery; and compared risk of death in people undergoing bariatric to mortality rates of the general population.

**Results:** Of the 35,887 people undergoing bariatric surgery, 9,175 (25.6%) had pre-existing diabetes. During a mean follow-up of 5.3 years, 801 people died, of whom 293 (36.6%) had pre-existing diabetes. The risk of all-cause mortality in people with diabetes was 26% higher compared to those without (adjusted hazard ratio (aHR): 1.26, 95%CI: 1.08-1.46) whilst cancer was 21% higher (aHR 1.21, 1.14-1.77). Participants with diabetes before bariatric surgery had increased risk for post-surgery cardiovascular events compared to patients without pre-existing diabetes (aHR myocardial infarction: 2.08, 1.42-3.05; unstable angina: 1.80, 1.29-2.52; stroke: 1.61, 1.18-2.19; heart failure: 1.42, 1.14-1.77). Compared to the general population, age-standardised mortality rate ratio was 1.70 (1.52-1.91) and 1.35 (1.23-1.48) in people with and without pre-existing diabetes, respectively.

**Conclusions:** In patients who underwent bariatric surgery with pre-existing diabetes, the risk of death, cardiovascular events, and cancer was higher compared to those without diabetes, whose mortality risk after surgery still remains 35% higher compared to that of the general population.



**Keywords:** Bariatric surgery; cardiovascular; cancer; diabetes; mortality

**Highlights**

- Patients with diabetes carry a residual risk of cardiovascular, cancer, and mortality events after bariatric surgery: compared to patients without diabetes, the risk is 26% higher of all-cause mortality, 21% higher for cancer; 42% higher for heart failure; 61% higher for stroke; and double for myocardial infarction.
- The risk of death after bariatric surgery remains higher also in patients without diabetes compared to subjects of same age from the general population.

# INTRODUCTION

The latest global estimates from 2016 indicate that obesity is rapidly increasing, with over 650 million obese people worldwide.[1] In 2014, the prevalence of obesity in the UK and U.S. was 26%[2] and 36.5%, respectively.[3] Bariatric surgery is an effective treatment for weight loss in severe cases of obesity[4,5] and has been shown to reduce the risk of cardiovascular disease (CVD) and mortality in obese people.[6-9] Results from the Swedish Obese Subjects (SOS) study also demonstrated a reduction in the incidence of type 2 diabetes after bariatric surgery and improvements in glycaemic control.[4] More recent data from Sweden show reduction in all-cause mortality and cardiovascular events after bariatric surgery compared to obese patients with diabetes who did not undergo surgery.[10] It is unclear, however, whether the presence of diabetes before surgery alters the association of bariatric surgery with cardiovascular and mortality outcomes. The Longitudinal Assessment of Bariatric Surgery - 1 (LABS-1) study found no independent association of diabetes on a composite outcome at 30 days (including death, deep vein thrombosis, pulmonary embolism, any intervention and hospital stay) in the presence of other risk factors.[11] In contrast, data from the Italian Society of Obesity Surgery (SICOB) including 13,431 patients, found a low risk of early mortality following a bariatric procedure, although the risk in patients with diabetes was double that of the risk in patients without diabetes.[12] International guidelines recommend bariatric surgery for adults with a body mass index (BMI) of 40kg/m$^2$ or more, or between 35kg/m$^2$-40kg/m$^2$ or greater in the presence of other significant diseases including type 2 diabetes.[13, 14,15] In light of these guidelines and the limited and inconsistent previous findings on mortality outcomes after bariatric surgery in presence of pre-existing diabetes, we aimed to examine all-cause and cardiovascular mortality, incidence of cardiovascular and cancer events, following bariatric surgery in adults with and without pre-existing diabetes in England and to estimate the risk of all-cause mortality following bariatric surgery in people with and without diabetes compared to the general population.



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## METHODS

### Data source, study population and exposure definition

The Hospital Episodes Statistics (HES) dataset contains details of all emergency and elective inpatient admissions funded by the National Health Service (NHS) in England. Diagnoses and procedures are coded using the International Classification of Diseases 10th revision (ICD-10) and the Office of Population Census and Surveys V.4 (OPCS-4), respectively. The Office for National Statistics (ONS) mortality dataset contains the date and cause of death (coded using ICD-10) for all deaths registered in England. This longitudinal cohort analysis made use of the linked HES-ONS mortality data to identify all adult patients resident in England undergoing bariatric surgery procedures from April 2006 to March 2014 using the OPCS-4 codes. We considered a participant as having bariatric surgery if any code from the bariatric surgery code list appeared as the primary procedure code in the patients' records in addition to the ICD-10 code for obesity (E66) as their primary diagnosis to keep our exposure definition as specific as possible (**Supplementary Table S1**). Each participant entered the study on the date of admission for bariatric surgery after 1$^{st}$ April 2006 and was censored at the date of the outcome of interest or the end of the follow-up i.e. 1$^{st}$ April 2014. Patients with baseline cardiovascular disease or gastric cancer were excluded from the analysis. Pre-existing diabetes was defined by ICD-10 codes E10-E14 on or before the index date.

### Main outcome measures

The main outcomes assessed in this study were all-cause mortality and CVD mortality. Information on in-hospital deaths was extracted from `discharge method' information in HES, which was further supplemented by ONS linkage. All other deaths were extracted from ONS. The cause of death was considered to be cardiovascular if the underlying cause of death was a cardiovascular event (**Supplementary Table S2**). We also assessed the incidence of cardiovascular events including myocardial infarction (MI), unstable angina, stroke, heart failure and cancer (code lists: **Supplementary Table S1**). Lastly, we assessed mortality rates in people with and without pre-existing diabetes undergoing bariatric surgery compared to the UK general population.

### Statistical Analysis

Participant characteristics were described using proportions and were compared between people with and without pre-existing diabetes using chi-squared tests. Average follow-up time overall and by diabetes status was calculated. Time-to-event for all-cause mortality, cardiovascular mortality, and incidence of MI, unstable angina, stroke, heart failure, and cancer were compared between people with and without pre-existing diabetes using Kaplan-Meier survival curves and survival distributions were compared using a log-rank test. Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% CIs comparing people with and without pre-existing diabetes, adjusting for age, sex, index of multiple deprivation (IMD) score, ethnicity, geographic region, procedure type, and Charlson comorbidity index (an index to define comorbidities in patients) modified to exclude pre-existing diabetes and effect modification by procedure type was also assessed. Proportional hazards assumption was checked using Schoenfeld residuals. Risk for all-cause mortality at 30 days was estimated using the same method as above. Lastly, we used the mortality data stratified by age for England and Wales in 2015 (https://www.ons.gov.uk/) and corresponding events and person-years in our dataset to estimate with negative binomial regression all-cause mortality rate ratio following bariatric surgery in people with and without pre-existing diabetes compared to the general population.

**Sensitivity Analysis**

A restricted definition of bariatric surgery was used including codes only for primary operations (**Supplementary Table S2**) and HR and mortality rate ratio were recalculated as participants with revision/secondary operations may be at a higher risk of adverse events due to the revision of surgery. Lastly, a sensitivity analysis restricted the definition of bariatric surgery to only include codes exclusively used for bariatric surgery was also performed (**Supplementary Table S2**).



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## RESULTS

**Participant characteristics**

A total of 38,060 participants underwent a bariatric surgery procedure between April 2006 and March 2014. After excluding participants with baseline CVD, gastric cancer or gastric bubble/balloon procedure (n=1,552) and missing information on age, sex or residence recorded as outside of England (n=634), 35,887 participants remained, of which 9,175 (25.6%) had a record of diabetes at the time of bariatric surgery. Approximately 85% of the bariatric surgery procedures were performed in participants aged between 30 to 59 years (**Table 1**). The proportion of women with pre-existing diabetes undergoing bariatric surgery was slightly lower compared those without diabetes (68.1% vs. 80.7%, respectively) and 31.0% patients undergoing bariatric surgery were from the most deprived areas compared to the 10.6% from the least deprived areas. People with pre-existing diabetes had higher Charlson comorbidity score compared to people without diabetes (4.2% people in the diabetes group with Charlson score ≥5 vs. 1.6% in people without diabetes). Bypass procedures constituted half of the total bariatric procedures (**Supplementary Table S3**); however, people with pre-existing diabetes had a higher proportion of bypass procedure and lower proportion of gastric banding compared to people without diabetes (55.2% vs. 50.1% bypass and 19.9% vs. 24.1% gastric banding, respectively).

**All-cause and cardiovascular mortality**

During a mean follow-up of 5.3 years (standard deviation, 2.0 years), there were 801 deaths of which 293 (36.6%) were in people with pre-existing diabetes and 508 (63.4%) in people without. There was no statistically significant difference in the 30-day mortality following bariatric surgery by diabetes status (adjusted HR comparing people with diabetes to without diabetes: 1.58, 95% CI 0.90-2.77). In people with pre-existing diabetes, the incidence for all-cause mortality was 6.3 per 1,000 person-years (95% CI 5.6-7.1) compared to 3.5 per 1,000 person-years (95% CI 3.2-3.8) in people without (**Supplementary Figure S1**). For long-term mortality, Kaplan-Meier curves revealed a greater mortality risk in people with pre-existing diabetes compared to those without ($p<0.001$) (**Figure 1**). After adjusting for age, sex, IMD score, ethnicity, geographic region, Charlson comorbidity index and procedure type, the risk of all-cause mortality in people with pre-existing diabetes was 26% higher compared to those without (HR 1.26, 95% CI 1.08-1.46) (**Figure 2**). There was no interaction in the association between diabetes status and mortality by procedure type (p for interaction=0.344). There were only 50 CVD deaths of which 16 (32.0%) were in the diabetes group. Further multivariable analyses were not carried out in this cohort, due to the small number of events in the diabetes group.

**Cardiovascular events and cancer**

The incidence ranged from 0.3 per 1,000 person-years and 1.5 per 1,000 person-years for MI to 5.0 per 1,000 person-years and 8.4 per 1,000 person-years for cancer in people with and without pre-existing diabetes respectively (**Supplementary Figure S1**). Of the 121 incident MIs, 71 (58.7%) were reported in people with pre-existing diabetes. In the multivariable analysis, diabetes was associated with over two-fold increase in the risk of an MI after bariatric surgery compared to those without (HR 2.08, 95% CI 1.42-3.05) (**Figure 2**). Diabetes was also associated with an increased risk of unstable angina (69 events in people with pre-existing diabetes vs 87 in people without, HR 1.80, 95% CI 1.29-2.52). Similarly, people with pre-existing diabetes were more likely to have a stroke compared to those without (77 vs 114 events, respectively; HR 1.61, 95% CI 1.18-2.19). The risk of heart failure after bariatric surgery was higher in people with pre-existing diabetes compared to people without (153 vs 207 events respectively; HR 1.42, 95% CI 1.14-1.77). Lastly, 1,092 individuals developed cancer during the follow-up, of whom 379 (34.7%) had pre-existing diabetes. The risk of cancer was 21% higher in the people with pre-existing diabetes compared to people without (HR 1.21, 95% CI 1.07-1.38) (Figure 2).

**Mortality compared to the general population**

The age-specific mortality rates were higher in the diabetes group compared to the general population for younger ages with progressively lower differences in older people (**Supplementary Figure S2; Figure 3**). People without pre-existing diabetes who underwent bariatric surgery had a 35% increased risk of all-cause mortality compared to the general population (age-standardised mortality rate ratio: 1.35, 95% CI 1.23-1.48; Figure 3). In comparison, people with pre-existing diabetes and bariatric surgery had a 70% increased risk of all-cause mortality compared (age-standardised mortality rate ratio: 1.70, 95% CI 1.52-1.91) (Figure 3).

**Sensitivity Analyses**

The estimates remained similar to the main analysis when the definition of bariatric surgery was restricted to only include primary procedure codes. Similarly, when restricting the definition of bariatric surgery to only codes exclusively used for bariatric surgery, the risk of all-cause mortality in the diabetes group was 33% higher (HR 1.33, 95% CI 1.10-1.60) (**Supplementary Table S4**).



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## DISCUSSION

**Principal Findings**

In this large population-based study, we found the risk of all-cause mortality to be 26% higher after bariatric surgery in people with pre-existing diabetes compared to those without diabetes. The risk of all cardiovascular outcomes including MI, stroke, unstable angina, and heart failure was also greater in adults with pre-existing diabetes, with the risk of MI being over twice as high in adults with pre-existing diabetes compared to people without diabetes. Similarly, the rate of cancer was 21% higher following bariatric surgery in people with pre-existing diabetes compared with people without. Notably, the risk of death following bariatric surgery remained higher in patients without diabetes when compared to that of the general population.

**Strengths and limitations**

To our knowledge, this is the largest study to comprehensively examine the risk of mortality and other complications following bariatric surgery by diabetes status. Data from HES captured diagnoses, procedures, and other comorbidities for all hospital admissions in England and mortality data were further confirmed through linkage with ONS, hence the outcome ascertainment in our study was robust. However, these data are primarily collected for administrative and financial purposes. Therefore, we did not have information on baseline BMI or the change in BMI after bariatric surgery or HbA1c before surgery. Nevertheless, in the UK, until 2014 bariatric surgery was only offered to people with a BMI of $40kg/m^2$ or more, or between $35kg/m^2$-$40kg/m^2$ or greater in the presence of other significant disease including diabetes.[13] A study including 756 patients undergoing bariatric surgery at Brigham and Women's Hospital, Boston found the mean BMI to be 47 (standard deviation, 6.8) and 47 (7.3) in people with and without diabetes and no statistically significant difference between the two groups.[16] Therefore, we believe the BMI of participants was at least $35kg/m^2$. Additionally, due to the nature of data collection for HES, we also did not have information on duration and severity of diabetes and glycaemic control before and after bariatric surgery and residual confounding may be present. Furthermore, owing to similar limitations of data recording, we could not further stratify the group without diabetes into euglycaemia and prediabetes. We included all codes for diabetes rather than specific type 2 diabetes as the type of diabetes is not very well phenotyped in HES and some patients have codes for both type 1 and type 2 over time.[17] Nevertheless, around 85% of the participants were identified as having type 2 diabetes.[17] Lastly, when comparing age-specific mortality rates with the general population, we could only include age 35-74 as the number of events in other age groups was either very small or nil.

**Comparison with current literature**

We found that, in spite of no significant difference in 30-day mortality, the risk of long-term mortality and CVD outcomes following bariatric surgery is higher in people with pre-existing diabetes compared to those without. The Emerging Risk Factors Collaboration study including 123,205 deaths among 820,900 people found that people with diabetes have 70% higher risk of death from any cause compared to those without.[18] Our study supports a similar hypothesis whereby people with diabetes who undergo bariatric surgery are still at higher risk of all-cause mortality and other outcomes compared to those without diabetes, despite similar short-term mortality and biochemical and anthropometric improvements which take place bariatric surgery.[4] Therefore, people with diabetes who undergo bariatric surgery may need closer monitoring, well-beyond the first year post-surgery.

Currently, there are no studies comparing long-term mortality and CVD outcomes following bariatric surgery between people with and without pre-existing diabetes. Nevertheless, data from SICOB including 34 deaths within the first 60 days following 13,431 bariatric surgery procedures found a significant difference between the mortality proportions by diabetes status, i.e. 0.4% of participants without diabetes died within the first 60 days compared with 0.8% participants with diabetes.[12] One potential explanation of our findings could be a higher number of existing comorbidities in people with diabetes as the risk of mortality after adjusting for Charlson comorbidity index was 26%. Another potential explanation could be metabolic “memory” phenomenon, whereby following a prolonged duration of diabetes the complications persist and progress despite adequate glycaemic control.[19] This phenomenon has been seen in many trials involving patients with type 2 diabetes including the United Kingdom Prospective Diabetes Study (UKPDS)[20] and several other studies.[21-23] The degree of weight loss is known to be the major driver for improvements in cardiovascular risk factors[24,25] as well as glycaemic improvement.[26] A study using data from 3,193 patients with gastric bypass from Virginia Commonwealth University Medical Center found that after one year of surgery people with diabetes had significantly lower weight loss and higher BMI compared to people without diabetes,[27] which may potentially explain why people with diabetes in our study have worse outcomes than people without diabetes. A study including 232 morbidly obese patients with type 2 diabetes found the mortality rate in morbidly obese non-operated people with type 2 diabetes to be 28%.[28] In comparison, crude all-cause mortality in the diabetes group undergoing bariatric surgery in our study was 3.19%. Therefore, although the rate of all-cause mortality after bariatric surgery in people with type 2 diabetes is significantly higher than the general population, the rate is considerably lower in relation to non-operated obese type 2 patients.

**Conclusion**

Using the largest population-based cohort of bariatric surgery patients to date, we found that despite the reported improvements in biomarkers and outcomes after surgery, and no significant difference in 30-day mortality between people with and without diabetes, people with diabetes carry a residual risk of adverse CVD outcomes and mortality, suggesting that patients with pre-existing diabetes may need closer monitoring and risk factor control in clinical care following bariatric surgery; further studies should explore the potential reasons for this excessive risk in people with diabetes. Moreover, based on our findings, patients with pre-existing diabetes undergoing bariatric surgery should be made aware of such residual risk before the procedure as well as in patients without diabetes it should be recognised that the risk of death after surgery remains higher compared to subjects from the general population.

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**DISCLOSURE**

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MJD: Consultant, advisory board member and speaker for Novo Nordisk, Sanofi-Aventis, Lilly, Merck Sharp & Dohme, Boehringer Ingelheim, AstraZeneca and Janssen and as a speaker for Mitsubishi Tanabe Pharma Corporation. Grants in support of investigator and investigator initiated trials from Novo Nordisk, Sanofi-Aventis and Lilly.
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All other authors declare there is no duality of interest in connection with their involvement in this study.
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**ETHICS**

As only pseudonymised information was used in this study, ethics approval was not needed.

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# REFERENCES

1. Obesity and overweight Fact sheet. 2018. (Accessed August 20, 2018, at http://www.who.int/mediacentre/factsheets/fs311/en/)

2. Health & Social Care Information Centre. Statistics on Obesity, Physical Activity and Diet England, 2016. Leeds: Health and Social Care Information Centre; 2016.

3. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011–2014. NCHS data brief 2015;219:1-8 PubMed .

4. Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med 2004;351:2683-93 PubMed .

5. Buchwald H. Bariatric surgery for morbid obesity: Health implications for patients, health professionals and third-party payers. Journal of the American College of Surgeons 2005;200:593-604.

6. Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric Surgery and Long-term Cardiovascular Events. Jama-Journal of the American Medical Association 2012;307:56-65.

7. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. New England Journal of Medicine 2007;357:753-61.

8. Johnson BL, Blackhurst DW, Latham BB, et al. Bariatric Surgery Is Associated with a Reduction in Major Macrovascular and Microvascular Complications in Moderately to Severely Obese Patients with Type 2 Diabetes Mellitus. Journal of the American College of Surgeons 2013;216:545-56.

9. Romeo S, Maglio C, Burza MA, et al. Cardiovascular Events After Bariatric Surgery in Obese Subjects With Type 2 Diabetes. Diabetes Care 2012;35:2613-7 PubMed .

10. Eliasson B, Liakopoulos V, Franzen S, et al. Cardiovascular disease and mortality in patients with type 2 diabetes after bariatric surgery in Sweden: a nationwide, matched, observational cohort study. Lancet Diabetes & Endocrinology 2015;3:847-54 PubMed .

11. Flum DR, Belle SH, King WC, et al. Perioperative Safety in the Longitudinal Assessment of Bariatric Surgery. N Engl J Med 2009;361:445-54.

12. Morino M, Toppino M, Forestieri P, Angrisani L, Allaix ME, Scopinaro N. Mortality after bariatric surgery - Analysis of 13,871 morbidly obese patients from a National Registry. Annals of Surgery 2007;246:1002-9 PubMed .

13. National Institute for Health and Care Excellence. Obesity: identification, assessment and management. London: National Institute for Health and Care Excellence; 2014.

14. Fried M, Yumuk V, Oppert JM, et al. Interdisciplinary European Guidelines on Metabolic and Bariatric Surgery. Obesity Surgery 2014;24:42-55 PubMed .

15. American Diabetes Association. Standards of Medical Care in Diabetes-2016. Diabetes Care 2016;39 (suppl 1):S1-S106.

16. Xourafas D, Ardestani A, Ashley SW, Tavakkoli A. Impact of Weight-Loss Surgery and Diabetes Status on Serum ALT Levels. Obesity Surgery 2012;22:1540-7 PubMed .

17. Zaccardi F, Webb DR, Davies MJ, et al. Risk factors and outcome differences in hypoglycaemia-related hospital admissions: A case-control study in England. Diabetes, Obesity and Metabolism 2017.

18. Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;2011:829-41 PubMed .

19. Cefalu WT, Rosenstock J, LeRoith D, Blonde L, Riddle MC. Getting to the "Heart" of the Matter on Diabetic Cardiovascular Disease: "Thanks for the Memory". Diabetes Care 2016;39:664-7 PubMed .

20. Turner RC, Cull CA, Frighi V, Holman RR, Grp UPDS. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus - Progressive requirement for multiple therapies (UKPDS 49). Jama-Journal of the American Medical Association 1999;281:2005-12.

21. Ismail-Beigi F, Craven T, Banerji MA, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. Lancet 2010;376:419-30 PubMed .

22. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. New England Journal of Medicine 2008;358:2560-72.

23. Duckworth WC, McCarren M, Abraira C. Glucose control and cardiovascular complications: The VA Diabetes Trial. Diabetes Care 2001;24:942-5 PubMed .

24. Wing RR, Lang W, Wadden TA, et al. Benefits of Modest Weight Loss in Improving Cardiovascular Risk Factors in Overweight and Obese Individuals With Type 2 Diabetes. Diabetes Care 2011;34:1481-6 PubMed .

25. Gregg EW, Jakicic JM, Lewis CE, et al. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial. Lancet Diabetes & Endocrinology 2016;4:913-21 PubMed .

26. Dixon JB, O'Brien PE, Playfair J, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes - A randomized controlled trial. Jama-Journal of the American Medical Association 2008;299:316-23.

27. Carbonell AM, Wolfe LG, Meador JG, Sugerman HJ, Kellum JM, Maher JW. Does diabetes affect weight loss after gastric bypass? Surgery for Obesity and Related Diseases 2008;4:441-4.

28. Long S, MacDonald KG, Swanson M, et al. The gastric bypass operation reduces the progression and mortality of non-insulin dependent-diabetes mellitus. Gastroenterology 1996;110:A1400-A.

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## FIGURE LEGENDS

**Figure 1 - Kaplan Meier plots for all outcomes comparing people with and without diabetes**

Blue, solid line: without diabetes; Red, dotted line: with diabetes. Log-rank test p<0.001 for all outcomes.

**Figure 2 - Multivariable hazard ratio comparing mortality and other outcomes in people with and without diabetes after bariatric surgery**

Estimates adjusted for age, sex, IMD score, ethnicity, region, modified Charlson Index and procedure type.

**Figure 3 - Age-specific and age-standardised rate ratio for all-cause mortality following bariatric surgery in people with and without diabetes compared to the general population**

Mortality rate ratios following bariatric surgery in patients with (full red squares) and without (empty blue squares) pre-existing diabetes compared to the general population (England and Wales, 2015).

**Table 1** - Characteristics of the study population by diabetes status

| | Overall | | No Diabetes | | Diabetes | |
|---|---|---|---|---|---|---|
| | **N = 35,887** | **%** | **n = 26,712** | **%** | **n = 9,175** | **%** |
| **Age in years†** | | | | | | |
| <20 | 159 | 0.4 | 143 | 0.5 | 10+ ǂ | ǂ |
| 20-29 | 3,082 | 8.6 | 2,814 | 10.5 | 268 | 2.9 |
| 30-39 | 8,165 | 22.8 | 6,903 | 25.8 | 1,262 | 13.8 |
| 40-49 | 12,764 | 35.6 | 9,519 | 35.6 | 3,245 | 35.4 |
| 50-59 | 9,007 | 25.1 | 5,815 | 21.8 | 3,192 | 34.8 |
| 60-69 | 2,605 | 7.3 | 1,459 | 5.5 | 1,146 | 12.5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 70-79 | 100+ ǂ | ǂ | 50+ ǂ | ǂ | 45 | 0.5 |
| ≥80 | ǂ | ǂ | ǂ | ǂ | ǂ | ǂ |
| **Sex†** | | | | | | |
| Male | 8,070 | 22.5 | 5,145 | 19.3 | 2,925 | 31.9 |
| Female | 27,817 | 77.5 | 21,567 | 80.7 | 6,250 | 68.1 |
| **IMD Score†** | | | | | | |
| Quintile 1 (most deprived) | 11,132 | 31.0 | 8,445 | 31.6 | 2,687 | 29.3 |
| Quintile 2 | 8,930 | 24.9 | 6,661 | 24.9 | 2,269 | 24.7 |
| Quintile 3 | 6,684 | 18.6 | 4,873 | 18.2 | 1,811 | 19.7 |
| Quintile 4 | 5,245 | 14.6 | 3,819 | 14.3 | 1,426 | 15.5 |
| Quintile 5 (least deprived) | 3,815 | 10.6 | 2,846 | 10.7 | 969 | 10.6 |
| Unknown/missing | 81 | 0.2 | 68 | 0.3 | 12 | 0.1 |
| **Ethnicity†** | | | | | | |
| White | 25,834 | 72.0 | 19,032 | 71.3 | 6,802 | 74.1 |
| Asian or Asian British | 728 | 2.0 | 470 | 1.8 | 258 | 2.8 |
| Black or Black British | 1,458 | 4.1 | 1,111 | 4.2 | 347 | 3.8 |
| Mixed | 342 | 1.0 | 264 | 1.0 | 78 | 0.9 |
| Other Ethnic Group | 494 | 1.4 | 361 | 1.4 | 133 | 1.5 |
| Unknown | 7,031 | 19.6 | 5,474 | 20.5 | 1,557 | 17.0 |
| **Region†** | | | | | | |
| North East | 3,579 | 10.0 | 2,662 | 10.0 | 917 | 10.0 |
| North West | 2,316 | 6.5 | 1,915 | 7.2 | 401 | 4.4 |
| Yorkshire & Humber | 4,745 | 13.2 | 3,770 | 14.1 | 975 | 10.6 |
| East Midlands | 2,679 | 7.5 | 2,050 | 7.7 | 629 | 6.9 |
| West Midlands | 3,599 | 10.0 | 2,503 | 9.4 | 1,096 | 11.9 |
| East of England | 2,082 | 5.8 | 1,282 | 4.8 | 800 | 8.7 |
| London | 8,334 | 23.2 | 6,352 | 23.8 | 1,982 | 21.6 |
| South East | 5,393 | 15.0 | 3,925 | 14.7 | 1,468 | 16.0 |
| South West | 3,090 | 8.6 | 2,192 | 8.2 | 898 | 9.8 |
| Unknown | 70 | 0.2 | 61 | 0.2 | 9 | 0.1 |
| **Charlson Comorbidity Score†** | | | | | | |
| 0 | 28617 | 79.7 | 21775 | 81.5 | 6842 | 74.6 |
| 1 to 4 | 6451 | 18.0 | 4504 | 16.9 | 1947 | 21.2 |
| 5+ | 819 | 2.3 | 433 | 1.6 | 386 | 4.2 |
| **Procedure Type†** | | | | | | |
| Gastric Bypass | 18,437 | 51.4 | 13,374 | 50.1 | 5,063 | 55.2 |
| Gastric Banding | 8,259 | 23.0 | 6,431 | 24.1 | 1,828 | 19.9 |
| Sleeve Gastrectomy | 5,809 | 16.2 | 4,429 | 16.6 | 1,380 | 15.0 |
| Gastroplasty | 3,382 | 9.4 | 2,478 | 9.3 | 904 | 9.9 |
| **Year of Surgery†** | | | | | | |
| 2006 - 2010 | 17,100 | 47.7 | 13,276 | 49.7 | 3,824 | 41.7 |
| 2011 -2014 | 18,787 | 52.4 | 13,436 | 50.3 | 5,351 | 58.3 |

† p-value for comparison between people with and without diabetes <0.01
ǂ one cell with <5 value

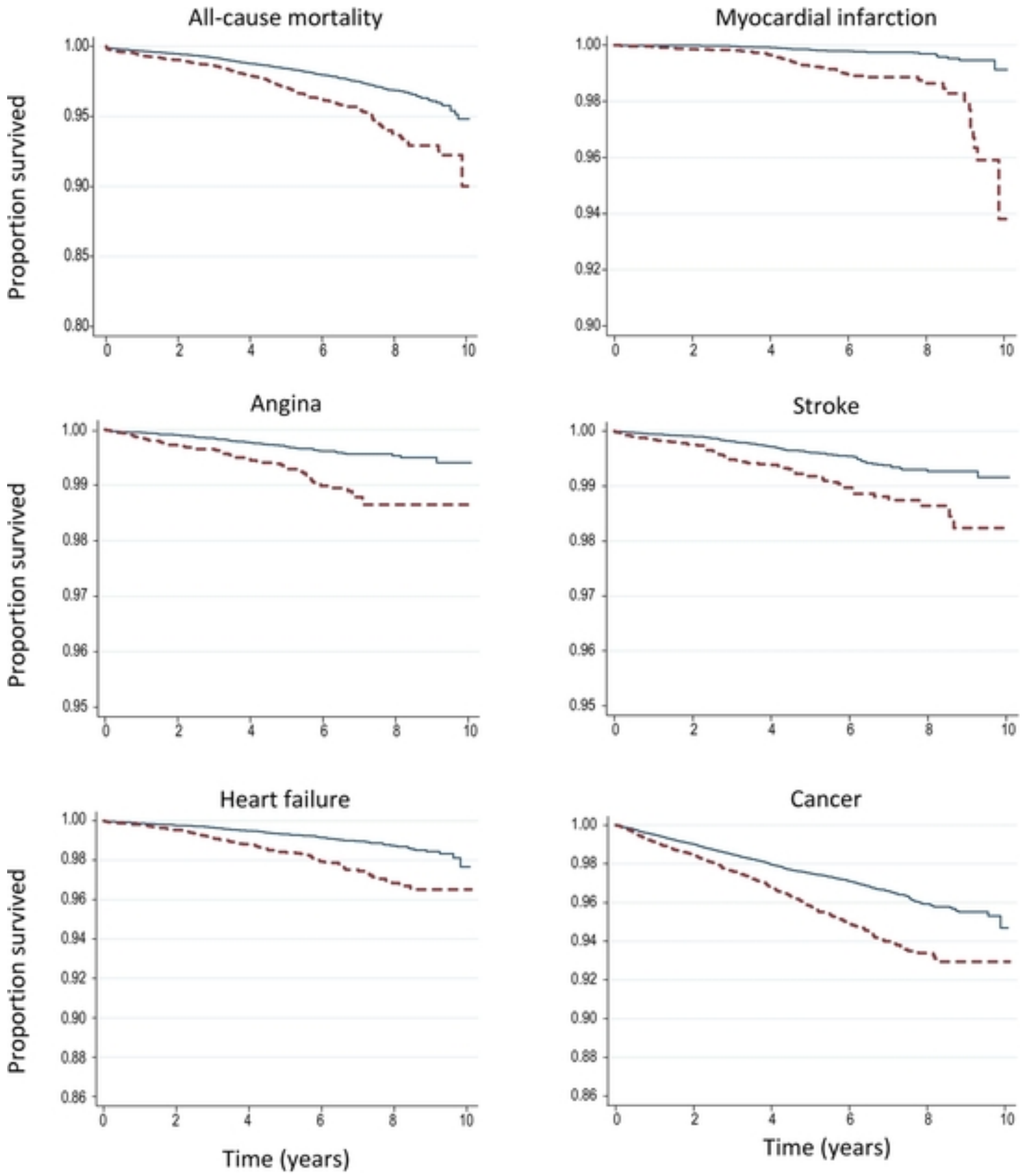


Figure 1 - Kaplan Meier plots for all outcomes comparing people with and without diabetes

Blue, solid line: without diabetes; Red, dotted line: with diabetes. Log-rank test $p<0.001$ for all outcomes.

192x222mm (72 x 72 DPI)

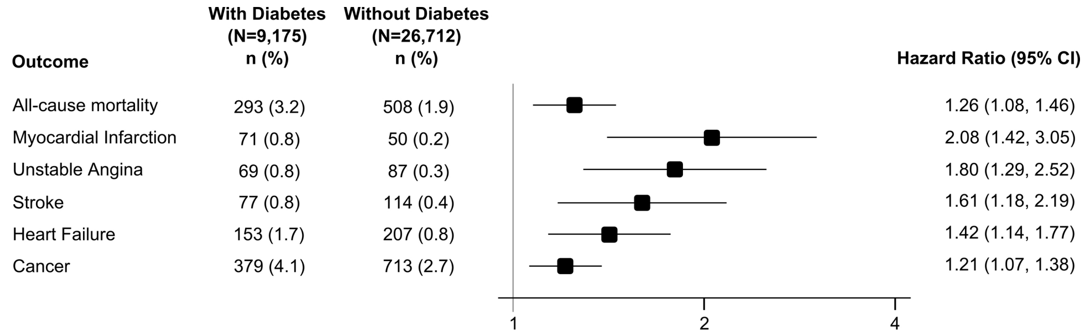


Figure 2 - Multivariable hazard ratio comparing mortality and other outcomes in people with and without diabetes after bariatric surgery

Estimates adjusted for age, sex, IMD score, ethnicity, region, modified Charlson Index and procedure type.

1057x320mm (72 x 72 DPI)

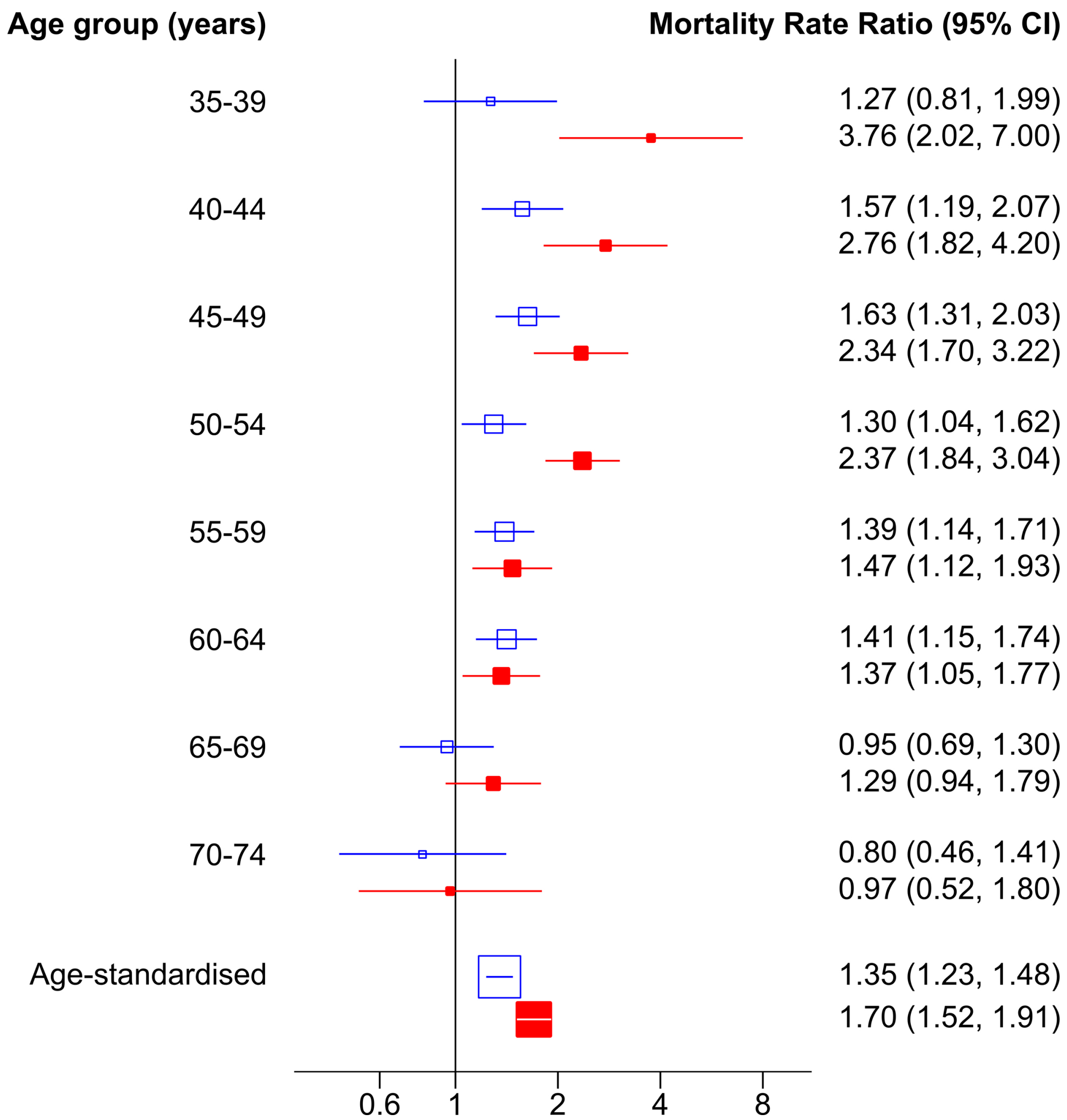


Figure 3 - Age-specific and age-standardised rate ratio for all-cause mortality following bariatric surgery in people with and without diabetes compared to the general population

Mortality rate ratios following bariatric surgery in patients with (full red squares) and without (empty blue squares) pre-existing diabetes compared to the general population (England and Wales, 2015).

890x932mm (72 x 72 DPI)

# Supplementary Material

## Cardiovascular, cancer and mortality events after bariatric surgery in people with and without pre-existing diabetes: A nationwide study

Nafeesa N Dhalwani[1], Francesco Zaccardi[1], Hina Waheed[2], Jemma Mytton[2], Dimitris Papamargaritis[1], David Webb[1], Felicity Evison[2], Richard Lilford[3], Melanie J Davies[1,4], Kamlesh Khunti[1]

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[4]Leicester Biomedical Research Centre, UK

## Supplementary Table S1 - Classification for OPCS-4 Codes for bariatric surgery

| Exclusive |
|---|
| G284 - Sleeve gastrectomy and duodenal switch |
| G285 - Sleeve gastrectomy NEC |
| G303 - Partitioning of stomach using band |
| G716 - Duodenal switch |
| G304 - Partitioning of stomach using staples |
| G321 - Bypass of stomach by anastomosis of stomach to transposed jejunum |
| G301 - Gastroplasty NEC |
| G320 - Conversion from previous anastomosis of stomach to transposed jejunum |
| G322 - Revision of anastomosis of stomach to transposed jejunum |
| G323 - Conversion to anastomosis of stomach to transposed jejunum |
| **Non exclusive** |
| G312 - Bypass of stomach by anastomosis of stomach to duodenum |
| G331 - Bypass of stomach by anastomosis of stomach to jejunum NEC |
| G281 - Partial gastrectomy and anastomosis of stomach to duodenum |
| G282 - Partial gastrectomy and anastomosis of stomach to transposed jejunum |
| G283 - Partial gastrectomy and anastomosis of stomach to jejunum NEC |
| G302 - Partitioning of stomach NEC |
| G310 - Conversion from previous anastomosis of stomach to duodenum |
| G313 - Revision of anastomosis of stomach to duodenum |
| G314 - Conversion to anastomosis of stomach to duodenum |
| G330 - Conversion from previous anastomosis of stomach to jejunum NEC |
| G332 - Revision of anastomosis of stomach to jejunum NEC |
| G333 - Conversion to anastomosis of stomach to jejunum NEC |
| G335 - Closure of connection of stomach to jejunum NEC |
| G336 - Attention to connection of stomach to jejunum |
| G324 - Closure of connection of stomach to transposed jejunum |
| G325 - Attention to connection of stomach to transposed jejunum |
| **Primary operation** |
| G284 - Sleeve gastrectomy and duodenal switch |
| G285 - Sleeve gastrectomy NEC |
| G303 - Partitioning of stomach using band |
| G716 - Duodenal switch |
| G304 - Partitioning of stomach using staples |
| G321 - Bypass of stomach by anastomosis of stomach to transposed jejunum |
| G301 - Gastroplasty NEC |
| G312 - Bypass of stomach by anastomosis of stomach to duodenum |
| G331 - Bypass of stomach by anastomosis of stomach to jejunum NEC |
| G281 - Partial gastrectomy and anastomosis of stomach to duodenum |
| G282 - Partial gastrectomy and anastomosis of stomach to transposed jejunum |
| G283 - Partial gastrectomy and anastomosis of stomach to jejunum NEC |
| G302 - Partitioning of stomach NEC |
| **Revision/Secondary operation** |
| G310 - Conversion from previous anastomosis of stomach to duodenum |
| G313 - Revision of anastomosis of stomach to duodenum |
| G314 - Conversion to anastomosis of stomach to duodenum |
| G320 - Conversion from previous anastomosis of stomach to transposed jejunum |
| G322 - Revision of anastomosis of stomach to transposed jejunum |
| G323 - Conversion to anastomosis of stomach to transposed jejunum |
| G330 - Conversion from previous anastomosis of stomach to jejunum NEC |
| G332 - Revision of anastomosis of stomach to jejunum NEC |
| G333 - Conversion to anastomosis of stomach to jejunum NEC |
| G335 - Closure of connection of stomach to jejunum NEC |
| G336 - Attention to connection of stomach to jejunum |
| G324 - Closure of connection of stomach to transposed jejunum |
| G325 - Attention to connection of stomach to transposed jejunum |

## Supplementary Table S2 - ICD-10 codes for exposures and outcomes

| Conditions | ICD-10 Codes |
|---|---|
| Myocardial Infarction | I21-I22, I25.2, 125.6 |
| Unstable Angina | I20.0 |
| Stroke | I60-I63 |
| Heart failure | I11.0, I13.0, I13.2, I25.5, I42.0, I42.9, I50.0, I50.1, I50.9 |
| Cancer | C00-C99 |
| Diabetes | E10-E14 |

## Supplementary Table S3 - Number of patients identified through each code and category

| Codes | Category | No Diabetes | Diabetes |
|---|---|---|---|
| G281 - Partial gastrectomy and anastomosis of stomach to duodenum | ByP | 8 | * |
| G282 - Partial gastrectomy and anastomosis of stomach to transposed jejunum | ByP | 183 | 64 |
| G283 - Partial gastrectomy and anastomosis of stomach to jejunum NEC | ByP | 71 | 25 |
| G284 - Sleeve gastrectomy and duodenal switch | ByP | 49 | 11 |
| G285 - Sleeve gastrectomy NEC | SG | 4429 | 1,380 |
| G301 - Gastroplasty NEC | GPl | 322 | 119 |
| G302 - Partitioning of stomach NEC | GPl | 414 | 115 |
| G303 - Partitioning of stomach using band | GB | 6,431 | 1,828 |
| G304 - Partitioning of stomach using staples | GPl | 1,742 | 670 |
| G310 - Conversion from previous anastomosis of stomach to duodenum | ByP | 6 | * |
| G312 - Bypass of stomach by anastomosis of stomach to duodenum | ByP | 93 | 41 |
| G313 - Revision of anastomosis of stomach to duodenum | ByP | * | * |
| G314 - Conversion to anastomosis of stomach to duodenum | ByP | * | 0 |
| G320 - Conversion from previous anastomosis of stomach to transposed jejunum | ByP | - | - |
| G321 - Bypass of stomach by anastomosis of stomach to transposed jejunum | ByP | 5,119 | 2,031 |
| G322 - Revision of anastomosis of stomach to transposed jejunum | ByP | 16 | * |
| G323 - Conversion to anastomosis of stomach to transposed jejunum | ByP | * | * |
| G324 - Closure of connection of stomach to transposed jejunum | ByP | * | * |
| G325 - Attention to connection of stomach to transposed jejunum | ByP | * | 0 |
| G330 - Conversion from previous anastomosis of stomach to jejunum NEC | ByP | - | - |
| G331 - Bypass of stomach by anastomosis of stomach to jejunum NEC | ByP | 7,756 | 2,869 |
| G332 - Revision of anastomosis of stomach to jejunum NEC | ByP | 28 | 6 |
| G333 - Conversion to anastomosis of stomach to jejunum NEC | ByP | 13 | * |
| G335 - Closure of connection of stomach to jejunum NEC | ByP | * | * |
| G336 - Attention to connection of stomach to jejunum | ByP | * | 0 |
| G716 - Duodenal switch | ByP | 16 | * |
| **Total** | | **26,712** | **9,175** |

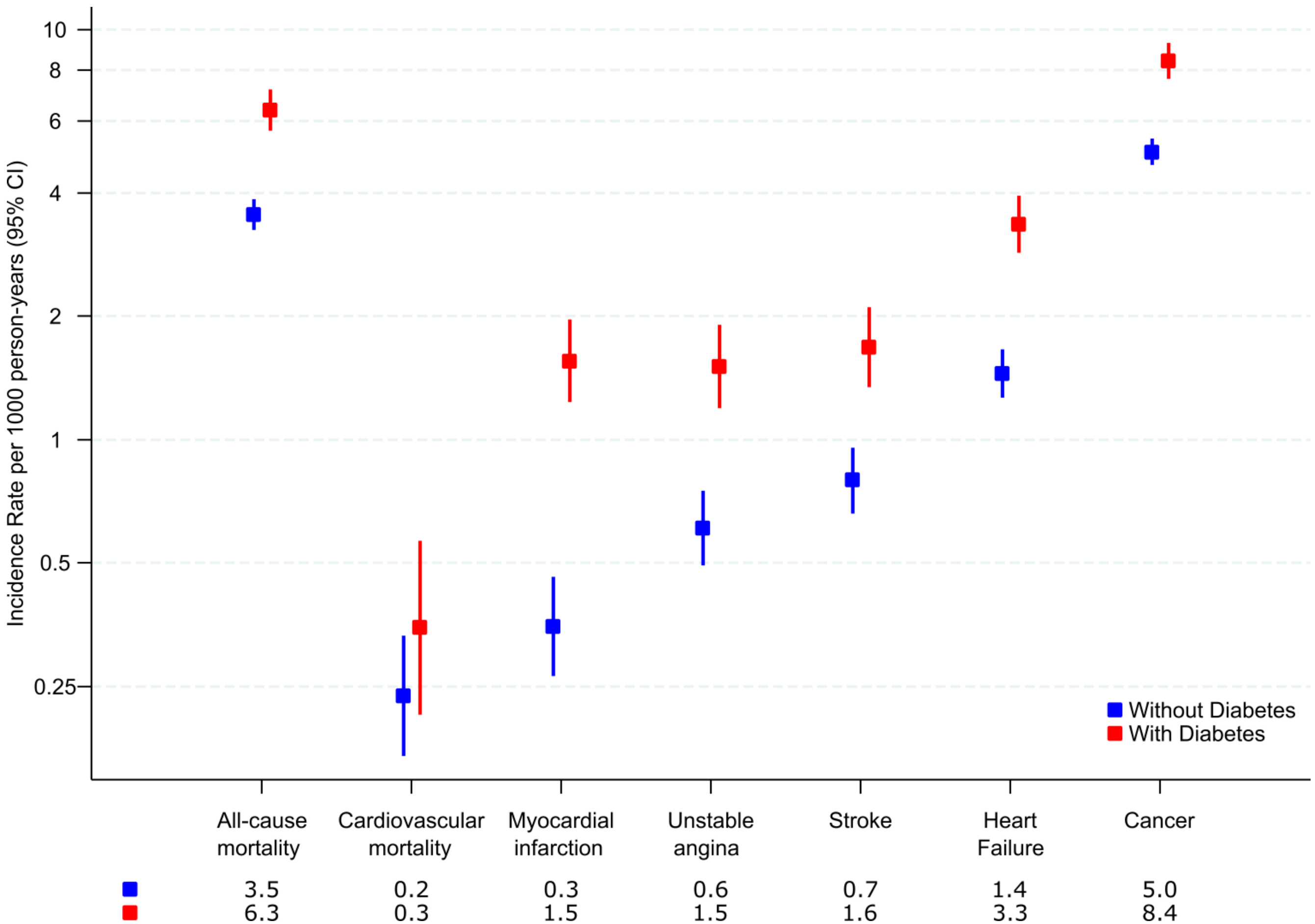
ByP=Bypass procedures, GPl=Gastroplasty, SG = Sleeve Gastrectomy, GB=Gastric Banding
* number <5

## Supplementary Table S4 - Multivariable cox proportional hazards regression models comparing mortality and other outcomes by diabetes status after bariatric surgery

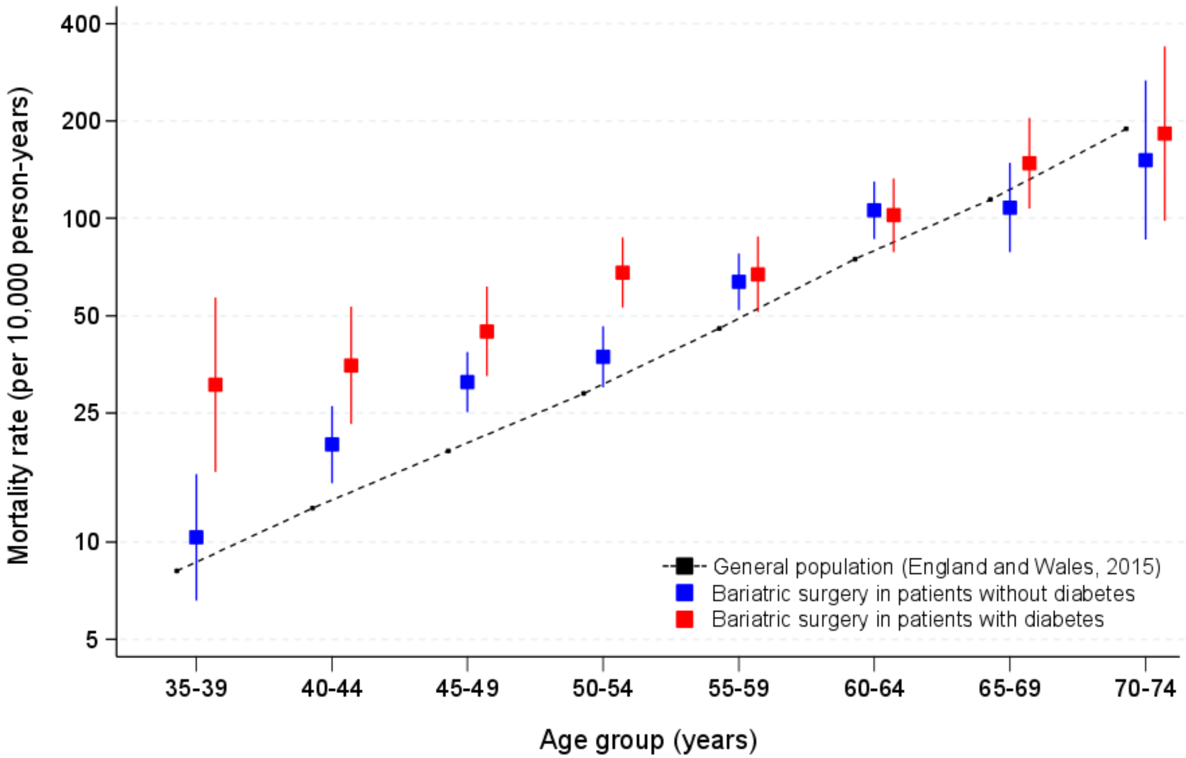
| | All-cause mortality | Myocardial Infarction | Unstable Angina | Stroke | Heart failure | Cancer |
|---|---|---|---|---|---|---|
| **Using only exclusive bariatric surgery codes** | | | | | | |
| Hazard Ratio (95% CI)* | 1.33 (1.10-1.60) | 1.66 (1.08-2.56)[b] | 1.83 (1.24-2.46) | 1.70 (1.18-2.46)[c] | 1.63 (1.26-2.11)[d] | 1.30 (1.11-1.51)[e] |
| **Using only primary bariatric surgery codes** | | | | | | |
| Hazard Ratio (95% CI)* | 1.26 (1.08-1.47) | 2.08 (1.42-3.04)[b] | 1.80 (1.29-2.51) | 1.58 (1.16-2.15)[c] | 1.41 (1.13-1.75)[d] | 1.22 (1.07-1.38)[e] |

*Using people without diabetes as a reference, adjusted for age, sex, IMD score, ethnicity, region, procedure type, [b] additionally excluding MI from Charlson index, [c] additionally excluding stroke from Charlson index, [d] additionally excluding heart failure from Charlson index [e] additionally excluding cancer from Charlson index

**Supplementary Figure S1 - Incidence rates (95% CI) for all outcomes following bariatric surgery in people with and without diabetes**



## Supplementary Figure S2 - Age-specific mortality rates in the general population, compared to people with and without diabetes



# STROBE Statement—Checklist of items that should be included in reports of *cohort* studies

## Cardiovascular, cancer and mortality events after bariatric surgery in people with and without pre-existing diabetes: A nationwide study

| | Item No | Recommendation | Page |
|---|---|---|---|
| **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 | 1 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 4 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 4-5 |
| 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 | 4-5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5-6 |
| 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 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 5 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 5 |
| | | (*c*) Explain how missing data were addressed | 5 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | NA |
| | | (*e*) Describe any sensitivity analyses | 5-6 |
| **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 | 7 |
| | | (b) Give reasons for non-participation at each stage | 7 |
| | | (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 | 7 |
| | | (b) Indicate number of participants with missing data for each variable of interest | 7 |

| | | | |
|---|---|---|---|
| | | (c) Summarise follow-up time (eg, average and total amount) | 7 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 7-8 |
| 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 | 7-8 |
| | | (*b*) Report category boundaries when continuous variables were categorized | NA |
| | | (*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 | 9 |
| **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 | 10-11 |
| 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 | 12-13 |
| **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 | 14 |

*Give information separately for exposed and unexposed groups.

**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 http://www.strobe-statement.org.