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## Long-term effects of bariatric surgery on acute kidney injury: A propensity-matched cohort in the United Kingdom Clinical Practice Research Datalink

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1 **Title** Long-term effects of bariatric surgery on acute kidney injury: A propensity-  
2 matched cohort in the United Kingdom Clinical Practice Research Datalink

4 **Running headline** Bariatric surgery and acute kidney injury

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3 32 **ABSTRACT**  
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5 33 **Objective:** Bariatric surgery is an effective method of weight reduction and has been  
6  
7 34 associated with acute kidney injury (AKI) as a perioperative event. However, the long-term  
8  
9 35 effects of the weight reduction after surgery on AKI are unknown. The objective of this  
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11 36 study is to quantify the association of bariatric surgery with later risk of AKI.  
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14 37 **Design:** This study uses a propensity-score matched cohort of patients from the United  
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16 38 Kingdom Clinical Practice Research Datalink database with and without bariatric surgery to  
17  
18 39 compare rates of AKI episodes derived from linkage to the Hospital Episode Statistics.  
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20

21 40 **Setting:** England, United Kingdom  
22

23 41 **Participants:** We included 2,643 patients with bariatric surgery and 2,595 patients without.  
24  
25

26 42 **Results:** Results were compatible with an increased risk of AKI in the first 30 days following  
27  
28 43 surgery compared with patients without surgery, but AKI incidence was substantially  
29  
30 44 decreased in patients with bariatric surgery during long-term follow-up (rate ratio 0.37, 95%  
31  
32 45 CI 0.23, 0.61) even after accounting for chronic kidney disease status at baseline. Over the  
33  
34 46 whole period of follow-up, bariatric surgery had a net protective effect on risk of AKI (rate  
35  
36 47 ratio 0.45, 95% CI 0.28, 0.72).  
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38

39 48 **Conclusions:** Bariatric surgery was associated with strong protective effects on AKI  
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41 49 incidence during long-term follow-up. While the risk of AKI may be increased within the first  
42  
43 50 30 days, the net effect seen was beneficial.  
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48 52 **Keywords:** Acute Kidney Injury; Obesity; Bariatric Surgery; Clinical Practice Research  
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50 53 Datalink  
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3 54 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 5 55 • This study uses high quality data from linked databases in England (Clinical Practice  
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7 56 Research Datalink and Hospital Episode Statistics) to describe long-term effects of  
8  
9  
10 57 bariatric surgery on acute kidney injury (AKI) for the first time.  
11  
12 58 • Data are captured prospectively and continuously thus allowing follow-up of patients  
13  
14 59 over long time periods.  
15  
16 60 • Outcome measures are obtained with standardised ICD-10 codes, which have been  
17  
18 61 shown to accurately identify AKI.  
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20  
21 62 • Only AKI events recorded during a hospital admission were included in the analysis  
22  
23 63 likely representing the more serious events of AKI.  
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25  
26 64 • The study population was mostly female, of middle age, and had a history of type 2  
27  
28 65 diabetes mellitus. Thus the results might not be applicable for other groups suffering  
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30 66 from obesity such as adolescents.  
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## 67 INTRODUCTION

68 The proportions of overweight and obese adults in England in 2014 are estimated to be  
69 61.7% and 25.6%, respectively, and are increasing over time<sup>1</sup>. Obesity is associated with  
70 serious health consequences including type 2 diabetes mellitus (T2DM), cardiovascular  
71 diseases, cancers, and chronic kidney disease (CKD)<sup>2-4</sup>. Bariatric surgery has been shown to  
72 be a highly effective intervention for achieving weight loss and reducing the burden of co-  
73 morbidities, such as T2DM, metabolic syndrome, and hypertension<sup>5 6</sup>. A recent  
74 observational study on recipients of bariatric surgery from the United Kingdom (UK)  
75 confirmed sustained weight loss as well as resolution of T2DM and hypertension over a  
76 period of 4 years<sup>7</sup>.

77 Acute kidney injury (AKI) is defined as a sudden (over hours or days) drop in kidney function  
78 characterised by increased serum creatinine and/or reduced urine output. AKI has been  
79 linked to increased in-hospital mortality, length of hospital stay, and subsequent  
80 development of CKD<sup>8</sup>. While T2DM, CKD, and obesity have been described as risk factors for  
81 AKI, it can also be precipitated by nephrotoxic drugs, surgical interventions, and sepsis<sup>8-10</sup>.  
82 AKI has been described as a short-term complication of bariatric surgery, stemming from  
83 rhabdomyolysis<sup>10-16</sup>. In addition, AKI has been linked to nephrolithiasis, which can develop  
84 over time after Roux-En-Y Gastric Bypass surgery<sup>11 17</sup>. To the best of our knowledge, no  
85 studies have been published examining the long-term effects of bariatric surgery on AKI.

86 In this study, we investigate the long-term effects of bariatric surgery on AKI to see whether  
87 the expected reduction in BMI has any impact on subsequent renal health. We used  
88 routinely collected electronic health record data from primary and secondary care. For this,  
89 we conducted a matched cohort study using prospectively collected data from patients in  
90 the United Kingdom Clinical Practice Research Datalink (CPRD).

## 91 **METHODS**

### 92 **Study design**

93 We undertook a matched cohort study using prospectively collected data from CPRD  
94 patients registered before 31st December 2014 linked to the Hospital Episodes Statistics  
95 (HES) database to investigate long-term effects of bariatric surgery on AKI.

96

### 97 **Data source**

98 The CPRD database contains anonymised, routinely collected data on approximately 10  
99 million patients in participating primary care practices in the UK, including demographic  
100 characteristics, current and previous diagnoses, prescribing, test results, and lifestyle  
101 factors. Diagnoses, signs, and symptoms are recorded using Read codes<sup>18</sup>. Patients are  
102 broadly representative of the UK population and the data have been validated for a wide  
103 range of outcomes<sup>19-21</sup>. The HES database contains patient data from hospital admissions to  
104 English hospitals within the National Health Service<sup>22</sup>. For each hospital admission, the  
105 diagnoses are recorded using standardised codes of the International Classification of  
106 Diseases, Tenth Revision (ICD-10)<sup>23 24</sup>. Data from 70% of CPRD practices in England has been  
107 linked at patient level with HES admission data thus allowing the combined analysis of data  
108 from primary and acute hospital care for a subset of patients<sup>19</sup>.

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### 110 **Cohort design and propensity matching**

111 A detailed description of how the cohort was constructed is described elsewhere<sup>7</sup>. In brief,  
112 records of patients who underwent bariatric surgery (n=3,882) between 1997 and 2015  
113 were matched to individuals who did not undergo surgery (n=3,882) using propensity  
114 scores.

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3 115 Study population matching and the propensity score incorporated information on age, sex,  
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5 116 calendar period, history of T2DM, hypertension, coronary heart disease, cerebrovascular  
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7 117 disease, peripheral vascular disease, other atheroma, use of insulin, use of oral antidiabetic  
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9 118 medication, use of statins, smoking status, and alcohol consumption.

11 119 Patients with bariatric surgery were identified using Read codes for surgery in the CPRD  
12  
13 120 database (S1 Appendix) and were included in the study if they had been registered in the  
14  
15 121 CPRD  $\geq 12$  months prior to the intervention. We excluded those with a record of prior  
16  
17 122 bariatric surgery reversal.

18  
19 123 For the comparison group, the inclusion criteria were to have at least one BMI  
20  
21 124 measurement  $\geq 40$  kg/m<sup>2</sup>,  $\geq 12$  months of follow-up prior to the index date in the database,  
22  
23 125 and no prior record of bariatric surgery or bariatric surgery reversal.

24  
25 126 The study sample was restricted to eligible patients registered at practices linked to the HES  
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27 127 database and information on AKI events was obtained, resulting in a final cohort comprising  
28  
29 128 2,643 patients who underwent bariatric surgery, and 2,595 patients who did not.

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31 129 Follow-up started on the day of surgery for those with bariatric surgery, and for the  
32  
33 130 comparison group who did not undergo bariatric surgery, on the surgery date of their  
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35 131 matched case. Patient records were censored at the earliest of: AKI, death, leaving the  
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37 132 practice, latest data collection from current practice, or end of linkage period to the HES  
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39 133 database.

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### 42 135 **Outcomes and covariates**

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44 136 The primary outcome of this study was the incidence rate of the first AKI episode during  
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46 137 follow-up in patients with and without bariatric surgery. AKI episodes were obtained from  
47  
48 138 the HES database using ICD-10 codes: N17.0 (“Acute kidney failure with tubular necrosis”),



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3 139 N17.1 (“Acute renal failure with acute cortical necrosis), N17.2 (“Acute renal failure with  
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5 140 medullary necrosis”), N17.8 (“Other acute renal failure”), N17.9 (“Acute kidney failure,  
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7 141 unspecified”), and N19 (“Unspecified kidney failure”). In this cohort, events coded with  
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9 142 N17.1, N17.2, and N17.8 were not found. AKI events that occurred before the start of  
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11 143 follow-up were recorded as a binary variable “history of AKI”, while AKI events occurring  
12  
13 144 during follow-up were used to analyse AKI incidence.

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16 145 Recorded serum creatinine values from the CPRD database were not routinely standardised  
17  
18 146 with isotope-dilution mass spectrometry before 2013. Thus, we assumed all measurements  
19  
20 147 to be unstandardized and multiplied the creatinine measures with the factor 0.95 before  
21  
22 148 calculating the estimated glomerular filtration rate (eGFR) using the “Chronic Kidney Disease  
23  
24 149 Epidemiology Collaboration” (CKD-EPI) equation<sup>25</sup>. Ethnicity was not considered in the eGFR  
25  
26 150 calculation due to incomplete recording in the database and the low proportion of Afro-  
27  
28 151 Caribbean people in the population. CKD stages were defined according to eGFR values in  
29  
30 152 ml/min/1.73m<sup>2</sup> according to current guidelines<sup>26</sup>: eGFR ≥60 = no known CKD; eGFR 45-59 =  
31  
32 153 stage 3a; eGFR 30-44 = stage 3b; eGFR 15-29 = stage 4; eGFR <15 = stage 5. Baseline CKD  
33  
34 154 status was derived from eGFR measurements in the year prior to start of follow-up by: 1)  
35  
36 155 taking the last two measurements before the index date ≥90 days apart – with the higher  
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38 156 eGFR value corresponding to the CKD baseline status, or 2) taking the most recent serum  
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40 157 creatinine result if only one suitable test result was available. Since serum creatinine is more  
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42 158 likely to be tested in the acutely unwell or in people who are routinely monitored as part of  
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44 159 incentivised programs (e.g. people with diabetes), patients without measurements of CKD  
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46 160 baseline status were assumed to have no CKD<sup>27</sup> and were analysed as such.

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## 163 **Statistical Analysis**

164 Though propensity score matching was employed to minimise confounding, we compared  
165 the distribution of baseline characteristics between the exposed and unexposed groups to  
166 check for any imbalances that may be relevant to the outcome of AKI. The baseline  
167 distribution of categorical variables was analysed using percentages and  $\chi^2$ -tests.  
168 Continuous variables were analysed as means with standard deviations for normally  
169 distributed variables and medians with interquartile ranges for non-normally distributed  
170 variables. Differences in continuous variables were analysed with Student's t-tests or  
171 Wilcoxon rank sum tests for normally and non-normally distributed data, respectively.  
172 The association between bariatric surgery and AKI was analysed using a Poisson regression  
173 model with a time to first event analysis. P-values were calculated using Wald tests. In order  
174 to separate short-term effects of the surgery from potential long-term effects, we analysed  
175 the association separately for: a) events within the first 30 days, and b) events after 30 days.  
176 When the cohort was initially constructed, propensity score matching was used to deal with  
177 confounding<sup>7</sup>. This study uses a subset of this cohort since patients from practices without  
178 linkage between the CPRD and HES databases had to be excluded (as AKI was assessed using  
179 hospital admission data). To identify variables for the multivariable model, potential  
180 confounders that were not deemed to be on the causal pathway were added individually to  
181 the univariable model. If the addition changed the effect estimate  $\geq 10\%$  these variables  
182 were included in the multivariable model. Consequently, history of AKI, history of taking oral  
183 antidiabetics, and BMI at baseline were included (S2 Appendix). In addition, age at baseline,  
184 sex, calendar period (1997-2005, 2006-2010, 2011-2015), and CKD status at baseline were  
185 selected *a priori* as forced variables. For models with <40 outcomes, only age and sex were  
186 included in the multivariable model due to data sparsity.

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3 187 The 5% bands of patients with the highest and lowest propensity scores were excluded from  
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5 188 the primary analysis (“trimming”) since these contain patients that are treated in stark  
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7 189 contrast to their health status, potentially causing bias<sup>28</sup>.

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10 190 Heterogeneity of effect estimates between the calendar periods was tested with a  
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12 191 Likelihood Ratio Test.

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14 192 The analysis was performed for all patients with bariatric surgery and also further stratified  
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16 193 by type of surgery. Patients with stage 5 CKD (baseline eGFR < 15 ml/min/1.73m<sup>2</sup>) were  
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18 194 excluded from the analyses since this constitutes end-stage renal failure (ESRD). In addition,  
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20 195 patients with missing data in ≥1 variable of the multivariable model were excluded from  
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22 196 both uni- and multivariable analyses.

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25 197 All analyses were performed with Stata 14.1.

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### 29 30 199 **Subgroup analyses**

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32 200 Several planned sensitivity analyses were undertaken: 1) To determine the net effect of the  
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34 201 intervention we calculated the risk of AKI over the whole period of follow-up; 2) The  
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36 202 prevalence of decreased kidney function in the CPRD database was similar to that in a  
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38 203 nationally representative kidney disease registry<sup>27</sup> indicating that patients with missing  
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40 204 eGFR measurements are unlikely to have CKD. To identify potential differences in the effect  
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42 205 between patients with known and unknown eGFR measurements, we restricted the analysis  
43  
44 206 to a) patients known to have no CKD at baseline (baseline eGFR ≥ 60 ml/min/1.73m<sup>2</sup>), b)  
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46 207 patients without known CKD at baseline (as above but including patients with missing  
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48 208 creatinine values at baseline and assuming these individuals to have no CKD), and c)  
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50 209 patients with known CKD at baseline.<sup>27</sup>; 3) Moreover, to investigate the effect in a group of  
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52 210 particular interest which is under more scrutiny for measuring kidney function we restricted

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3 211 the analysis to patients with: a) T2DM, and b) a history of taking insulin; 4) To avoid  
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5 212 misclassification of low eGFR values as AKI <sup>29</sup> we excluded patients with stage 4 CKD at  
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7 213 baseline; 5) We restricted the analysis to ICD-10 codes N17.0 and N17.9, which have a high  
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9 214 positive predictive value for AKI <sup>24</sup>; 6) We increased the immediate post-surgery time span  
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11 215 from 30 to 60 days; and 7) We included people with extreme propensity scores.  
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### 16 217 **Ethical approval**

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18 218 This study was approved by the London School of Hygiene & Tropical Medicine ethics  
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20 219 committee (LSHTM MSc Ethics Ref: 11065) and the Independent Scientific Advisory  
21  
22 220 Committee on Medicines & Healthcare Products Regulatory Agency database research  
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25 221 (approval number: 16\_106R).  
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3 222 **RESULTS**  
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5 223 Since linkage to the HES-database was only possible for patients whose GPs had agreed for  
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7 224 their practice data to be linked to HES (S3 Appendix), there were 2,643 patients with  
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9 225 bariatric surgery and 2,595 people without surgery resulting in a cohort of overall 5,238  
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11 226 people with a median follow-up of 2.9 years (Table 1).  
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227 *Table 1: Baseline data for CPRD/HES-linked cohort study of people with bariatric surgery and*  
 228 *the corresponding propensity score-matched\* comparison cohort*  
 229 *(data are n (%) unless otherwise specified)*

	Bariatric Surgery (n = 2,643)	Matched Comparison group without surgery (n = 2,595)	p-value <sup>1</sup>
<b>Follow-up (years), median (IQR)</b>	2.9 (3.2)	2.9 (3.4)	0.616
<b>Age (years), mean (SD)</b>	45.2 (10.7)	45.0 (10.8)	0.417
17 – 39, n (%)	818 (31.0)	826 (31.8)	
40 – 49, n (%)	945 (35.8)	928 (35.8)	0.727
50 – 85, n (%)	880 (33.3)	841 (32.4)	
<b>BMI at baseline, mean (SD)</b>	44.9 (8.9)	42.2 (6.5)	<0.001
13 – 34, n (%)	297 (11.2)	287 (11.1)	
35 – 39, n (%)	448 (17.0)	456 (17.6)	
40 – 44, n (%)	625 (23.7)	1,118 (43.1)	<0.001
45 – 49, n (%)	571 (21.6)	438 (16.9)	
50 – 94, n (%)	667 (25.2)	253 (9.8)	
Missing, n (%)	35 (1.3)	43 (1.7)	
<b>Female</b>	2,131 (80.6)	2,131 (82.1)	0.166
<b>History of</b>			
<b>Cerebrovascular disease</b>	37 (1.4)	26 (1.0)	0.186
<b>Coronary heart disease</b>	104 (3.9)	82 (3.2)	0.130
<b>Peripheral vascular disease</b>	11 (0.4)	15 (0.6)	0.405
<b>Other atheroma</b>	0	<5 <sup>2</sup>	0.313
<b>T2DM</b>	900 (34.1)	853 (32.9)	0.365
<b>Taking oral antidiabetic</b>	571 (21.6)	455 (17.5)	<0.001
<b>Taking insulin</b>	180 (6.8)	156 (6.0)	0.238
<b>Hypertension</b>	890 (33.7)	869 (33.5)	0.886
<b>Statin use</b>	699 (26.4)	640 (24.7)	0.139
<b>AKI</b>	30 (1.1)	11 (0.4)	0.003
<b>Alcohol status</b>			
<b>Non-drinker</b>	435 (16.5)	397 (15.3)	
<b>Ex-drinker</b>	278 (10.5)	236 (9.1)	
<b>Current drinker (amount unknown)</b>	15 (0.6)	13 (0.5)	
<2 units/day	659 (24.9)	644 (24.8)	0.366
3-6 units/day	862 (32.6)	909 (35.0)	
>6 units/day	170 (6.4)	164 (6.3)	
<b>Unknown</b>	224 (8.5)	232 (8.9)	
<b>Smoking status</b>			
<b>Non-smoker</b>	1,126 (42.6)	1,151 (44.4)	
<b>Current smoker</b>	403 (15.3)	345 (13.3)	0.093
<b>Ex-smoker</b>	1,112 (42.1)	1,099 (42.4)	
<b>Unknown</b>	<5 <sup>2</sup>	0	
<b>CKD at baseline</b>			
<b>Baseline CKD status absent</b>	1,119 (42.3)	1,299 (50.1)	
<b>No CKD</b>	1,470 (55.6)	1,242 (47.9)	
<b>Stage 3a</b>	27 (1.0)	37 (1.4)	<0.001
<b>Stage 3b</b>	16 (0.6)	10 (0.4)	
<b>Stage 4</b>	10 (0.4)	5 (0.2)	
<b>Stage 5</b>	<5 <sup>2</sup>	<5 <sup>2</sup>	
<b>Type of bariatric surgery</b>			
<b>Gastric band</b>	1,193 (45.1)		
<b>Sleeve gastrectomy</b>	364 (13.8)		
<b>Gastric bypass</b>	1,075 (40.7)		
<b>Other</b>	11 (0.4)		
<b>ICD-10 code for AKI during follow-up</b>	<b>n = 44</b>	<b>n = 62</b>	
<b>N17.0 (Acute kidney failure with tubular necrosis)</b>	<5 <sup>2</sup>	<5 <sup>2</sup>	
<b>N17.9 (Acute kidney failure, unspecified)</b>	38 (86.4)	52 (83.9)	0.927
<b>N19 (Unspecified kidney failure)</b>	5 (11.4)	8 (12.9)	

<sup>1</sup> categorical variables:  $\chi^2$ -test; continuous variables: t-test + SD if normally distributed, rank sum test + IQR if non-normally distributed

<sup>2</sup>cell counts <5 have been suppressed to ensure anonymity

\*In the original study, each surgery patient was matched 1:1 to the person without surgery with the closest propensity score, choosing matches at random where more than one possible match had the same score<sup>7</sup>

AKI = acute kidney injury, BMI = body mass index, CKD = chronic kidney disease, ICD-10 = International Classification of Diseases, Tenth Revision, IQR = interquartile range, SD = standard deviation, T2DM = type 2 diabetes mellitus

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3 231 This cohort was comparable to the cohort from the original study regarding sex, mean age,  
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5 232 mean BMI, history of T2DM, type of bariatric surgery and the imbalance of BMI at baseline  
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7 233 <sup>7</sup>. More patients in the intervention group had a history of AKI compared to the comparison  
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9 234 group (1.1% vs. 0.4%). Of the 106 included events during follow-up, 84.9% were classified  
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11 235 with the ICD-10 code N17.9 (“acute kidney failure, unspecified”), 12.3% were coded as N19  
12  
13 236 (“unspecified kidney failure”), and 2.8% had a code of N17.0 (“Acute kidney failure with  
14  
15 237 tubular necrosis”). CKD status at baseline was unknown for about half of the patients in  
16  
17 238 each group with a slightly higher proportion in the unexposed group (50.1% vs. 42.3%). The  
18  
19 239 majority of the patients with creatinine tests at baseline did not have CKD (96.2 %).  
20  
21 240 The number of AKI events recorded in the first 30 days of follow-up was low. All five events  
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23 241 happened in patients with bariatric surgery and none were recorded in the control group,  
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25 242 which is consistent with the possibility of an increased risk of AKI directly after surgery  
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27 243 (Table 2).  
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244 *Table 2: Association of bariatric surgery with first incident AKI, stratified by length of follow-*  
 245 *up. Unexposed refers to the propensity matched comparison group*

	PY	Events	Rate per 1000 PY (95% CI)	Crude RR (95% CI) <sup>1</sup>	p-value <sup>2</sup>	Adjusted RR (95% CI) <sup>3</sup>	p-value <sup>2</sup>
<b>All patients</b>							
<b>Day 1-30</b>							
Unexposed	203	0	0	-			
Bariatric surgery	199	5	25.1 (10.5, 60.4)	-			
<b>&gt; Day 30</b>							
Unexposed	7,882	54	6.9 (5.2, 8.9)	-			
Bariatric surgery	8,061	34	4.2 (3.0, 5.9)	0.62 (0.40, 0.95)	0.027	0.37 (0.23, 0.61)	<0.001
<b>All patients analysed by type of surgery<sup>4</sup></b>							
<b>Day 1-30</b>							
Unexposed							
Gastric band							
Sleeve gastrectomy							
Gastric bypass							
Other							
<b>&gt; Day 30</b>							
Unexposed	7,882	54	6.9 (5.2, 8.9)	-			
Gastric band	4,614	17	3.7 (2.3, 5.9)	0.54 (0.31, 0.93)	0.026		
Sleeve gastrectomy	728	<5 <sup>5</sup>	5.5 (2.1, 14.6)	0.80 (0.29, 2.21)	0.670		
Gastric bypass	2,655	13	4.9 (2.8, 8.4)	0.71 (0.39, 1.31)	0.277		
Other	63	0	-	-			
<b>All patients over whole period of follow-up</b>							
Unexposed	8,085	54	6.7 (5.1, 8.7)	-			
Bariatric surgery	8,259	39	4.7 (3.5, 6.5)	0.71 (0.47, 1.07)	0.099	0.45 (0.28, 0.72)	0.001

<sup>1</sup> Poisson regression model

<sup>2</sup> Wald test

<sup>3</sup> Poisson regression model adjusted for age at baseline, sex, calendar time, CKD at baseline, history of AKI, history of taking oral antidiabetics, and BMI at baseline

<sup>4</sup> No analysis for day 1-30 owing to sparse data

<sup>5</sup> Cell counts <5 have been suppressed to ensure anonymity

AKI = acute kidney injury, CKD = chronic kidney disease, PY = person-years, RR = rate ratio

246  
 247 From 30 days onwards, bariatric surgery had a protective association with AKI risk (crude RR  
 248 = 0.62, 95% CI 0.40, 0.95). The effect estimate of the multivariable model indicated an even  
 249 stronger protective effect associated with bariatric surgery (RR = 0.37, 95% CI 0.23, 0.61),  
 250 largely due to the confounding by AKI prior to baseline.  
 251 The analysis by type of surgery yielded protective effect estimates for all types but the  
 252 confidence intervals were wide and no comparison between individual procedures was  
 253 feasible. Sensitivity analyses yielded similar results (S4 Appendix). A sensitivity analysis  
 254 restricted to patients with known CKD at baseline could not be done owing to sparse data.  
 255 Investigation of the effect of bariatric surgery over the whole follow-up period resulted in a  
 256 protective net effect associated with the intervention in univariable (RR = 0.71, 95% CI 0.47,  
 257 1.07) and multivariable (RR = 0.45, 95% CI 0.28, 0.72) analyses.



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3 258 **DISCUSSION**  
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5 259 In this study using prospectively recorded routine healthcare data from a representative  
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7 260 sample in the UK, bariatric surgery was associated with a potentially increased risk of AKI  
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9 261 within the first 30 days after surgery (5 events in patients with bariatric surgery, no events in  
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11 262 control patients) but a strongly protective association thereafter (adjusted RR = 0.37, 95% CI  
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13 263 0.23, 0.61). The association was consistent across subgroups and sensitivity analyses. To the  
14  
15 264 best of our knowledge, this is the first study to describe long-term effects of bariatric  
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17 265 surgery on AKI.  
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21 266 AKI has been described as a perioperative event for bariatric surgery<sup>12 13 15 16</sup>. Our results  
22  
23 267 are consistent with an increased risk in the early stages after surgery, however our analysis  
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25 268 lacked enough early events to rule out chance as a reason for the results observed. Since  
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27 269 patients do not have kidney function measures routinely checked by their family physician  
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29 270 after bariatric surgery, many events could remain unnoticed. Patients with known CKD are  
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31 271 more thoroughly checked for AKI and are a valuable subgroup to investigate, but the  
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33 272 numbers in this dataset were too low to analyse.  
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37 273 This study uses high quality data from routine medical care in the UK. The healthcare system  
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39 274 allows universal patient access to primary and secondary care so that the data is  
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41 275 representative of the population. Patients are followed continuously while they are  
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43 276 registered with a general practitioner allowing prospective data capture over long  
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45 277 observation periods and avoiding problems with reverse causality. For the classification of  
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47 278 AKI episodes in the HES database, the ICD-10 codes N17.0 and N17.9 comprised 87.7% of all  
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49 279 events and have previously been shown to accurately identify AKI in a single centre study<sup>24</sup>.  
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53 280 Some limitations need to be considered. Even though the data is taken from a  
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55 281 representative sample of the UK population, the baseline data indicate that patients who  
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3 282 undergo bariatric surgery are mostly female, of middle age, and with a history of T2DM.  
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5 283 While the results were adjusted for age and sex they might not be applicable for other  
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7 284 groups suffering from obesity like adolescents. Linkage between the CPRD and HES  
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9 285 databases was restricted to England. However, there is no cogent reason why the results  
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11 286 should not be applicable to regions with similar healthcare systems, both in the UK and  
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13 287 internationally. We had insufficient data to determine whether the association with AKI  
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15 288 varied between different types of bariatric surgery; we found a protective effect for gastric  
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17 289 band but results were inconclusive for sleeve gastrectomy and gastric bypass.  
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19 290 Any misclassification of diagnostic codes is likely non-differential between the bariatric  
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21 291 surgery patients and the matched comparison group and would bias the effect towards the  
22  
23 292 null value. Another problem of primary care data is that not every patient is routinely  
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25 293 checked for their kidney function, as incentives of testing apply primarily for those at risk of  
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27 294 kidney disease due to diabetes and hypertension. The study relied on AKI events recorded in  
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29 295 HES as part of a hospital admission and over time, the awareness of the importance of AKI  
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31 296 has likely changed resulting in secular changes in recording of AKI<sup>30</sup>; analyses have adjusted  
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33 297 for calendar period to account for this<sup>23 31</sup>. Future studies with hospital creatinine data  
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35 298 should compare the AKI severity between the groups to investigate this issue. In general,  
36  
37 299 AKI diagnosed during hospitalisation is likely to represent more serious AKI events, though  
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39 300 we would argue these are the most clinically relevant outcomes. Moreover, a patient who  
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41 301 experienced a previous AKI episode might be under more scrutiny for detection of future  
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43 302 episodes. Since more patients in the bariatric surgery group had a history of AKI they might  
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45 303 have a higher chance of detection of an AKI episode during follow-up. This would bias the  
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47 304 estimate towards the null value and could indicate that the association we report is an  
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49 305 under-estimate.  
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3 306 In addition, CKD status at baseline was missing in almost half of the patient population.  
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5 307 However, a recent study indicated that the prevalence of CKD in the CPRD database was  
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7 308 comparable to that found in nationally representative registry studies<sup>27</sup>. This indicates that  
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9 309 patients without eGFR-measurements at baseline are unlikely to have CKD. In addition,  
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11 310 sensitivity analyses investigating the effect in patients with known or unknown CKD status at  
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13 311 baseline yielded comparable results.  
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15 312 Since access to bariatric surgery is restricted within the UK healthcare system, some  
16  
17 313 patients might have funded their operation privately, resulting in selection bias. In a recent  
18  
19 314 analysis about 40% of bariatric surgery operations in the UK were privately funded<sup>32</sup>. Thus,  
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21 315 the intervention group might have a higher socioeconomic status than the non-exposed  
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23 316 group, in which similar patients would not be able to afford surgery. Since the  
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25 317 socioeconomic background is an important determinant of health outcomes and was an  
26  
27 318 unmeasured potential confounder not considered in the matching process, this could have  
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29 319 led to more positive health outcomes in the intervention group irrespective of surgery and  
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31 320 to an overestimation of the effect. In this study setting it was not possible to determine  
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33 321 which patients had privately funded surgery.  
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35 322 Even though most baseline variables were evenly distributed due to the matching process  
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37 323 this does not guarantee that unmeasured variables are evenly distributed as well, which can  
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39 324 constitute residual confounding. Incorrect, imprecise, or missing measurements of  
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41 325 covariates could also have led to residual confounding. For the multivariable model,  
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43 326 adjusting for history of AKI led to the strongest change of the effect estimate. AKI events are  
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45 327 likely under-recorded in the HES database, for reasons described above, and thus residual  
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47 328 confounding is possible. Since adjusting for AKI history led to a stronger effect estimate, the  
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3 329 protective effect we report here may be an underestimate if AKI history is missing to the  
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5 330 same degree in surgery and non-surgery patients.  
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7 331 This study adds to the evidence of long term effects of bariatric surgery, and appears to be  
8  
9 332 the first study to quantify a long-term beneficial effect on AKI. Future studies with higher  
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11 333 patient numbers may be able to determine differences in effect between types of surgery,  
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13 334 investigate the effect in patients with CKD, and elucidate mechanisms of the association  
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15 335 between bariatric surgery and AKI.  
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3 337 **SUPPLEMENTARY INFORMATION**  
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5 338 Supplementary information is available at the *BMJ open* website.  
6  
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13

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17

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21

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23

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25

26 348 analysis, the writing of the report, or the decision to submit the paper for publication.  
27

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32 350 **CONFLICT OF INTEREST**  
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34 351 The authors have no conflicts of interest to disclose.  
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39 353 **DATA SHARING**  
40

41 354 The data were obtained from the Clinical Practice Research Datalink (CPRD). CPRD data  
42

43 355 governance does not allow us to distribute patient data to other parties. Researchers may  
44

45 356 apply for data access at [www.CPRD.com](http://www.CPRD.com). The codes used to produce the data for this study  
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47 357 are provided in the Supporting Information.  
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3 361 **CONTRIBUTIONS**  
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5 362 UK, DN, RLB, IJD, and LS were responsible for conceptualisation of the study and formulate  
6  
7 363 the research goals and aims. UK, DN, KEM, RM, KB, RLB, LS, and IJD developed the  
8  
9 364 methodology and models. UK, KEM, KB, IJD, and RM worked on the data curation. UK  
10  
11 365 performed the statistical analysis and wrote the original draft. UK, DN, KEM, RM, KB, RLB,  
12  
13  
14 366 LS, and IJD reviewed and commented the draft and gave input on editing.  
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- 3 1 **Long-term effects of bariatric surgery on acute kidney injury: A propensity-matched**
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- 5 2 **cohort in the United Kingdom Clinical Practice Research Datalink**
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- 9 4 **Supporting Information**
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- 12 5
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- 14 6 **Overview**
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- 16 7 S1 Appendix – Code List for Identification of patients with bariatric surgery
- 17
- 18 8 S2 Appendix – Association of potential confounders with bariatric surgery and AKI
- 19
- 20 9 S3 Appendix – Patient selection from the original cohort
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- 22 10 S4 Appendix – Sensitivity Analyses
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11 **S1 Appendix**

12 *Appendix 1: Code List for identification of patients with bariatric surgery from the CPRD database as*  
13 *published by Douglas et al. [7]*

14	<i>Read code</i>	<i>description</i>
15	76132.00	Laparoscopic adjustable gastric banding
16	76134.00	Partitioning of stomach using staples
17	76131.11	Mason vertical banded gastroplasty
18	76133.00	Partitioning of stomach using band
19	76116.00	Laparoscopic sleeve gastrectomy
20	76115.00	Sleeve gastrectomy NEC
21	76425.00	Duodenal switch
22	76135.00	Partitioning of stomach NEC
23	76114.00	Sleeve gastrectomy and duodenal switch
24	76166.00	Laparoscopic gastric bypass

25 **S2 Appendix**

26 *Appendix 2: Identification of potential confounders in the association of bariatric surgery (exposure)*  
 27 *and the endpoint of incident AKI (outcome) in patients of the linked CPRD/HES cohort*

	RR (95%CI)	Change in %	Selection for multivariable model
<b>Crude effect estimate</b>	0.62 (0.40, 0.95)		
<b>Effect estimates when individually adjusting for</b>			
<b>Age</b>	0.62 (0.40, 0.95)	0.2 %	yes (a priori)
<b>Sex</b>	0.60 (0.39, 0.92)	2.7 %	yes (a priori)
<b>Calendar Time</b>	0.61 (0.40, 0.94)	0.9%	yes (a priori)
<b>CKD status at baseline</b>	0.59 (0.38, 0.91)	4.4 %	yes (a priori)
<b>BMI at baseline</b>	0.53 (0.34, 0.83)	13.9 %	yes
<b>Alcohol Status</b>	0.61 (0.40, 0.93)	1.3 %	no
<b>Smoking Status</b>	0.61 (0.40, 0.94)	0.3 %	no
<b>History of cerebrovascular disease</b>	0.61 (0.40, 0.94)	0.6 %	no
<b>History of coronary heart disease</b>	0.60 (0.39, 0.91)	3.3 %	no
<b>History of peripheral vascular disease</b>	0.64 (0.41, 0.98)	3.2 %	no
<b>History of other atheroma</b>	0.62 (0.40, 0.95)	0.0 %	no
<b>History of diabetes</b>	0.60 (0.39, 0.92)	2.7%	no
<b>History of taking oral antidiabetics</b>	0.55 (0.36, 0.85)	10.4%	yes
<b>History of taking insulin</b>	0.57 (0.37, 0.87)	7.9 %	no
<b>History of hypertension</b>	0.61 (0.40, 0.94)	1.1 %	no
<b>History of statin use</b>	0.58 (0.38, 0.89)	5.5 %	no
<b>History of AKI</b>	0.42 (0.26, 0.67)	31.9 %	yes

Variables were added individually to the univariable model testing the association between bariatric surgery and AKI. If the addition of the respective variable changed the model  $\geq 10\%$  then the variable was selected to be included in the multivariable model.

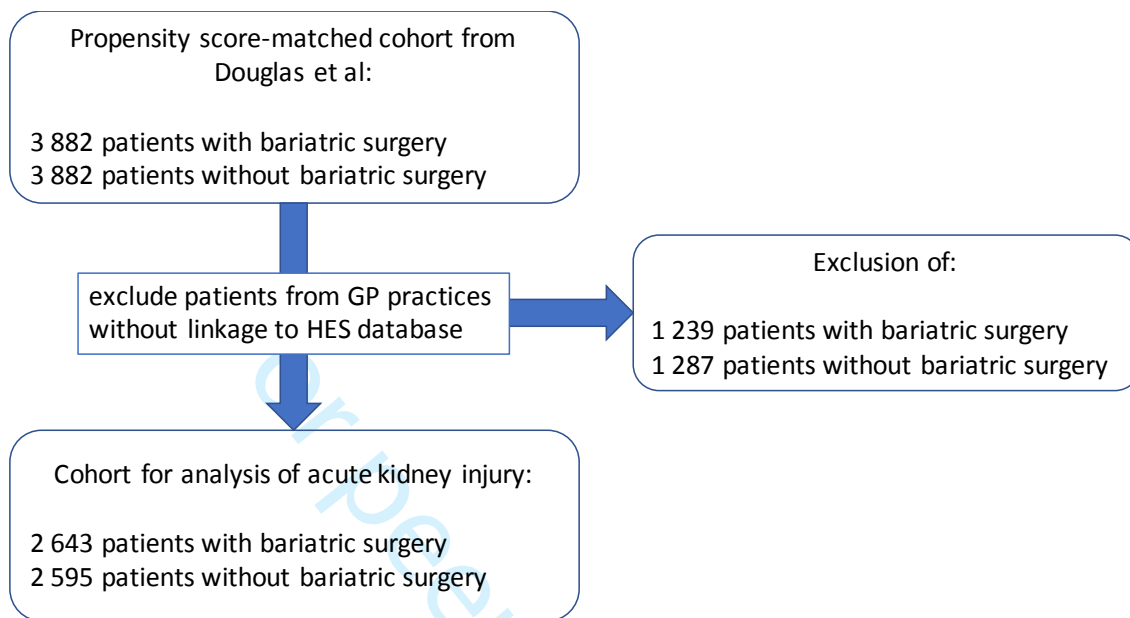
AKI = acute kidney injury, BMI = body mass index, CKD = chronic kidney disease

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29 **S3 Appendix**

30 *Appendix 3: Patient selection from the original cohort as described in Douglas et al [7]*

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33

34 **S4 Appendix**35 *Appendix 4: Sensitivity analyses for the association of bariatric surgery with acute kidney injury*

	PY	Events	Rate per 1000 PY (95% CI)	Crude RR (95% CI) <sup>1</sup>	p-value <sup>2</sup>	Adjusted RR (95% CI) <sup>3</sup>	p-value <sup>2</sup>
<b>Restricted to patients without CKD at baseline (available serum creatinine measures + eGFR ≥60)</b>							
<b>Day 1-30</b>							
Unexposed	98	0	0	-			
Bariatric surgery	111	<5 <sup>b</sup>	36.2 (13.6, 96.3)	-			
<b>&gt;Day 30</b>							
Unexposed	3,550	27	7.6 (5.2, 11.1)	-			
Bariatric surgery	4,311	22	5.1 (3.4, 7.7)	0.67 (0.38, 1.18)	0.165	0.53 (0.29, 1.00)	0.050
<b>Restricted to patients without known CKD at baseline (available serum creatinine measures + eGFR ≥60 or missing eGFR at baseline)</b>							
<b>Day 1-30</b>							
Unexposed	199	0	0	-			
Bariatric surgery	195	<5 <sup>b</sup>	20.5 (7.7, 54.7)	-			
<b>&gt;Day 30</b>							
Unexposed	7,735	42	5.4 (4.0, 7.3)	-			
Bariatric surgery	7,930	27	3.4 (2.3, 5.0)	0.63 (0.39, 1.02)	0.058	0.42 (0.25, 0.73)	0.002
<b>Excluding patients with CKD stage 4</b>							
<b>Day 1-30</b>							
Unexposed	203	0	0	-			
Bariatric surgery	198	5	25.2 (10.5, 60.6)	-			
<b>&gt; Day 30</b>							
Unexposed	7,875	52	6.6 (5.0, 8.7)	-			
Bariatric surgery	8,037	32	4.0 (2.8, 5.6)	0.60 (0.39, 0.94)	0.024	0.35 (0.21, 0.59)	<0.001
<b>Restricted to patients with T2DM</b>							
<b>Day 1-30</b>							
Unexposed	65	0	0	-			
Bariatric surgery	69	<5 <sup>b</sup>	43.6 (14.1, 135.1)	-			
<b>&gt;Day 30</b>							
Unexposed	2,325	33	14.2 (10.1, 20.0)	-			
Bariatric surgery	2,548	18	7.1 (4.5, 11.2)	0.50 (0.28, 0.88)	0.017	0.25 (0.13, 0.51)	<0.001
<b>Restricted to patients with a history of taking insulin</b>							
<b>Day 1-30</b>							
Unexposed	11	0	0	-			
Bariatric surgery	13	0	0	-			
<b>&gt;Day 30</b>							
Unexposed	321	11	34.3 (19.0, 61.9)	-			
Bariatric surgery	502	9	17.9 (9.3, 34.5)	0.52 (0.22, 1.26)	0.150	0.22 (0.08, 0.64)	0.005
<b>Restricted to ICD-10 codes N17.0 and N17.9</b>							
<b>Day 1-30</b>							
Unexposed	202	0	0	-			
Bariatric surgery	199	5	25.2 (10.5, 60.5)	-			
<b>&gt;Day 30</b>							
Unexposed	7,871	48	6.1 (4.6, 8.1)	-			
Bariatric surgery	8,055	31	3.8 (2.7, 5.5)	0.63 (0.40, 0.99)	0.046	0.40 (0.24, 0.67)	<0.001
<b>Having an initial post-surgery time span of 60 days instead of 30</b>							
<b>Day 1-60</b>							
Unexposed	403	<5 <sup>b</sup>	2.5 (0.3, 17.6)	-			
Bariatric surgery	395	6	15.2 (6.8, 33.8)	6.11 (0.74, 50.8)	0.094	<sup>4</sup>	
<b>&gt; Day 60</b>							
Unexposed	7,682	53	6.9 (5.3, 9.0)	-			
Bariatric surgery	7,864	33	4.2 (3.0, 5.9)	0.61 (0.39, 0.94)	0.025	0.38 (0.23, 0.63)	<0.001
				Test for interaction <sup>5</sup>	0.011		

Including patients with extreme propensity scores							
<b>Day 1-30</b>							
Unexposed	208	0	0	-			
Bariatric surgery	206	5	24.3 (10.1, 58.3)	-			
<b>&gt; Day 30</b>							
Unexposed	8,054	59	7.3 (5.7, 9.5)	-			
Bariatric surgery	8,324	34	4.1 (2.9, 5.7)	0.56 (0.37, 0.85)	0.007	0.33 (0.20, 0.54)	<0.001

<sup>1</sup> Poisson regression model

<sup>2</sup> Wald test for RR, Likelihood-Ratio Test for interaction

<sup>3</sup> Poisson regression model adjusted for age at baseline, sex, calendar time, CKD at baseline, history of AKI, history of taking oral antidiabetics, and BMI at baseline

<sup>4</sup> No analysis for day 1-30 owing to sparse data

<sup>5</sup> Test for interaction of the effect estimate with the time periods 1-30 days and >30 days

<sup>6</sup> cell counts <5 have been suppressed to ensure anonymity

AKI = acute kidney injury, CKD = chronic kidney disease, PY = person-years, RR = rate ratio

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For peer review only

**Supporting Information:****STROBE statement checklist to ensure appropriate reporting of study information of long-term effects of acute kidney injury for the propensity-matched cohort study of patients with and without bariatric surgery**

	Item No	Report
<b>Title and abstract</b>	1	<p>(a) Indicate the study's design with a commonly used term in the title or the abstract</p> <p>“Long-term effects of bariatric surgery on acute kidney injury: A propensity-matched cohort in the United Kingdom Clinical Practice Research Datalink”</p> <p>b) Provide in the abstract an informative and balanced summary of what was done and what was found</p> <p>Abstract: on page 2 containing Background, Methods, Results and Conclusions</p>
<b>Introduction</b>		
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported</p> <p>See page 4 for description of background;</p> <p>Rationale (p4): “To the best of our knowledge, no studies have been published examining the long-term effects of bariatric surgery on AKI.”</p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses</p> <p>Page 4: “In this study, we investigate the long-term effects of bariatric surgery on AKI to see whether the expected reduction in BMI has any impact on subsequent renal health.”</p>
<b>Methods</b>		
Study design	4	<p>Present key elements of study design early in the paper</p> <p>See page 5: “We undertook a matched cohort study using prospectively collected data from CPRD patients registered before 31st December 2014 linked to the Hospital Episodes Statistics (HES) database to investigate long-term effects of bariatric surgery on AKI.”</p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</p> <p>Page 5: “The CPRD database contains anonymised, routinely collected data on approximately 10 million patients in participating primary care practices in the UK, including demographic characteristics, current and previous diagnoses, prescribing, test results, and lifestyle factors. [...] The HES database contains patient data from hospital admissions to English hospitals within the National Health Service [...]. Data from 70% of CPRD practices in England has been linked at patient level with HES admission data thus allowing the combined analysis of data from primary and acute hospital care for a subset of patients.”</p> <p>“A detailed description of how the cohort was constructed is described elsewhere. In brief, records of patients who underwent bariatric surgery (n=3,882) between 1997 and 2015 were matched to individuals who did not undergo surgery (n=3,882) using propensity scores.”</p> <p>Page 6: “Follow-up started on the day of surgery for those with bariatric surgery, and for the comparison group who did not undergo bariatric surgery, on the surgery date</p>

		of their matched case. Patient records were censored at the earliest of: AKI, death, leaving the practice, latest data collection from current practice, or end of linkage period to the HES database.”
Participants	6	<p>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p>Page 6: “Patients with bariatric surgery were identified using Read codes for surgery in the CPRD database (S1 Appendix) and were included in the study if they had been registered in the CPRD <math>\geq 12</math> months prior to the intervention. We excluded those with a record of prior bariatric surgery reversal.</p> <p>For the comparison group, the inclusion criteria were to have at least one BMI measurement <math>\geq 40</math> kg/m<sup>2</sup>, <math>\geq 12</math> months of follow-up prior to the index date in the database, and no prior record of bariatric surgery or bariatric surgery reversal.”</p> <p>Page 5: “The CPRD database contains anonymised, routinely collected data on approximately 10 million patients in participating primary care practices in the UK, including demographic characteristics, current and previous diagnoses, prescribing, test results, and lifestyle factors. Diagnoses, signs, and symptoms are recorded using Read codes [...]. The HES database contains patient data from hospital admissions to English hospitals within the National Health Service “</p>
		(b) For matched studies, give matching criteria and number of exposed and unexposed
		<p>Page 6: “Study population matching and the propensity score incorporated information on age, sex, calendar period, history of T2DM, hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, other atheroma, use of insulin, use of oral antidiabetic medication, use of statins, smoking status, and alcohol consumption.”</p> <p>“The study sample was restricted to eligible patients registered at practices linked to the HES database and information on AKI events was obtained, resulting in a final cohort comprising 2,643 patients who underwent bariatric surgery, and 2,595 patients who did not.”</p>
Variables	7	<p>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</p> <p>Page 6/7: “AKI episodes were obtained from the HES database using ICD-10 codes: N17.0 (“Acute kidney failure with tubular necrosis”), N17.1 (“Acute renal failure with acute cortical necrosis”), N17.2 (“Acute renal failure with medullary necrosis”), N17.8 (“Other acute renal failure”), N17.9 (“Acute kidney failure, unspecified”), and N19 (“Unspecified kidney failure”). In this cohort, events coded with N17.1, N17.2, and N17.8 were not found. AKI events that occurred before the start of follow-up were recorded as a binary variable “history of AKI”, while AKI events occurring during follow-up were used to analyse AKI incidence.</p> <p>Recorded serum creatinine values from the CPRD database were not routinely standardised with isotope-dilution mass spectrometry before 2013. Thus, we assumed all measurements to be unstandardized and multiplied the creatinine measures with the factor 0.95 before calculating the estimated glomerular filtration rate (eGFR) using the “Chronic Kidney Disease Epidemiology Collaboration” (CKD-EPI) equation.</p>



Ethnicity was not considered in the eGFR calculation due to incomplete recording in the database and the low proportion of Afro-Caribbean people in the population. CKD stages were defined according to eGFR values in ml/min/1.73m<sup>2</sup> according to current guidelines: eGFR  $\geq 60$  = no known CKD; eGFR 45-59 = stage 3a; eGFR 30-44 = stage 3b; eGFR 15-29 = stage 4; eGFR  $< 15$  = stage 5. Baseline CKD status was derived from eGFR measurements in the year prior to start of follow-up by: 1) taking the last two measurements before the index date  $\geq 90$  days apart – with the higher eGFR value corresponding to the CKD baseline status, or 2) taking the most recent serum creatinine result if only one suitable test result was available. Since serum creatinine is more likely to be tested in the acutely unwell or in people who are routinely monitored as part of incentivised programs (e.g. people with diabetes), patients without measurements of CKD baseline status were assumed to have no CKD and were analysed as such.”

Page 6: “Study population matching and the propensity score incorporated information on age, sex, calendar period, history of T2DM, hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, other atheroma, use of insulin, use of oral antidiabetic medication, use of statins, smoking status, and alcohol consumption.”

Page 8: “When the cohort was initially constructed, propensity score matching was used to deal with confounding. This study uses a subset of this cohort since patients from practices without linkage between the CPRD and HES databases had to be excluded (as AKI was assessed using hospital admission data). To identify variables for the multivariable model, potential confounders that were not deemed to be on the causal pathway were added individually to the univariable model. If the addition changed the effect estimate  $\geq 10\%$  these variables were included in the multivariable model. Consequently, history of AKI, history of taking oral antidiabetics, and BMI at baseline were included (S2 Appendix). In addition, age at baseline, sex, calendar period (1997-2005, 2006-2010, 2011-2015), and CKD status at baseline were selected a priori as forced variables.”

Page 8: “In order to separate short-term effects of the surgery from potential long-term effects, we analysed the association separately for: a) events within the first 30 days, and b) events after 30 days.”

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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
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Page 5: “The CPRD database contains anonymised, routinely collected data on approximately 10 million patients in participating primary care practices in the UK, including demographic characteristics, current and previous diagnoses, prescribing, test results, and lifestyle factors. Diagnoses, signs, and symptoms are recorded using Read codes [...] The HES database contains patient data from hospital admissions to English hospitals within the National Health Service. For each hospital admission, the diagnoses are recorded using standardised codes of the International Classification of Diseases, Tenth Revision (ICD-10). Data from 70% of CPRD practices in England has been linked at patient level with HES admission data thus allowing the combined analysis of data from primary and acute hospital care for a subset of patients.”

Page 5: “Patients with bariatric surgery were identified using Read codes for surgery in the CPRD database (S1 Appendix) and were included in the study if they had been

registered in the CPRD  $\geq 12$  months prior to the intervention. We excluded those with a record of prior bariatric surgery reversal.”

Page 6/7: “AKI episodes were obtained from the HES database using ICD-10 codes: N17.0 (“Acute kidney failure with tubular necrosis”), N17.1 (“Acute renal failure with acute cortical necrosis”), N17.2 (“Acute renal failure with medullary necrosis”), N17.8 (“Other acute renal failure”), N17.9 (“Acute kidney failure, unspecified”), and N19 (“Unspecified kidney failure”).”

Bias	9	Describe any efforts to address potential sources of bias
		Page 9: “The 5% bands of patients with the highest and lowest propensity scores were excluded from the primary analysis (“trimming”) since these contain patients that are treated in stark contrast to their health status, potentially causing bias.”
Study size	10	Explain how the study size was arrived at
		Pages 5/6: “A detailed description of how the cohort was constructed is described elsewhere. In brief, records of patients who underwent bariatric surgery (n=3,882) between 1997 and 2015 were matched to individuals who did not undergo surgery (n=3,882) using propensity scores.” [...] “The study sample was restricted to eligible patients registered at practices linked to the HES database and information on AKI events was obtained, resulting in a final cohort comprising 2,643 patients who underwent bariatric surgery, and 2,595 patients who did not.”
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		Page 7: “Recorded serum creatinine values from the CPRD database were not routinely standardised with isotope-dilution mass spectrometry before 2013. Thus, we assumed all measurements to be unstandardized and multiplied the creatinine measures with the factor 0.95 before calculating the estimated glomerular filtration rate (eGFR) using the “Chronic Kidney Disease Epidemiology Collaboration” (CKD-EPI) equation. Ethnicity was not considered in the eGFR calculation due to incomplete recording in the database and the low proportion of Afro-Caribbean people in the population. CKD stages were defined according to eGFR values in ml/min/1.73m <sup>2</sup> according to current guidelines: eGFR $\geq 60$ = no known CKD; eGFR 45-59 = stage 3a; eGFR 30-44 = stage 3b; eGFR 15-29 = stage 4; eGFR $< 15$ = stage 5. Baseline CKD status was derived from eGFR measurements in the year prior to start of follow-up by: 1) taking the last two measurements before the index date $\geq 90$ days apart – with the higher eGFR value corresponding to the CKD baseline status, or 2) taking the most recent serum creatinine result if only one suitable test result was available. Since serum creatinine is more likely to be tested in the acutely unwell or in people who are routinely monitored as part of incentivised programs (e.g. people with diabetes), patients without measurements of CKD baseline status were assumed to have no CKD and were analysed as such.”
		Page 8: “In addition, age at baseline, sex, calendar period (1997-2005, 2006-2010, 2011-2015), and CKD status at baseline were selected a priori as forced variables.”
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		Page 8/9: “The association between bariatric surgery and AKI was analysed using a Poisson regression model with a time to first event analysis. P-values were calculated

1 using Wald tests. In order to separate short-term effects of the surgery from potential  
2 long-term effects, we analysed the association separately for: a) events within the first  
3 30 days, and b) events after 30 days. When the cohort was initially constructed,  
4 propensity score matching was used to deal with confounding. This study uses a  
5 subset of this cohort since patients from practices without linkage between the CPRD  
6 and HES databases had to be excluded (as AKI was assessed using hospital admission  
7 data). To identify variables for the multivariable model, potential confounders that  
8 were not deemed to be on the causal pathway were added individually to the  
9 univariable model. If the addition changed the effect estimate  $\geq 10\%$  these variables  
10 were included in the multivariable model. Consequently, history of AKI, history of  
11 taking oral antidiabetics, and BMI at baseline were included (S2 Appendix). In  
12 addition, age at baseline, sex, calendar period (1997-2005, 2006-2010, 2011-2015),  
13 and CKD status at baseline were selected a priori as forced variables. For models with  
14  $< 40$  outcomes, only age and sex were included in the multivariable model due to data  
15 sparsity.

16 The 5% bands of patients with the highest and lowest propensity scores were excluded  
17 from the primary analysis (“trimming”) since these contain patients that are treated in  
18 stark contrast to their health status, potentially causing bias.

19 Heterogeneity of effect estimates between the calendar periods was tested with a  
20 Likelihood Ratio Test.

21 The analysis was performed for all patients with bariatric surgery and also further  
22 stratified by type of surgery. Patients with stage 5 CKD (baseline eGFR  $< 15$   
23 ml/min/1.73m<sup>2</sup>) were excluded from the analyses since this constitutes end-stage  
24 renal failure (ESRD). In addition, patients with missing data in  $\geq 1$  variable of the  
25 multivariable model were excluded from both uni- and multivariable analyses.”

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26 (b) Describe any methods used to examine subgroups and interactions

27 page 8: “In order to separate short-term effects of the surgery from potential long-term  
28 effects, we analysed the association separately for: a) events within the first 30 days,  
29 and b) events after 30 days.”

30 page 9: “Heterogeneity of effect estimates between the calendar periods was tested  
31 with a Likelihood Ratio Test.”

32 Page 9: “The analysis was performed for all patients with bariatric surgery and also  
33 further stratified by type of surgery.”

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34 (c) Explain how missing data were addressed

35 page 7: “Since serum creatinine is more likely to be tested in the acutely unwell or in  
36 people who are routinely monitored as part of incentivised programs (e.g. people with  
37 diabetes), patients without measurements of CKD baseline status were assumed to  
38 have no CKD and were analysed as such.”

39 page 9: “In addition, patients with missing data in  $\geq 1$  variable of the multivariable  
40 model were excluded from both uni- and multivariable analyses.”

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41 (d) If applicable, explain how loss to follow-up was addressed

42 page 6: “Patient records were censored at the earliest of: AKI, death, leaving the  
43 practice, latest data collection from current practice, or end of linkage period to the

HES database.”

(e) Describe any sensitivity analyses

Pages 9/10: “Several planned sensitivity analyses were undertaken: 1) To determine the net effect of the intervention we calculated the risk of AKI over the whole period of follow-up; 2) The prevalence of decreased kidney function in the CPRD database was similar to that in a nationally representative kidney disease registry indicating that patients with missing eGFR measurements are unlikely to have CKD. To identify potential differences in the effect between patients with known and unknown eGFR measurements, we restricted the analysis to a) patients known to have no CKD at baseline (baseline eGFR  $\geq 60$  ml/min/1.73m<sup>2</sup>), b) patients without known CKD at baseline (as above but including patients with missing creatinine values at baseline and assuming these individuals to have no CKD), and c) patients with known CKD at baseline.; 3) Moreover, to investigate the effect in a group of particular interest which is under more scrutiny for measuring kidney function we restricted the analysis to patients with: a) T2DM, and b) a history of taking insulin; 4) To avoid misclassification of low eGFR values as AKI we excluded patients with stage 4 CKD at baseline; 5) We restricted the analysis to ICD-10 codes N17.0 and N17.9, which have a high positive predictive value for AKI; 6) We increased the immediate post-surgery time span from 30 to 60 days; and 7) We included people with extreme propensity scores.”

## 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  see S3 Appendix  (b) Give reasons for non-participation at each stage  not applicable  (c) Consider use of a flow diagram  see S3 Appendix
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  page 12: see Table 1  (b) Indicate number of participants with missing data for each variable of interest  page 12: see Table 1  (c) Summarise follow-up time (eg, average and total amount)  page 12: see Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time  page 12: see Table 1
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

1		adjusted for and why they were included
2		
3		page 13: see Table 2
4		(b) Report category boundaries when continuous variables were categorized
5		
6		
7		page 12: see Table 1
8		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
9		meaningful time period
10		
11		not applicable
12		
13	Other analyses	17 Report other analyses done—eg analyses of subgroups and interactions, and
14		sensitivity analyses
15		
16		Page 13: see table 2
17		see S4 Appendix
18		
19	<b>Discussion</b>	
20	Key results	18 Summarise key results with reference to study objectives
21		
22		Page 15: “In this study using prospectively recorded routine healthcare data from a
23		representative sample in the UK, bariatric surgery was associated with a potentially
24		increased risk of AKI within the first 30 days after surgery (5 events in patients with
25		bariatric surgery, no events in control patients) but a strongly protective association
26		thereafter (adjusted RR = 0.37, 95% CI 0.23, 0.61). The association was consistent
27		across subgroups and sensitivity analyses. To the best of our knowledge, this is the
28		first study to describe long-term effects of bariatric surgery on AKI.”
29		
30		
31	Limitations	19 Discuss limitations of the study, taking into account sources of potential bias or
32		imprecision. Discuss both direction and magnitude of any potential bias
33		
34		Pages 15-18: “Some limitations need to be considered. Even though the data is taken
35		from a representative sample of the UK population, the baseline data indicate that
36		patients who undergo bariatric surgery are mostly female, of middle age, and with a
37		history of T2DM. While the results were adjusted for age and sex they might not be
38		applicable for other groups suffering from obesity like adolescents. Linkage between
39		the CPRD and HES databases was restricted to England. However, there is no cogent
40		reason why the results should not be applicable to regions with similar healthcare
41		systems, both in the UK and internationally. We had insufficient data to determine
42		whether the association with AKI varied between different types of bariatric surgery;
43		we found a protective effect for gastric band but results were inconclusive for sleeve
44		gastrectomy and gastric bypass.
45		Any misclassification of diagnostic codes is likely non-differential between the
46		bariatric surgery patients and the matched comparison group and would bias the effect
47		towards the null value. Another problem of primary care data is that not every patient
48		is routinely checked for their kidney function, as incentives of testing apply primarily
49		for those at risk of kidney disease due to diabetes and hypertension. The study relied
50		on AKI events recorded in HES as part of a hospital admission and over time, the
51		awareness of the importance of AKI has likely changed resulting in secular changes in
52		recording of AKI ; analyses have adjusted for calendar period to account for this.
53		Future studies with hospital creatinine data should compare the AKI severity between
54		the groups to investigate this issue. In general, AKI diagnosed during hospitalisation
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58		
59		
60		

is likely to represent more serious AKI events, though we would argue these are the most clinically relevant outcomes. Moreover, a patient who experienced a previous AKI episode might be under more scrutiny for detection of future episodes. Since more patients in the bariatric surgery group had a history of AKI they might have a higher chance of detection of an AKI episode during follow-up. This would bias the estimate towards the null value and could indicate that the association we report is an under-estimate.

In addition, CKD status at baseline was missing in almost half of the patient population. However, a recent study indicated that the prevalence of CKD in the CPRD database was comparable to that found in nationally representative registry studies. This indicates that patients without eGFR-measurements at baseline are unlikely to have CKD. In addition, sensitivity analyses investigating the effect in patients with known or unknown CKD status at baseline yielded comparable results. Since access to bariatric surgery is restricted within the UK healthcare system, some patients might have funded their operation privately, resulting in selection bias. In a recent analysis about 40% of bariatric surgery operations in the UK were privately funded. Thus, the intervention group might have a higher socioeconomic status than the non-exposed group, in which similar patients would not be able to afford surgery. Since the socioeconomic background is an important determinant of health outcomes and was an unmeasured potential confounder not considered in the matching process, this could have led to more positive health outcomes in the intervention group irrespective of surgery and to an overestimation of the effect. In this study setting it was not possible to determine which patients had privately funded surgery. Even though most baseline variables were evenly distributed due to the matching process this does not guarantee that unmeasured variables are evenly distributed as well, which can constitute residual confounding. Incorrect, imprecise, or missing measurements of covariates could also have led to residual confounding. For the multivariable model, adjusting for history of AKI led to the strongest change of the effect estimate. AKI events are likely under-recorded in the HES database, for reasons described above, and thus residual confounding is possible. Since adjusting for AKI history led to a stronger effect estimate, the protective effect we report here may be an underestimate if AKI history is missing to the same degree in surgery and non-surgery patients.“

Interpretation	20	<p>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence</p> <p>Page 18: “This study adds to the evidence of long term effects of bariatric surgery, and appears to be the first study to quantify a long-term beneficial effect on AKI. Future studies with higher patient numbers may be able to determine differences in effect between types of surgery, investigate the effect in patients with CKD, and elucidate mechanisms of the association between bariatric surgery and AKI.”</p>
Generalisability	21	<p>Discuss the generalisability (external validity) of the study results</p> <p>Page 15/16: “Even though the data is taken from a representative sample of the UK population, the baseline data indicate that patients who undergo bariatric surgery are mostly female, of middle age, and with a history of T2DM. While the results were adjusted for age and sex they might not be applicable for other groups suffering from obesity like adolescents. Linkage between the CPRD and HES databases was restricted to England. However, there is no cogent reason why the results should not</p>

be applicable to regions with similar healthcare systems, both in the UK and internationally.”

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#### Other information

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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
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RM is supported by a Sir Henry Wellcome Postdoctoral Fellowship from the Wellcome Trust. KB holds a Sir Henry Dale fellowship jointly funded by the Wellcome Trust and the Royal Society. RLB is an NIHR Research Professor and supported by funding from the Rosetrees Trust and the Sir Jules Thorn Charitable Trust. LS is supported by a senior clinical fellowship from the Wellcome Trust. IJD is funded by an unrestricted grant from GlaxoSmithKline.

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\*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>.

# BMJ Open

## Long-term effects of bariatric surgery on acute kidney injury: A propensity-matched cohort in the United Kingdom Clinical Practice Research Datalink

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1 **Title** Long-term effects of bariatric surgery on acute kidney injury: A propensity-  
2 matched cohort in the United Kingdom Clinical Practice Research Datalink

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10 **Running headline** Bariatric surgery and acute kidney injury

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3 32 **ABSTRACT**

4 33 **Objective:** Bariatric surgery is an effective method of weight reduction and has been  
5  
6 34 associated with acute kidney injury (AKI) as a perioperative event. However, the long-term  
7  
8 35 effects of the weight reduction after surgery on AKI are unknown. The objective of this  
9  
10 36 study is to quantify the association of bariatric surgery with later risk of AKI.

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13 37 **Design:** This study uses a propensity-score matched cohort of patients from the United  
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15 38 Kingdom Clinical Practice Research Datalink database with and without bariatric surgery to  
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17 39 compare rates of AKI episodes derived from linkage to the Hospital Episode Statistics.

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20 40 **Setting:** England, United Kingdom

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22 41 **Participants:** We included 2,643 patients with bariatric surgery and 2,595 patients without.

23  
24 42 **Results:** Results were compatible with an increased risk of AKI in the first 30 days following  
25  
26 43 surgery compared with patients without surgery, but AKI incidence was substantially  
27  
28 44 decreased in patients with bariatric surgery during long-term follow-up (rate ratio 0.37, 95%  
29  
30 45 CI 0.23, 0.61) even after accounting for chronic kidney disease status at baseline. Over the  
31  
32 46 whole period of follow-up, bariatric surgery had a net protective effect on risk of AKI (rate  
33  
34 47 ratio 0.45, 95% CI 0.28, 0.72).

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37 48 **Conclusions:** Bariatric surgery was associated with strong protective effects on AKI  
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39 49 incidence during long-term follow-up. While the risk of AKI may be increased within the first  
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41 50 30 days, the net effect seen was beneficial.

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47 52 **Keywords:** Acute Kidney Injury; Obesity; Bariatric Surgery; Clinical Practice Research  
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49 53 Datalink

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3 54 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 5 55 • This study uses high quality data from linked databases in England (Clinical Practice  
6  
7 56 Research Datalink and Hospital Episode Statistics) to describe long-term effects of  
8  
9 57 bariatric surgery on acute kidney injury (AKI) for the first time.  
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11  
12 58 • Data are captured prospectively and continuously thus allowing follow-up of patients  
13  
14 59 over long time periods.  
15  
16 60 • Outcome measures are obtained with standardised ICD-10 codes, which have been  
17  
18 61 shown to accurately identify AKI.  
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20  
21 62 • Only AKI events recorded during a hospital admission were included in the analysis  
22  
23 63 likely representing the more serious events of AKI.  
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26 64 • The study population was mostly female, of middle age, and had a history of type 2  
27  
28 65 diabetes mellitus. Thus the results might not be applicable for other groups suffering  
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30 66 from obesity such as adolescents.  
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## 67 INTRODUCTION

68 The proportions of overweight and obese adults in England in 2014 are estimated to be  
69 61.7% and 25.6%, respectively, and are increasing over time<sup>1</sup>. Obesity is associated with  
70 serious health consequences including type 2 diabetes mellitus (T2DM), cardiovascular  
71 diseases, cancers, and chronic kidney disease (CKD)<sup>2-4</sup>. Bariatric surgery has been shown to  
72 be a highly effective intervention for achieving weight loss and reducing the burden of co-  
73 morbidities, such as T2DM, metabolic syndrome, and hypertension<sup>5 6</sup>. A recent  
74 observational study on recipients of bariatric surgery from the United Kingdom (UK)  
75 confirmed sustained weight loss as well as resolution of T2DM and hypertension over a  
76 period of 4 years<sup>7</sup>.

77 Acute kidney injury (AKI) is defined as a sudden (over hours or days) drop in kidney function  
78 characterised by increased serum creatinine and/or reduced urine output. AKI has been  
79 linked to increased in-hospital mortality, length of hospital stay, and subsequent  
80 development of CKD<sup>8</sup>. While T2DM, CKD, and obesity have been described as risk factors for  
81 AKI, it can also be precipitated by nephrotoxic drugs, surgical interventions, and sepsis<sup>8-10</sup>.  
82 AKI has been described as a short-term complication of bariatric surgery, stemming from  
83 rhabdomyolysis<sup>10-16</sup>. In addition, AKI has been linked to nephrolithiasis, which can develop  
84 over time after Roux-En-Y Gastric Bypass surgery<sup>11 17</sup>. To the best of our knowledge, no  
85 studies have been published examining the long-term effects of bariatric surgery on AKI.

86 In this study, we investigate the long-term effects of bariatric surgery on AKI to see whether  
87 the expected reduction in BMI has any impact on subsequent renal health. We used  
88 routinely collected electronic health record data from primary and secondary care. For this,  
89 we conducted a matched cohort study using prospectively collected data from patients in  
90 the United Kingdom Clinical Practice Research Datalink (CPRD).

## 91 **METHODS**

### 92 **Study design**

93 We undertook a matched cohort study using prospectively collected data from CPRD  
94 patients registered before 31st December 2014 linked to the Hospital Episodes Statistics  
95 (HES) database to investigate long-term effects of bariatric surgery on AKI.

96

### 97 **Data source**

98 The CPRD database contains anonymised, routinely collected data on approximately 10  
99 million patients in participating primary care practices in the UK, including demographic  
100 characteristics, current and previous diagnoses, prescribing, test results, and lifestyle  
101 factors. Diagnoses, signs, and symptoms are recorded using Read codes<sup>18</sup>. Patients are  
102 broadly representative of the UK population and the data have been validated for a wide  
103 range of outcomes<sup>19-21</sup>. The HES database contains patient data from hospital admissions to  
104 English hospitals within the National Health Service<sup>22</sup>. For each hospital admission, the  
105 diagnoses are recorded using standardised codes of the International Classification of  
106 Diseases, Tenth Revision (ICD-10)<sup>23 24</sup>. Data from 70% of CPRD practices in England has been  
107 linked at patient level with HES admission data thus allowing the combined analysis of data  
108 from primary and acute hospital care for a subset of patients<sup>19</sup>.

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### 110 **Cohort design and propensity matching**

111 A detailed description of how the cohort was constructed is described elsewhere<sup>7</sup>. In brief,  
112 records of patients who underwent bariatric surgery (n=3,882) between 1997 and 2015  
113 were matched to individuals who did not undergo surgery (n=3,882) using propensity  
114 scores.

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3 115 Study population matching and the propensity score incorporated information on age, sex,  
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5 116 calendar period, history of T2DM, hypertension, coronary heart disease, cerebrovascular  
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7 117 disease, peripheral vascular disease, other atheroma, use of insulin, use of oral antidiabetic  
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9 118 medication, use of statins, smoking status, and alcohol consumption.

11 119 Patients with bariatric surgery were identified using Read codes for surgery in the CPRD  
12  
13 120 database (S1 Appendix) and were included in the study if they had been registered in the  
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15 121 CPRD  $\geq 12$  months prior to the intervention. We excluded those with a record of prior  
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17 122 bariatric surgery reversal.

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19 123 For the comparison group, the inclusion criteria were to have at least one BMI  
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21 124 measurement  $\geq 40$  kg/m<sup>2</sup> during their CPRD registration, which could span 10 years or more,  
22  
23 125  $\geq 12$  months of follow-up prior to the index date in the database, and no prior record of  
24  
25 126 bariatric surgery or bariatric surgery reversal. Based on this, it is therefore possible that the  
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27 127 BMI recorded closest to the index date was lower than 40 kg/m<sup>2</sup>.

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29 128 The study sample was restricted to eligible patients registered at practices linked to the HES  
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31 129 database and information on AKI events was obtained, resulting in a final cohort comprising  
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33 130 2,643 patients who underwent bariatric surgery, and 2,595 patients who did not.

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35 131 Follow-up started on the day of surgery for those with bariatric surgery, and for the  
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37 132 comparison group who did not undergo bariatric surgery, on the surgery date of their  
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39 133 matched case. Patient records were censored at the earliest of: AKI, death, leaving the  
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41 134 practice, latest data collection from current practice, or end of linkage period to the HES  
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43 135 database.

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### 139 **Outcomes and covariates**

140 The primary outcome of this study was the incidence rate of the first AKI episode during  
141 follow-up in patients with and without bariatric surgery. AKI episodes were obtained from  
142 the HES database using ICD-10 codes: N17.0 (“Acute kidney failure with tubular necrosis”),  
143 N17.1 (“Acute renal failure with acute cortical necrosis), N17.2 (“Acute renal failure with  
144 medullary necrosis”), N17.8 (“Other acute renal failure”), N17.9 (“Acute kidney failure,  
145 unspecified”), and N19 (“Unspecified kidney failure”). In this cohort, events coded with  
146 N17.1, N17.2, and N17.8 were not found. AKI events that occurred before the start of  
147 follow-up were recorded as a binary variable “history of AKI”, while AKI events occurring  
148 during follow-up were used to analyse AKI incidence.

149 Recorded serum creatinine values from the CPRD database were not routinely standardised  
150 with isotope-dilution mass spectrometry before 2013. Thus, we assumed all measurements  
151 to be unstandardized and multiplied the creatinine measures with the factor 0.95 before  
152 calculating the estimated glomerular filtration rate (eGFR) using the “Chronic Kidney Disease  
153 Epidemiology Collaboration” (CKD-EPI) equation<sup>25</sup>. Ethnicity was not considered in the eGFR  
154 calculation due to incomplete recording in the database and the low proportion of Afro-  
155 Caribbean people in the population. CKD stages were defined according to eGFR values in  
156 ml/min/1.73m<sup>2</sup> according to current guidelines<sup>26</sup>: eGFR ≥60 = no known CKD; eGFR 45-59 =  
157 stage 3a; eGFR 30-44 = stage 3b; eGFR 15-29 = stage 4; eGFR <15 = stage 5. Baseline CKD  
158 status was derived from eGFR measurements in the year prior to start of follow-up by: 1)  
159 taking the last two measurements before the index date ≥90 days apart – with the higher  
160 eGFR value corresponding to the CKD baseline status, or 2) taking the most recent serum  
161 creatinine result if only one suitable test result was available. Since serum creatinine is more  
162 likely to be tested in the acutely unwell or in people who are routinely monitored as part of

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3 163 incentivised programs (e.g. people with diabetes), patients without measurements of CKD  
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5 164 baseline status were assumed to have no CKD<sup>27</sup> and were analysed as such.  
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## 14 167 **Statistical Analysis**

15 168 Though propensity score matching was employed to minimise confounding, we compared  
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17 169 the distribution of baseline characteristics between the exposed and unexposed groups to  
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19 170 check for any imbalances that may be relevant to the outcome of AKI. The baseline  
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21 171 distribution of categorical variables was analysed using percentages and  $\chi^2$ -tests.  
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23 172 Continuous variables were analysed as means with standard deviations for normally  
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25 173 distributed variables and medians with interquartile ranges for non-normally distributed  
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27 174 variables. Differences in continuous variables were analysed with Student's t-tests or  
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29 175 Wilcoxon rank sum tests for normally and non-normally distributed data, respectively.  
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32 176 The association between bariatric surgery and AKI was analysed using a Poisson regression  
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34 177 model with a time to first event analysis. P-values were calculated using Wald tests. In order  
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36 178 to separate short-term effects of the surgery from potential long-term effects, we analysed  
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38 179 the association separately for: a) events within the first 30 days, and b) events after 30 days.  
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41 180 When the cohort was initially constructed, propensity score matching was used to deal with  
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43 181 confounding<sup>7</sup>. This study uses a subset of this cohort since patients from practices without  
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45 182 linkage between the CPRD and HES databases had to be excluded (as AKI was assessed using  
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47 183 hospital admission data). To identify variables for the multivariable model, potential  
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49 184 confounders that were not deemed to be on the causal pathway were added individually to  
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51 185 the univariable model. If the addition changed the effect estimate  $\geq 10\%$  these variables  
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53 186 were included in the multivariable model. Consequently, history of AKI, history of taking oral  
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3 187 antidiabetics, and BMI at baseline were included (S2 Appendix). In addition, age at baseline,  
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5 188 sex, calendar period (1997-2005, 2006-2010, 2011-2015), and CKD status at baseline were  
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7 189 selected *a priori* as forced variables. For models with <40 outcomes, only age and sex were  
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9 190 included in the multivariable model due to data sparsity.

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12 191 The 5% bands of patients with the highest and lowest propensity scores were excluded from  
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14 192 the primary analysis (“trimming”) since these contain patients that are treated in stark  
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16 193 contrast to their health status, potentially causing bias<sup>28</sup>.

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19 194 Heterogeneity of effect estimates between the calendar periods was tested with a  
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21 195 Likelihood Ratio Test.

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24 196 The analysis was performed for all patients with bariatric surgery and also further stratified  
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26 197 by type of surgery. Patients with stage 5 CKD (baseline eGFR < 15 ml/min/1.73m<sup>2</sup>) were  
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28 198 excluded from the analyses since this constitutes end-stage renal failure (ESRD). In addition,  
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30 199 patients with missing data in ≥1 variable of the multivariable model were excluded from  
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32 200 both uni- and multivariable analyses.

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35 201 All analyses were performed with Stata 14.1.

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### 39 203 **Subgroup analyses**

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42 204 Several planned sensitivity analyses were undertaken: 1) To determine the net effect of the  
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44 205 intervention we calculated the risk of AKI over the whole period of follow-up; 2) The  
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46 206 prevalence of decreased kidney function in the CPRD database was similar to that in a  
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48 207 nationally representative kidney disease registry<sup>27</sup> indicating that patients with missing  
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50 208 eGFR measurements are unlikely to have CKD. To identify potential differences in the effect  
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52 209 between patients with known and unknown eGFR measurements, we restricted the analysis  
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54 210 to a) patients known to have no CKD at baseline (baseline eGFR ≥ 60 ml/min/1.73m<sup>2</sup>), b)

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3 211 patients without known CKD at baseline (as above but including patients with missing  
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5 212 creatinine values at baseline and assuming these individuals to have no CKD), and c)  
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7 213 patients with known CKD at baseline.<sup>27</sup>; 3) Moreover, to investigate the effect in a group of  
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9 214 particular interest which is under more scrutiny for measuring kidney function we restricted  
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11 215 the analysis to patients with: a) T2DM, and b) a history of taking insulin; 4) To avoid  
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13 216 misclassification of low eGFR values as AKI <sup>29</sup> we excluded patients with stage 4 CKD at  
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15 217 baseline; 5) We restricted the analysis to ICD-10 codes N17.0 and N17.9, which have a high  
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17 218 positive predictive value for AKI <sup>24</sup>; 6) We increased the immediate post-surgery time span  
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19 219 from 30 to 60 days; 7) We included people with extreme propensity scores; and 8) We  
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21 220 excluded patients with a BMI<35 kg/m<sup>2</sup> at baseline.  
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## 222 **Ethical approval**

223 This study was approved by the London School of Hygiene & Tropical Medicine ethics  
224 committee (LSHTM MSc Ethics Ref: 11065) and the Independent Scientific Advisory  
225 Committee on Medicines & Healthcare Products Regulatory Agency database research  
226 (approval number: 16\_106R).

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3 227 **RESULTS**  
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5 228 Since linkage to the HES-database was only possible for patients whose GPs had agreed for  
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7 229 their practice data to be linked to HES (S3 Appendix), there were 2,643 patients with  
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9 230 bariatric surgery and 2,595 people without surgery resulting in a cohort of overall 5,238  
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11 231 people with a median follow-up of 2.9 years (Table 1). The median follow-up prior to  
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13 232 baseline was similar between the groups: 8.8 years (IQR: 8.1 years) for patients with  
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15 233 bariatric surgery and 9.3 years (IQR: 8.0 years) for people without surgery.  
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234 *Table 1: Baseline data for CPRD/HES-linked cohort study of people with bariatric surgery and*  
 235 *the corresponding propensity score-matched\* comparison cohort*  
 236 *(data are n (%) unless otherwise specified)*

	Bariatric Surgery (n = 2,643)	Matched Comparison group without surgery (n = 2,595)	p-value <sup>1</sup>
<b>Follow-up (years), median (IQR)</b>	2.9 (3.2)	2.9 (3.4)	0.616
<b>Age (years), mean (SD)</b>	45.2 (10.7)	45.0 (10.8)	0.417
17 – 39, n (%)	818 (31.0)	826 (31.8)	
40 – 49, n (%)	945 (35.8)	928 (35.8)	0.727
50 – 85, n (%)	880 (33.3)	841 (32.4)	
<b>BMI at baseline, mean (SD)</b>	44.9 (8.9)	42.2 (6.5)	<0.001
13 – 34, n (%)	297 (11.2)	287 (11.1)	
35 – 39, n (%)	448 (17.0)	456 (17.6)	
40 – 44, n (%)	625 (23.7)	1,118 (43.1)	<0.001
45 – 49, n (%)	571 (21.6)	438 (16.9)	
50 – 94, n (%)	667 (25.2)	253 (9.8)	
Missing, n (%)	35 (1.3)	43 (1.7)	
<b>Female</b>	2,131 (80.6)	2,131 (82.1)	0.166
<b>History of</b>			
<b>Cerebrovascular disease</b>	37 (1.4)	26 (1.0)	0.186
<b>Coronary heart disease</b>	104 (3.9)	82 (3.2)	0.130
<b>Peripheral vascular disease</b>	11 (0.4)	15 (0.6)	0.405
<b>Other atheroma</b>	0	<5 <sup>2</sup>	0.313
<b>T2DM</b>	900 (34.1)	853 (32.9)	0.365
<b>Taking oral antidiabetic</b>	571 (21.6)	455 (17.5)	<0.001
<b>Taking insulin</b>	180 (6.8)	156 (6.0)	0.238
<b>Hypertension</b>	890 (33.7)	869 (33.5)	0.886
<b>Statin use</b>	699 (26.4)	640 (24.7)	0.139
<b>AKI</b>	30 (1.1)	11 (0.4)	0.003
<b>Alcohol status</b>			
<b>Non-drinker</b>	435 (16.5)	397 (15.3)	
<b>Ex-drinker</b>	278 (10.5)	236 (9.1)	
<b>Current drinker (amount unknown)</b>	15 (0.6)	13 (0.5)	
<2 units/day	659 (24.9)	644 (24.8)	0.366
3-6 units/day	862 (32.6)	909 (35.0)	
>6 units/day	170 (6.4)	164 (6.3)	
<b>Unknown</b>	224 (8.5)	232 (8.9)	
<b>Smoking status</b>			
<b>Non-smoker</b>	1,126 (42.6)	1,151 (44.4)	
<b>Current smoker</b>	403 (15.3)	345 (13.3)	0.093
<b>Ex-smoker</b>	1,112 (42.1)	1,099 (42.4)	
<b>Unknown</b>	<5 <sup>2</sup>	0	
<b>CKD at baseline</b>			
<b>Baseline CKD status absent</b>	1,119 (42.3)	1,299 (50.1)	
<b>No CKD</b>	1,470 (55.6)	1,242 (47.9)	
<b>Stage 3a</b>	27 (1.0)	37 (1.4)	<0.001
<b>Stage 3b</b>	16 (0.6)	10 (0.4)	
<b>Stage 4</b>	10 (0.4)	5 (0.2)	
<b>Stage 5</b>	<5 <sup>2</sup>	<5 <sup>2</sup>	
<b>Type of bariatric surgery</b>			
<b>Gastric band</b>	1,193 (45.1)		
<b>Sleeve gastrectomy</b>	364 (13.8)		
<b>Gastric bypass</b>	1,075 (40.7)		
<b>Other</b>	11 (0.4)		
<b>ICD-10 code for AKI during follow-up</b>	<b>n = 44</b>	<b>n = 62</b>	
<b>N17.0 (Acute kidney failure with tubular necrosis)</b>	<5 <sup>2</sup>	<5 <sup>2</sup>	
<b>N17.9 (Acute kidney failure, unspecified)</b>	38 (86.4)	52 (83.9)	0.927
<b>N19 (Unspecified kidney failure)</b>	5 (11.4)	8 (12.9)	

<sup>1</sup> categorical variables:  $\chi^2$ -test; continuous variables: t-test + SD if normally distributed, rank sum test + IQR if non-normally distributed

<sup>2</sup>cell counts <5 have been suppressed to ensure anonymity

\*In the original study, each surgery patient was matched 1:1 to the person without surgery with the closest propensity score, choosing matches at random where more than one possible match had the same score<sup>7</sup>

AKI = acute kidney injury, BMI = body mass index, CKD = chronic kidney disease, ICD-10 = International Classification of Diseases, Tenth Revision, IQR = interquartile range, SD = standard deviation, T2DM = type 2 diabetes mellitus

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3 238 This cohort was comparable to the cohort from the original study regarding sex, mean age,  
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5 239 mean BMI, history of T2DM, type of bariatric surgery and the imbalance of BMI at baseline  
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7 240 <sup>7</sup>. More patients in the intervention group had a history of AKI compared to the comparison  
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9 241 group (1.1% vs. 0.4%). Of the 106 included events during follow-up, 84.9% were classified  
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11 242 with the ICD-10 code N17.9 (“acute kidney failure, unspecified”), 12.3% were coded as N19  
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13 243 (“unspecified kidney failure”), and 2.8% had a code of N17.0 (“Acute kidney failure with  
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15 244 tubular necrosis”). CKD status at baseline was unknown for about half of the patients in  
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17 245 each group with a slightly higher proportion in the unexposed group (50.1% vs. 42.3%). The  
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19 246 majority of the patients with creatinine tests at baseline did not have CKD (96.2 %).  
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21 247 The number of AKI events recorded in the first 30 days of follow-up was low. All five events  
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23 248 happened in patients with bariatric surgery and none were recorded in the control group,  
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25 249 which is consistent with the possibility of an increased risk of AKI directly after surgery  
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30 250 (Table 2).  
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251 *Table 2: Association of bariatric surgery with first incident AKI, stratified by length of follow-*  
 252 *up. Unexposed refers to the propensity matched comparison group*

	PY	Events	Rate per 1000 PY (95% CI)	Crude RR (95% CI) <sup>1</sup>	p-value <sup>2</sup>	Adjusted RR (95% CI) <sup>3</sup>	p-value <sup>2</sup>
<b>All patients</b>							
<b>Day 1-30</b>							
Unexposed	203	0	0	-			
Bariatric surgery	199	5	25.1 (10.5, 60.4)	-			
<b>&gt; Day 30</b>							
Unexposed	7,882	54	6.9 (5.2, 8.9)	-			
Bariatric surgery	8,061	34	4.2 (3.0, 5.9)	0.62 (0.40, 0.95)	0.027	0.37 (0.23, 0.61)	<0.001
<b>All patients analysed by type of surgery<sup>4</sup></b>							
<b>Day 1-30</b>							
Unexposed							
Gastric band							
Sleeve gastrectomy							
Gastric bypass							
Other							
<b>&gt; Day 30</b>							
Unexposed	7,882	54	6.9 (5.2, 8.9)	-			
Gastric band	4,614	17	3.7 (2.3, 5.9)	0.54 (0.31, 0.93)	0.026		
Sleeve gastrectomy	728	<5 <sup>5</sup>	5.5 (2.1, 14.6)	0.80 (0.29, 2.21)	0.670		
Gastric bypass	2,655	13	4.9 (2.8, 8.4)	0.71 (0.39, 1.31)	0.277		
Other	63	0	-	-			
<b>All patients over whole period of follow-up</b>							
Unexposed	8,085	54	6.7 (5.1, 8.7)	-			
Bariatric surgery	8,259	39	4.7 (3.5, 6.5)	0.71 (0.47, 1.07)	0.099	0.45 (0.28, 0.72)	0.001

<sup>1</sup> Poisson regression model

<sup>2</sup> Wald test

<sup>3</sup> Poisson regression model adjusted for age at baseline, sex, calendar time, CKD at baseline, history of AKI, history of taking oral antidiabetics, and BMI at baseline

<sup>4</sup> No analysis for day 1-30 owing to sparse data

<sup>5</sup> Cell counts <5 have been suppressed to ensure anonymity

AKI = acute kidney injury, CKD = chronic kidney disease, PY = person-years, RR = rate ratio

253  
 254 From 30 days onwards, bariatric surgery had a protective association with AKI risk (crude RR  
 255 = 0.62, 95% CI 0.40, 0.95). The effect estimate of the multivariable model indicated an even  
 256 stronger protective effect associated with bariatric surgery (RR = 0.37, 95% CI 0.23, 0.61),  
 257 largely due to the confounding by AKI prior to baseline.  
 258 The analysis by type of surgery yielded protective effect estimates for all types but the  
 259 confidence intervals were wide and no comparison between individual procedures was  
 260 feasible. Sensitivity analyses yielded similar results (S4 Appendix). A sensitivity analysis  
 261 restricted to patients with known CKD at baseline could not be done owing to sparse data.  
 262 Investigation of the effect of bariatric surgery over the whole follow-up period resulted in a  
 263 protective net effect associated with the intervention in univariable (RR = 0.71, 95% CI 0.47,  
 264 1.07) and multivariable (RR = 0.45, 95% CI 0.28, 0.72) analyses.

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3 265 **DISCUSSION**  
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5 266 In this study using prospectively recorded routine healthcare data from a representative  
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7 267 sample in the UK, bariatric surgery was associated with a potentially increased risk of AKI  
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9 268 within the first 30 days after surgery (5 events in patients with bariatric surgery, no events in  
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11 269 control patients) but a strongly protective association thereafter (adjusted RR = 0.37, 95% CI  
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13 270 0.23, 0.61). The association was consistent across subgroups and sensitivity analyses. To the  
14  
15 271 best of our knowledge, this is the first study to describe long-term effects of bariatric  
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17 272 surgery on AKI.  
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21 273 AKI has been described as a perioperative event for bariatric surgery<sup>12 13 15 16</sup>. Our results  
22  
23 274 are consistent with an increased risk in the early stages after surgery, however our analysis  
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25 275 lacked enough early events to rule out chance as a reason for the results observed. Since  
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27 276 patients do not have kidney function measures routinely checked by their family physician  
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29 277 after bariatric surgery, many events could remain unnoticed. Patients with known CKD are  
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31 278 more thoroughly checked for AKI and are a valuable subgroup to investigate, but the  
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33 279 numbers in this dataset were too low to analyse.  
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37 280 This study uses high quality data from routine medical care in the UK. The healthcare system  
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39 281 allows universal patient access to primary and secondary care so that the data is  
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41 282 representative of the population. Patients are followed continuously while they are  
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43 283 registered with a general practitioner allowing prospective data capture over long  
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45 284 observation periods and avoiding problems with reverse causality. For the classification of  
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47 285 AKI episodes in the HES database, the ICD-10 codes N17.0 and N17.9 comprised 87.7% of all  
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49 286 events and have previously been shown to accurately identify AKI in a single centre study<sup>24</sup>.  
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53 287 Some limitations need to be considered. Even though the data is taken from a  
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55 288 representative sample of the UK population, the baseline data indicate that patients who  
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3 289 undergo bariatric surgery are mostly female, of middle age, and with a history of T2DM.  
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5 290 While the results were adjusted for age and sex they might not be applicable for other  
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7 291 groups suffering from obesity like adolescents. Linkage between the CPRD and HES  
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9 292 databases was restricted to England. However, there is no cogent reason why the results  
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11 293 should not be applicable to regions with similar healthcare systems, both in the UK and  
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13 294 internationally. We had insufficient data to determine whether the association with AKI  
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15 295 varied between different types of bariatric surgery; we found a protective effect for gastric  
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17 296 band but results were inconclusive for sleeve gastrectomy and gastric bypass.  
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19 297 Misclassification of diagnostic codes is likely non-differential between the bariatric surgery  
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21 298 patients and the matched comparison group and would bias the effect towards the null  
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23 299 value. However, it is also conceivable during the immediate post-operative period those  
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25 300 undergoing bariatric surgery might have been under more scrutiny to detect potential AKI  
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27 301 events than people without surgery. In this case our current relative risk estimate for the  
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29 302 immediate postoperative period would be an overestimate. Another problem of primary  
30  
31 303 care data is that not every patient is routinely checked for their kidney function, as  
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33 304 incentives of testing apply primarily for those at risk of kidney disease due to diabetes and  
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35 305 hypertension. The study relied on AKI events recorded in HES as part of a hospital admission  
36  
37 306 and over time, the awareness of the importance of AKI has likely changed resulting in  
38  
39 307 secular changes in recording of AKI<sup>30</sup>; analyses have adjusted for calendar period to account  
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41 308 for this<sup>23 31</sup>. Future studies with hospital creatinine data should compare the AKI severity  
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43 309 between the groups to investigate this issue. In general, AKI diagnosed during  
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45 310 hospitalisation is likely to represent more serious AKI events, though we would argue these  
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47 311 are the most clinically relevant outcomes. Moreover, a patient who experienced a previous  
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49 312 AKI episode might be under more scrutiny for detection of future episodes. Since more  
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3 313 patients in the bariatric surgery group had a history of AKI they might have a higher chance  
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5 314 of detection of an AKI episode during follow-up, which we adjusted for in our analyses.  
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7 315 In addition, CKD status at baseline was missing in almost half of the patient population.  
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10 316 However, a recent study indicated that the prevalence of CKD in the CPRD database was  
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12 317 comparable to that found in nationally representative registry studies<sup>27</sup>. This indicates that  
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14 318 patients without a GP record of eGFR-measurements at baseline are unlikely to have CKD. In  
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16 319 addition, sensitivity analyses investigating the effect in patients with known or unknown  
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18 320 CKD status at baseline yielded comparable results.  
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21 321 Since access to bariatric surgery is restricted within the UK healthcare system, some  
22  
23 322 patients might have funded their operation privately, resulting in selection bias. In a recent  
24  
25 323 analysis about 40% of bariatric surgery operations in the UK were privately funded<sup>32</sup>. Thus,  
26  
27 324 the intervention group might have a higher socioeconomic status than the non-exposed  
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29 325 group, in which similar patients would not be able to afford surgery. Since the  
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31 326 socioeconomic background is an important determinant of health outcomes and was an  
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33 327 unmeasured potential confounder not considered in the matching process, this could have  
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35 328 led to more positive health outcomes in the intervention group irrespective of surgery and  
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37 329 to an overestimation of the effect. In this study setting it was not possible to determine  
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39 330 which patients had privately funded surgery.  
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42 331 Even though most baseline variables were evenly distributed due to the matching process  
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44 332 this does not guarantee that unmeasured variables are evenly distributed as well, which can  
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46 333 constitute residual confounding. Incorrect, imprecise, or missing measurements of  
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48 334 covariates could also have led to residual confounding. For the multivariable model,  
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50 335 adjusting for history of AKI led to the strongest change of the effect estimate. AKI events are  
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52 336 likely under-recorded in the HES database, for reasons described above, and thus residual  
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3 337 confounding is possible. Since adjusting for AKI history led to a stronger effect estimate, the  
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5 338 protective effect we report here may be an underestimate if AKI history is missing to the  
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7 339 same degree in surgery and non-surgery patients.  
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9  
10 340 This study adds to the evidence of long term effects of bariatric surgery, and appears to be  
11  
12 341 the first study to quantify a long-term beneficial effect on AKI. Future studies with higher  
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14 342 patient numbers may be able to determine differences in effect between types of surgery,  
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16 343 investigate the effect in patients with CKD, and elucidate mechanisms of the association  
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18 344 between bariatric surgery and AKI.  
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3 346 **SUPPLEMENTARY INFORMATION**  
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5 347 Supplementary information is available at the *BMJ open* website.  
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7 348  
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9  
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13

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17

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21

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25

26 357 analysis, the writing of the report, or the decision to submit the paper for publication.  
27

28 358  
29

30 359 **CONFLICT OF INTEREST**  
31

32 360 The authors have no conflicts of interest to disclose.  
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34 361  
35

36 362 **DATA SHARING**  
37

38 363 The data were obtained from the Clinical Practice Research Datalink (CPRD). CPRD data  
39

40 364 governance does not allow us to distribute patient data to other parties. Researchers may  
41

42 365 apply for data access at [www.CPRD.com](http://www.CPRD.com). The codes used to produce the data for this study  
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44 366 are provided in the Supporting Information.  
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3 370 **CONTRIBUTIONS**  
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5 371 UK, DN, RLB, IJD, and LS were responsible for conceptualisation of the study and formulate  
6  
7 372 the research goals and aims. UK, DN, KEM, RM, KB, RLB, LS, and IJD developed the  
8  
9 373 methodology and models. UK, KEM, KB, IJD, and RM worked on the data curation. UK  
10  
11 374 performed the statistical analysis and wrote the original draft. UK, DN, KEM, RM, KB, RLB,  
12  
13  
14 375 LS, and IJD reviewed and commented the draft and gave input on editing.  
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28 447 [Algorithm-Best-Practice-Guidance-final-publication-0112141.pdf](https://www.thinkkidneys.nhs.uk/wp-content/uploads/2014/12/AKI-Warning-Algorithm-Best-Practice-Guidance-final-publication-0112141.pdf).
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3 1 **Long-term effects of bariatric surgery on acute kidney injury: A propensity-matched**  
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6 2 **cohort in the United Kingdom Clinical Practice Research Datalink**  
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10 4 **Supporting Information**  
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13 5

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15 6 **Overview**  
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18 7 S1 Appendix – Code List for Identification of patients with bariatric surgery  
19

20 8 S2 Appendix – Association of potential confounders with bariatric surgery and AKI  
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23 9 S3 Appendix – Patient selection from the original cohort  
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25 10 S4 Appendix – Sensitivity Analyses  
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11 **S1 Appendix**

12 *Appendix 1: Code List for identification of patients with bariatric surgery from the CPRD database as*  
13 *published by Douglas et al. [7]*

14	<i>Read code</i>	<i>description</i>
15	76132.00	Laparoscopic adjustable gastric banding
16	76134.00	Partitioning of stomach using staples
17	76131.11	Mason vertical banded gastroplasty
18	76133.00	Partitioning of stomach using band
19	76116.00	Laparoscopic sleeve gastrectomy
20	76115.00	Sleeve gastrectomy NEC
21	76425.00	Duodenal switch
22	76135.00	Partitioning of stomach NEC
23	76114.00	Sleeve gastrectomy and duodenal switch
24	76166.00	Laparoscopic gastric bypass



25 **S2 Appendix**

26 *Appendix 2: Identification of potential confounders in the association of bariatric surgery (exposure)*  
 27 *and the endpoint of incident AKI (outcome) in patients of the linked CPRD/HES cohort*

	RR (95%CI)	Change in %	Selection for multivariable model
<b>Crude effect estimate</b>	0.62 (0.40, 0.95)		
<b>Effect estimates when individually adjusting for</b>			
<b>Age</b>	0.62 (0.40, 0.95)	0.2 %	yes (a priori)
<b>Sex</b>	0.60 (0.39, 0.92)	2.7 %	yes (a priori)
<b>Calendar Time</b>	0.61 (0.40, 0.94)	0.9%	yes (a priori)
<b>CKD status at baseline</b>	0.59 (0.38, 0.91)	4.4 %	yes (a priori)
<b>BMI at baseline</b>	0.53 (0.34, 0.83)	13.9 %	yes
<b>Alcohol Status</b>	0.61 (0.40, 0.93)	1.3 %	no
<b>Smoking Status</b>	0.61 (0.40, 0.94)	0.3 %	no
<b>History of cerebrovascular disease</b>	0.61 (0.40, 0.94)	0.6 %	no
<b>History of coronary heart disease</b>	0.60 (0.39, 0.91)	3.3 %	no
<b>History of peripheral vascular disease</b>	0.64 (0.41, 0.98)	3.2 %	no
<b>History of other atheroma</b>	0.62 (0.40, 0.95)	0.0 %	no
<b>History of diabetes</b>	0.60 (0.39, 0.92)	2.7%	no
<b>History of taking oral antidiabetics</b>	0.55 (0.36, 0.85)	10.4%	yes
<b>History of taking insulin</b>	0.57 (0.37, 0.87)	7.9 %	no
<b>History of hypertension</b>	0.61 (0.40, 0.94)	1.1 %	no
<b>History of statin use</b>	0.58 (0.38, 0.89)	5.5 %	no
<b>History of AKI</b>	0.42 (0.26, 0.67)	31.9 %	yes

Variables were added individually to the univariable model testing the association between bariatric surgery and AKI. If the addition of the respective variable changed the model  $\geq 10\%$  then the variable was selected to be included in the multivariable model.

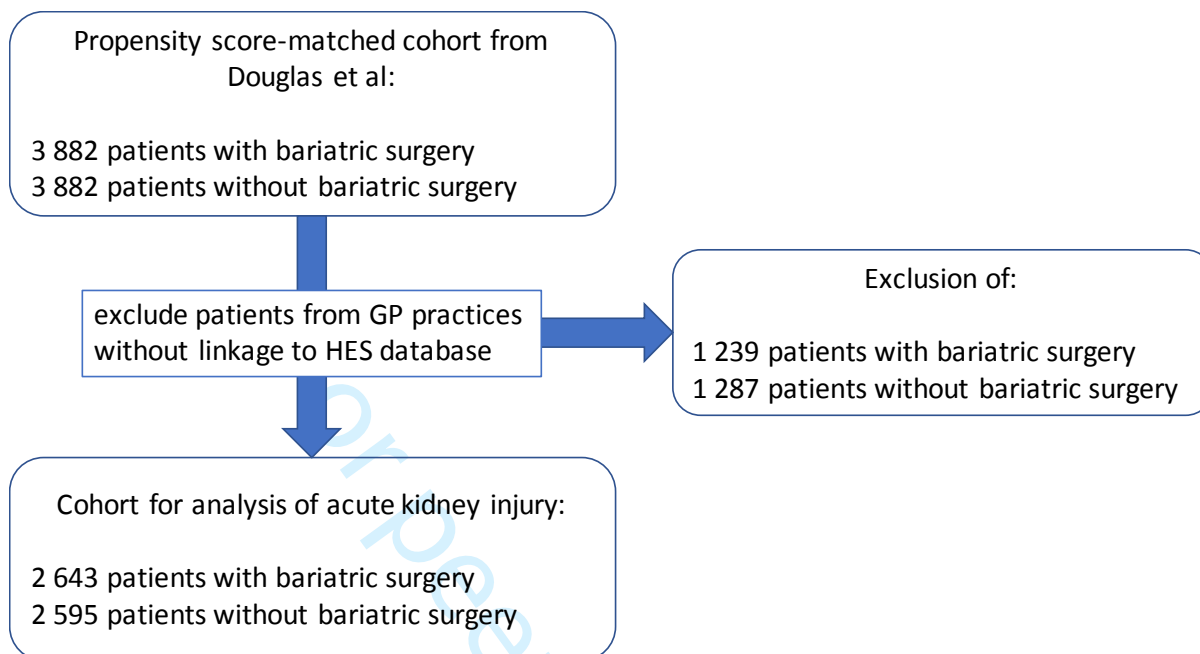
AKI = acute kidney injury, BMI = body mass index, CKD = chronic kidney disease

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29 **S3 Appendix**

30 *Appendix 3: Patient selection from the original cohort as described in Douglas et al [7]*

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34 **S4 Appendix**35 *Appendix 4: Sensitivity analyses for the association of bariatric surgery with acute kidney injury*

	PY	Events	Rate per 1000 PY (95% CI)	Crude RR (95% CI) <sup>1</sup>	p-value <sup>2</sup>	Adjusted RR (95% CI) <sup>3</sup>	p-value <sup>2</sup>
<b>Restricted to patients without CKD at baseline (available serum creatinine measures + eGFR ≥60)</b>							
<b>Day 1-30</b>							
Unexposed	98	0	0	-			
Bariatric surgery	111	<5 <sup>b</sup>	36.2 (13.6, 96.3)	-			
<b>&gt;Day 30</b>							
Unexposed	3,550	27	7.6 (5.2, 11.1)	-			
Bariatric surgery	4,311	22	5.1 (3.4, 7.7)	0.67 (0.38, 1.18)	0.165	0.53 (0.29, 1.00)	0.050
<b>Restricted to patients without known CKD at baseline (available serum creatinine measures + eGFR ≥60 or missing eGFR at baseline)</b>							
<b>Day 1-30</b>							
Unexposed	199	0	0	-			
Bariatric surgery	195	<5 <sup>b</sup>	20.5 (7.7, 54.7)	-			
<b>&gt;Day 30</b>							
Unexposed	7,735	42	5.4 (4.0, 7.3)	-			
Bariatric surgery	7,930	27	3.4 (2.3, 5.0)	0.63 (0.39, 1.02)	0.058	0.42 (0.25, 0.73)	0.002
<b>Excluding patients with CKD stage 4</b>							
<b>Day 1-30</b>							
Unexposed	203	0	0	-			
Bariatric surgery	198	5	25.2 (10.5, 60.6)	-			
<b>&gt; Day 30</b>							
Unexposed	7,875	52	6.6 (5.0, 8.7)	-			
Bariatric surgery	8,037	32	4.0 (2.8, 5.6)	0.60 (0.39, 0.94)	0.024	0.35 (0.21, 0.59)	<0.001
<b>Restricted to patients with T2DM</b>							
<b>Day 1-30</b>							
Unexposed	65	0	0	-			
Bariatric surgery	69	<5 <sup>b</sup>	43.6 (14.1, 135.1)	-			
<b>&gt;Day 30</b>							
Unexposed	2,325	33	14.2 (10.1, 20.0)	-			
Bariatric surgery	2,548	18	7.1 (4.5, 11.2)	0.50 (0.28, 0.88)	0.017	0.25 (0.13, 0.51)	<0.001
<b>Restricted to patients with a history of taking insulin</b>							
<b>Day 1-30</b>							
Unexposed	11	0	0	-			
Bariatric surgery	13	0	0	-			
<b>&gt;Day 30</b>							
Unexposed	321	11	34.3 (19.0, 61.9)	-			
Bariatric surgery	502	9	17.9 (9.3, 34.5)	0.52 (0.22, 1.26)	0.150	0.22 (0.08, 0.64)	0.005
<b>Restricted to ICD-10 codes N17.0 and N17.9</b>							
<b>Day 1-30</b>							
Unexposed	202	0	0	-			
Bariatric surgery	199	5	25.2 (10.5, 60.5)	-			
<b>&gt;Day 30</b>							
Unexposed	7,871	48	6.1 (4.6, 8.1)	-			
Bariatric surgery	8,055	31	3.8 (2.7, 5.5)	0.63 (0.40, 0.99)	0.046	0.40 (0.24, 0.67)	<0.001
<b>Having an initial post-surgery time span of 60 days instead of 30</b>							
<b>Day 1-60</b>							
Unexposed	403	<5 <sup>b</sup>	2.5 (0.3, 17.6)	-			
Bariatric surgery	395	6	15.2 (6.8, 33.8)	6.11 (0.74, 50.8)	0.094	<sup>4</sup>	
<b>&gt; Day 60</b>							
Unexposed	7,682	53	6.9 (5.3, 9.0)	-			
Bariatric surgery	7,864	33	4.2 (3.0, 5.9)	0.61 (0.39, 0.94)	0.025	0.38 (0.23, 0.63)	<0.001
				Test for interaction <sup>5</sup>	0.011		

Including patients with extreme propensity scores								
<b>Day 1-30</b>								
Unexposed	208	0	0	-				
Bariatric surgery	206	5	24.3 (10.1, 58.3)	-				
<b>&gt; Day 30</b>								
Unexposed	8,054	59	7.3 (5.7, 9.5)	-				
Bariatric surgery	8,324	34	4.1 (2.9, 5.7)	0.56 (0.37, 0.85)	0.007	0.33 (0.20, 0.54)	<0.001	
Excluding patients with BMI < 35 kg/m <sup>2</sup> at baseline								
<b>Day 1-30</b>								
Unexposed	180	0	0	-				
Bariatric surgery	175	<5 <sup>6</sup>	22.8 (8.6, 60.9)	-				
<b>&gt; Day 30</b>								
Unexposed	6,714	48	7.1 (5.4, 9.5)	-				
Bariatric surgery	7,100	32	4.5 (3.2, 6.4)	0.63 (0.40, 0.99)	0.043	0.39 (0.23, 0.65)	<0.001	

<sup>1</sup> Poisson regression model

<sup>2</sup> Wald test for RR, Likelihood-Ratio Test for interaction

<sup>3</sup> Poisson regression model adjusted for age at baseline, sex, calendar time, CKD at baseline, history of AKI, history of taking oral antidiabetics, and BMI at baseline

<sup>4</sup> No analysis for day 1-30 owing to sparse data

<sup>5</sup> Test for interaction of the effect estimate with the time periods 1-30 days and >30 days

<sup>6</sup> cell counts <5 have been suppressed to ensure anonymity

AKI = acute kidney injury, CKD = chronic kidney disease, PY = person-years, RR = rate ratio

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**Supporting Information:****STROBE statement checklist to ensure appropriate reporting of study information of long-term effects of acute kidney injury for the propensity-matched cohort study of patients with and without bariatric surgery**

	<b>Item No</b>	<b>Report</b>
<b>Title and abstract</b>	1	<p>(a) Indicate the study's design with a commonly used term in the title or the abstract</p> <p>“Long-term effects of bariatric surgery on acute kidney injury: A propensity-matched cohort in the United Kingdom Clinical Practice Research Datalink”</p> <p>b) Provide in the abstract an informative and balanced summary of what was done and what was found</p> <p>Abstract: on page 2 containing Background, Methods, Results and Conclusions</p>
<b>Introduction</b>		
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported</p> <p>See page 4 for description of background; Rationale (p4): “To the best of our knowledge, no studies have been published examining the long-term effects of bariatric surgery on AKI.”</p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses</p> <p>Page 4: “In this study, we investigate the long-term effects of bariatric surgery on AKI to see whether the expected reduction in BMI has any impact on subsequent renal health.”</p>
<b>Methods</b>		
Study design	4	<p>Present key elements of study design early in the paper</p> <p>See page 5: “We undertook a matched cohort study using prospectively collected data from CPRD patients registered before 31st December 2014 linked to the Hospital Episodes Statistics (HES) database to investigate long-term effects of bariatric surgery on AKI.”</p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</p> <p>Page 5: “The CPRD database contains anonymised, routinely collected data on approximately 10 million patients in participating primary care practices in the UK, including demographic characteristics, current and previous diagnoses, prescribing, test results, and lifestyle factors. [...] The HES database contains patient data from hospital admissions to English hospitals within the National Health Service [...]. Data from 70% of CPRD practices in England has been linked at patient level with HES admission data thus allowing the combined analysis of data from primary and acute hospital care for a subset of patients.”</p> <p>“A detailed description of how the cohort was constructed is described elsewhere. In brief, records of patients who underwent bariatric surgery (n=3,882) between 1997 and 2015 were matched to individuals who did not undergo surgery (n=3,882) using propensity scores.”</p> <p>Page 6: “Follow-up started on the day of surgery for those with bariatric surgery, and for the comparison group who did not undergo bariatric surgery, on the surgery date</p>

		of their matched case. Patient records were censored at the earliest of: AKI, death, leaving the practice, latest data collection from current practice, or end of linkage period to the HES database.”
Participants	6	<p>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p>Page 6: “Patients with bariatric surgery were identified using Read codes for surgery in the CPRD database (S1 Appendix) and were included in the study if they had been registered in the CPRD <math>\geq 12</math> months prior to the intervention. We excluded those with a record of prior bariatric surgery reversal.</p> <p>For the comparison group, the inclusion criteria were to have at least one BMI measurement <math>\geq 40</math> kg/m<sup>2</sup>, <math>\geq 12</math> months of follow-up prior to the index date in the database, and no prior record of bariatric surgery or bariatric surgery reversal.”</p> <p>Page 5: “The CPRD database contains anonymised, routinely collected data on approximately 10 million patients in participating primary care practices in the UK, including demographic characteristics, current and previous diagnoses, prescribing, test results, and lifestyle factors. Diagnoses, signs, and symptoms are recorded using Read codes [...]. The HES database contains patient data from hospital admissions to English hospitals within the National Health Service “</p> <hr/> <p>(b) For matched studies, give matching criteria and number of exposed and unexposed</p> <p>Page 6: “Study population matching and the propensity score incorporated information on age, sex, calendar period, history of T2DM, hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, other atheroma, use of insulin, use of oral antidiabetic medication, use of statins, smoking status, and alcohol consumption.”</p> <p>“The study sample was restricted to eligible patients registered at practices linked to the HES database and information on AKI events was obtained, resulting in a final cohort comprising 2,643 patients who underwent bariatric surgery, and 2,595 patients who did not.”</p>
Variables	7	<p>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</p> <p>Page 6/7: “AKI episodes were obtained from the HES database using ICD-10 codes: N17.0 (“Acute kidney failure with tubular necrosis”), N17.1 (“Acute renal failure with acute cortical necrosis”), N17.2 (“Acute renal failure with medullary necrosis”), N17.8 (“Other acute renal failure”), N17.9 (“Acute kidney failure, unspecified”), and N19 (“Unspecified kidney failure”). In this cohort, events coded with N17.1, N17.2, and N17.8 were not found. AKI events that occurred before the start of follow-up were recorded as a binary variable “history of AKI”, while AKI events occurring during follow-up were used to analyse AKI incidence.</p> <p>Recorded serum creatinine values from the CPRD database were not routinely standardised with isotope-dilution mass spectrometry before 2013. Thus, we assumed all measurements to be unstandardized and multiplied the creatinine measures with the factor 0.95 before calculating the estimated glomerular filtration rate (eGFR) using the “Chronic Kidney Disease Epidemiology Collaboration” (CKD-EPI) equation.</p>

Ethnicity was not considered in the eGFR calculation due to incomplete recording in the database and the low proportion of Afro-Caribbean people in the population. CKD stages were defined according to eGFR values in ml/min/1.73m<sup>2</sup> according to current guidelines: eGFR  $\geq 60$  = no known CKD; eGFR 45-59 = stage 3a; eGFR 30-44 = stage 3b; eGFR 15-29 = stage 4; eGFR  $< 15$  = stage 5. Baseline CKD status was derived from eGFR measurements in the year prior to start of follow-up by: 1) taking the last two measurements before the index date  $\geq 90$  days apart – with the higher eGFR value corresponding to the CKD baseline status, or 2) taking the most recent serum creatinine result if only one suitable test result was available. Since serum creatinine is more likely to be tested in the acutely unwell or in people who are routinely monitored as part of incentivised programs (e.g. people with diabetes), patients without measurements of CKD baseline status were assumed to have no CKD and were analysed as such.”

Page 6: “Study population matching and the propensity score incorporated information on age, sex, calendar period, history of T2DM, hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, other atheroma, use of insulin, use of oral antidiabetic medication, use of statins, smoking status, and alcohol consumption.”

Page 8: “When the cohort was initially constructed, propensity score matching was used to deal with confounding. This study uses a subset of this cohort since patients from practices without linkage between the CPRD and HES databases had to be excluded (as AKI was assessed using hospital admission data). To identify variables for the multivariable model, potential confounders that were not deemed to be on the causal pathway were added individually to the univariable model. If the addition changed the effect estimate  $\geq 10\%$  these variables were included in the multivariable model. Consequently, history of AKI, history of taking oral antidiabetics, and BMI at baseline were included (S2 Appendix). In addition, age at baseline, sex, calendar period (1997-2005, 2006-2010, 2011-2015), and CKD status at baseline were selected a priori as forced variables.”

Page 8: “In order to separate short-term effects of the surgery from potential long-term effects, we analysed the association separately for: a) events within the first 30 days, and b) events after 30 days.”

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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
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Page 5: “The CPRD database contains anonymised, routinely collected data on approximately 10 million patients in participating primary care practices in the UK, including demographic characteristics, current and previous diagnoses, prescribing, test results, and lifestyle factors. Diagnoses, signs, and symptoms are recorded using Read codes [...] The HES database contains patient data from hospital admissions to English hospitals within the National Health Service. For each hospital admission, the diagnoses are recorded using standardised codes of the International Classification of Diseases, Tenth Revision (ICD-10). Data from 70% of CPRD practices in England has been linked at patient level with HES admission data thus allowing the combined analysis of data from primary and acute hospital care for a subset of patients.”

Page 5: “Patients with bariatric surgery were identified using Read codes for surgery in the CPRD database (S1 Appendix) and were included in the study if they had been

registered in the CPRD  $\geq 12$  months prior to the intervention. We excluded those with a record of prior bariatric surgery reversal.”

Page 6/7: “AKI episodes were obtained from the HES database using ICD-10 codes: N17.0 (“Acute kidney failure with tubular necrosis”), N17.1 (“Acute renal failure with acute cortical necrosis”), N17.2 (“Acute renal failure with medullary necrosis”), N17.8 (“Other acute renal failure”), N17.9 (“Acute kidney failure, unspecified”), and N19 (“Unspecified kidney failure”).”

Bias	9	Describe any efforts to address potential sources of bias
		Page 9: “The 5% bands of patients with the highest and lowest propensity scores were excluded from the primary analysis (“trimming”) since these contain patients that are treated in stark contrast to their health status, potentially causing bias.”
Study size	10	Explain how the study size was arrived at
		Pages 5/6: “A detailed description of how the cohort was constructed is described elsewhere. In brief, records of patients who underwent bariatric surgery (n=3,882) between 1997 and 2015 were matched to individuals who did not undergo surgery (n=3,882) using propensity scores.” [...] “The study sample was restricted to eligible patients registered at practices linked to the HES database and information on AKI events was obtained, resulting in a final cohort comprising 2,643 patients who underwent bariatric surgery, and 2,595 patients who did not.”
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		Page 7: “Recorded serum creatinine values from the CPRD database were not routinely standardised with isotope-dilution mass spectrometry before 2013. Thus, we assumed all measurements to be unstandardized and multiplied the creatinine measures with the factor 0.95 before calculating the estimated glomerular filtration rate (eGFR) using the “Chronic Kidney Disease Epidemiology Collaboration” (CKD-EPI) equation. Ethnicity was not considered in the eGFR calculation due to incomplete recording in the database and the low proportion of Afro-Caribbean people in the population. CKD stages were defined according to eGFR values in ml/min/1.73m <sup>2</sup> according to current guidelines: eGFR $\geq 60$ = no known CKD; eGFR 45-59 = stage 3a; eGFR 30-44 = stage 3b; eGFR 15-29 = stage 4; eGFR $< 15$ = stage 5. Baseline CKD status was derived from eGFR measurements in the year prior to start of follow-up by: 1) taking the last two measurements before the index date $\geq 90$ days apart – with the higher eGFR value corresponding to the CKD baseline status, or 2) taking the most recent serum creatinine result if only one suitable test result was available. Since serum creatinine is more likely to be tested in the acutely unwell or in people who are routinely monitored as part of incentivised programs (e.g. people with diabetes), patients without measurements of CKD baseline status were assumed to have no CKD and were analysed as such.”
		Page 8: “In addition, age at baseline, sex, calendar period (1997-2005, 2006-2010, 2011-2015), and CKD status at baseline were selected a priori as forced variables.”
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		Page 8/9: “The association between bariatric surgery and AKI was analysed using a Poisson regression model with a time to first event analysis. P-values were calculated



1 using Wald tests. In order to separate short-term effects of the surgery from potential  
2 long-term effects, we analysed the association separately for: a) events within the first  
3 30 days, and b) events after 30 days. When the cohort was initially constructed,  
4 propensity score matching was used to deal with confounding. This study uses a  
5 subset of this cohort since patients from practices without linkage between the CPRD  
6 and HES databases had to be excluded (as AKI was assessed using hospital admission  
7 data). To identify variables for the multivariable model, potential confounders that  
8 were not deemed to be on the causal pathway were added individually to the  
9 univariable model. If the addition changed the effect estimate  $\geq 10\%$  these variables  
10 were included in the multivariable model. Consequently, history of AKI, history of  
11 taking oral antidiabetics, and BMI at baseline were included (S2 Appendix). In  
12 addition, age at baseline, sex, calendar period (1997-2005, 2006-2010, 2011-2015),  
13 and CKD status at baseline were selected a priori as forced variables. For models with  
14  $< 40$  outcomes, only age and sex were included in the multivariable model due to data  
15 sparsity.

16 The 5% bands of patients with the highest and lowest propensity scores were excluded  
17 from the primary analysis (“trimming”) since these contain patients that are treated in  
18 stark contrast to their health status, potentially causing bias.

19 Heterogeneity of effect estimates between the calendar periods was tested with a  
20 Likelihood Ratio Test.

21 The analysis was performed for all patients with bariatric surgery and also further  
22 stratified by type of surgery. Patients with stage 5 CKD (baseline eGFR  $< 15$   
23 ml/min/1.73m<sup>2</sup>) were excluded from the analyses since this constitutes end-stage  
24 renal failure (ESRD). In addition, patients with missing data in  $\geq 1$  variable of the  
25 multivariable model were excluded from both uni- and multivariable analyses.”

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26 (b) Describe any methods used to examine subgroups and interactions

27 page 8: “In order to separate short-term effects of the surgery from potential long-term  
28 effects, we analysed the association separately for: a) events within the first 30 days,  
29 and b) events after 30 days.”

30 page 9: “Heterogeneity of effect estimates between the calendar periods was tested  
31 with a Likelihood Ratio Test.”

32 Page 9: “The analysis was performed for all patients with bariatric surgery and also  
33 further stratified by type of surgery.”

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34 (c) Explain how missing data were addressed

35 page 7: “Since serum creatinine is more likely to be tested in the acutely unwell or in  
36 people who are routinely monitored as part of incentivised programs (e.g. people with  
37 diabetes), patients without measurements of CKD baseline status were assumed to  
38 have no CKD and were analysed as such.”

39 page 9: “In addition, patients with missing data in  $\geq 1$  variable of the multivariable  
40 model were excluded from both uni- and multivariable analyses.”

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41 (d) If applicable, explain how loss to follow-up was addressed

42 page 6: “Patient records were censored at the earliest of: AKI, death, leaving the  
43 practice, latest data collection from current practice, or end of linkage period to the

HES database.”

(e) Describe any sensitivity analyses

Pages 9/10: “Several planned sensitivity analyses were undertaken: 1) To determine the net effect of the intervention we calculated the risk of AKI over the whole period of follow-up; 2) The prevalence of decreased kidney function in the CPRD database was similar to that in a nationally representative kidney disease registry indicating that patients with missing eGFR measurements are unlikely to have CKD. To identify potential differences in the effect between patients with known and unknown eGFR measurements, we restricted the analysis to a) patients known to have no CKD at baseline (baseline eGFR  $\geq 60$  ml/min/1.73m<sup>2</sup>), b) patients without known CKD at baseline (as above but including patients with missing creatinine values at baseline and assuming these individuals to have no CKD), and c) patients with known CKD at baseline.; 3) Moreover, to investigate the effect in a group of particular interest which is under more scrutiny for measuring kidney function we restricted the analysis to patients with: a) T2DM, and b) a history of taking insulin; 4) To avoid misclassification of low eGFR values as AKI we excluded patients with stage 4 CKD at baseline; 5) We restricted the analysis to ICD-10 codes N17.0 and N17.9, which have a high positive predictive value for AKI; 6) We increased the immediate post-surgery time span from 30 to 60 days; and 7) We included people with extreme propensity scores.”

## 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  see S3 Appendix  (b) Give reasons for non-participation at each stage  not applicable  (c) Consider use of a flow diagram  see S3 Appendix
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  page 12: see Table 1  (b) Indicate number of participants with missing data for each variable of interest  page 12: see Table 1  (c) Summarise follow-up time (eg, average and total amount)  page 12: see Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time  page 12: see Table 1
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

1		adjusted for and why they were included
2		
3		page 13: see Table 2
4		(b) Report category boundaries when continuous variables were categorized
5		
6		
7		page 12: see Table 1
8		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
9		meaningful time period
10		
11		not applicable
12		
13	Other analyses	17 Report other analyses done—eg analyses of subgroups and interactions, and
14		sensitivity analyses
15		
16		Page 13: see table 2
17		see S4 Appendix
18		
19	<b>Discussion</b>	
20	Key results	18 Summarise key results with reference to study objectives
21		
22		Page 15: “In this study using prospectively recorded routine healthcare data from a
23		representative sample in the UK, bariatric surgery was associated with a potentially
24		increased risk of AKI within the first 30 days after surgery (5 events in patients with
25		bariatric surgery, no events in control patients) but a strongly protective association
26		thereafter (adjusted RR = 0.37, 95% CI 0.23, 0.61). The association was consistent
27		across subgroups and sensitivity analyses. To the best of our knowledge, this is the
28		first study to describe long-term effects of bariatric surgery on AKI.”
29		
30		
31	Limitations	19 Discuss limitations of the study, taking into account sources of potential bias or
32		imprecision. Discuss both direction and magnitude of any potential bias
33		
34		Pages 15-18: “Some limitations need to be considered. Even though the data is taken
35		from a representative sample of the UK population, the baseline data indicate that
36		patients who undergo bariatric surgery are mostly female, of middle age, and with a
37		history of T2DM. While the results were adjusted for age and sex they might not be
38		applicable for other groups suffering from obesity like adolescents. Linkage between
39		the CPRD and HES databases was restricted to England. However, there is no cogent
40		reason why the results should not be applicable to regions with similar healthcare
41		systems, both in the UK and internationally. We had insufficient data to determine
42		whether the association with AKI varied between different types of bariatric surgery;
43		we found a protective effect for gastric band but results were inconclusive for sleeve
44		gastrectomy and gastric bypass.
45		Any misclassification of diagnostic codes is likely non-differential between the
46		bariatric surgery patients and the matched comparison group and would bias the effect
47		towards the null value. Another problem of primary care data is that not every patient
48		is routinely checked for their kidney function, as incentives of testing apply primarily
49		for those at risk of kidney disease due to diabetes and hypertension. The study relied
50		on AKI events recorded in HES as part of a hospital admission and over time, the
51		awareness of the importance of AKI has likely changed resulting in secular changes in
52		recording of AKI ; analyses have adjusted for calendar period to account for this.
53		Future studies with hospital creatinine data should compare the AKI severity between
54		the groups to investigate this issue. In general, AKI diagnosed during hospitalisation
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57		
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60		

is likely to represent more serious AKI events, though we would argue these are the most clinically relevant outcomes. Moreover, a patient who experienced a previous AKI episode might be under more scrutiny for detection of future episodes. Since more patients in the bariatric surgery group had a history of AKI they might have a higher chance of detection of an AKI episode during follow-up. This would bias the estimate towards the null value and could indicate that the association we report is an under-estimate.

In addition, CKD status at baseline was missing in almost half of the patient population. However, a recent study indicated that the prevalence of CKD in the CPRD database was comparable to that found in nationally representative registry studies. This indicates that patients without eGFR-measurements at baseline are unlikely to have CKD. In addition, sensitivity analyses investigating the effect in patients with known or unknown CKD status at baseline yielded comparable results. Since access to bariatric surgery is restricted within the UK healthcare system, some patients might have funded their operation privately, resulting in selection bias. In a recent analysis about 40% of bariatric surgery operations in the UK were privately funded. Thus, the intervention group might have a higher socioeconomic status than the non-exposed group, in which similar patients would not be able to afford surgery. Since the socioeconomic background is an important determinant of health outcomes and was an unmeasured potential confounder not considered in the matching process, this could have led to more positive health outcomes in the intervention group irrespective of surgery and to an overestimation of the effect. In this study setting it was not possible to determine which patients had privately funded surgery. Even though most baseline variables were evenly distributed due to the matching process this does not guarantee that unmeasured variables are evenly distributed as well, which can constitute residual confounding. Incorrect, imprecise, or missing measurements of covariates could also have led to residual confounding. For the multivariable model, adjusting for history of AKI led to the strongest change of the effect estimate. AKI events are likely under-recorded in the HES database, for reasons described above, and thus residual confounding is possible. Since adjusting for AKI history led to a stronger effect estimate, the protective effect we report here may be an underestimate if AKI history is missing to the same degree in surgery and non-surgery patients.“

Interpretation	20	<p>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence</p> <p>Page 18: “This study adds to the evidence of long term effects of bariatric surgery, and appears to be the first study to quantify a long-term beneficial effect on AKI. Future studies with higher patient numbers may be able to determine differences in effect between types of surgery, investigate the effect in patients with CKD, and elucidate mechanisms of the association between bariatric surgery and AKI.”</p>
Generalisability	21	<p>Discuss the generalisability (external validity) of the study results</p> <p>Page 15/16: “Even though the data is taken from a representative sample of the UK population, the baseline data indicate that patients who undergo bariatric surgery are mostly female, of middle age, and with a history of T2DM. While the results were adjusted for age and sex they might not be applicable for other groups suffering from obesity like adolescents. Linkage between the CPRD and HES databases was restricted to England. However, there is no cogent reason why the results should not</p>

be applicable to regions with similar healthcare systems, both in the UK and internationally.”

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#### Other information

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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

RM is supported by a Sir Henry Wellcome Postdoctoral Fellowship from the Wellcome Trust. KB holds a Sir Henry Dale fellowship jointly funded by the Wellcome Trust and the Royal Society. RLB is an NIHR Research Professor and supported by funding from the Rosetrees Trust and the Sir Jules Thorn Charitable Trust. LS is supported by a senior clinical fellowship from the Wellcome Trust. IJD is funded by an unrestricted grant from GlaxoSmithKline.

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\*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>.

# BMJ Open

## Long-term effects of bariatric surgery on acute kidney injury: A propensity-matched cohort in the United Kingdom Clinical Practice Research Datalink

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1 **Title** Long-term effects of bariatric surgery on acute kidney injury: A propensity-  
2 matched cohort in the United Kingdom Clinical Practice Research Datalink

4 **Running headline** Bariatric surgery and acute kidney injury

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3 32 **ABSTRACT**

4 33 **Objective:** Bariatric surgery is an effective method of weight reduction and has been  
5  
6 34 associated with acute kidney injury (AKI) as a perioperative event. However, the long-term  
7  
8 35 effects of the weight reduction after surgery on AKI are unknown. The objective of this  
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10 36 study is to quantify the association of bariatric surgery with later risk of AKI.

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13 37 **Design:** This study uses a propensity-score matched cohort of patients from the United  
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15 38 Kingdom Clinical Practice Research Datalink database with and without bariatric surgery to  
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17 39 compare rates of AKI episodes derived from linkage to the Hospital Episode Statistics.

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20 40 **Setting:** England, United Kingdom

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22 41 **Participants:** We included 2,643 patients with bariatric surgery and 2,595 patients without.

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24 42 **Results:** Results were compatible with an increased risk of AKI in the first 30 days following  
25  
26 43 surgery compared with patients without surgery, but AKI incidence was substantially  
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28 44 decreased in patients with bariatric surgery during long-term follow-up (rate ratio 0.37, 95%  
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30 45 CI 0.23, 0.61) even after accounting for chronic kidney disease status at baseline. Over the  
31  
32 46 whole period of follow-up, bariatric surgery had a net protective effect on risk of AKI (rate  
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34 47 ratio 0.45, 95% CI 0.28, 0.72).

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36 48 **Conclusions:** Bariatric surgery was associated with protective effects on AKI incidence  
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38 49 during long-term follow-up. While the risk of AKI may be increased within the first 30 days,  
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40 50 the net effect seen was beneficial.

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45 52 **Keywords:** Acute Kidney Injury; Obesity; Bariatric Surgery; Clinical Practice Research  
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48 53 Datalink  
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3 54 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 5 55 • This study uses high quality data from linked databases in England (Clinical Practice  
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7 56 Research Datalink and Hospital Episode Statistics) to describe long-term effects of  
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9 57 bariatric surgery on acute kidney injury (AKI) for the first time.  
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11  
12 58 • Data are captured prospectively and continuously thus allowing follow-up of patients  
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14 59 over long time periods.  
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16 60 • Outcome measures are obtained with standardised ICD-10 codes, which have been  
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18 61 shown to accurately identify AKI, but do not allow grading of severity and may  
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20 62 therefore underestimate true AKI incidence.  
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23 63 • Only AKI events recorded during a hospital admission were included in the analysis  
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25 64 likely representing the more serious events of AKI.  
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28 65 • The study population was mostly female, of middle age, and had a history of type 2  
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30 66 diabetes mellitus. Thus the results might not be applicable for other groups suffering  
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32 67 from obesity such as adolescents.  
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## 68 INTRODUCTION

69 The proportions of overweight and obese adults in England in 2014 are estimated to be  
70 61.7% and 25.6%, respectively, and are increasing over time<sup>1</sup>. Obesity is associated with  
71 serious health consequences including type 2 diabetes mellitus (T2DM), cardiovascular  
72 diseases, cancers, and chronic kidney disease (CKD)<sup>2-4</sup>. Bariatric surgery has been shown to  
73 be a highly effective intervention for achieving weight loss and reducing the burden of co-  
74 morbidities, such as T2DM, metabolic syndrome, and hypertension<sup>5 6</sup>. A recent  
75 observational study on recipients of bariatric surgery from the United Kingdom (UK)  
76 confirmed sustained weight loss as well as resolution of T2DM and hypertension over a  
77 period of 4 years<sup>7</sup>.

78 Acute kidney injury (AKI) is defined as a sudden (over hours or days) drop in kidney function  
79 characterised by increased serum creatinine and/or reduced urine output. AKI has been  
80 linked to increased in-hospital mortality, length of hospital stay, and subsequent  
81 development of CKD<sup>8</sup>. While T2DM, CKD, and obesity have been described as risk factors for  
82 AKI, it can also be precipitated by nephrotoxic drugs, surgical interventions, and sepsis<sup>8-10</sup>.  
83 AKI has been described as a short-term complication of bariatric surgery, stemming from  
84 rhabdomyolysis<sup>10-16</sup>. In addition, AKI has been linked to nephrolithiasis, which can develop  
85 over time after Roux-En-Y Gastric Bypass surgery<sup>11 17</sup>. To the best of our knowledge, no  
86 studies have been published examining the long-term effects of bariatric surgery on AKI.

87 In this study, we investigate the long-term effects of bariatric surgery on AKI to see whether  
88 the expected reduction in BMI has any impact on subsequent renal health. We used  
89 routinely collected electronic health record data from primary and secondary care. For this,  
90 we conducted a matched cohort study using prospectively collected data from patients in  
91 the United Kingdom Clinical Practice Research Datalink (CPRD).

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3 92 **METHODS**

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5 93 **Patient and Public Involvement**

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7 94 Patients or public were not involved in the design or conduct of the study.  
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12 96 **Study design**

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14 97 We undertook a matched cohort study using prospectively collected data from CPRD  
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16 98 patients registered before 31st December 2014 linked to the Hospital Episodes Statistics  
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18 99 (HES) database to investigate long-term effects of bariatric surgery on AKI.  
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23 101 **Data source**

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25 102 The CPRD database contains anonymised, routinely collected data on approximately 10  
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27 103 million patients in participating primary care practices in the UK, including demographic  
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29 104 characteristics, current and previous diagnoses, prescribing, test results, and lifestyle  
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31 105 factors. Diagnoses, signs, and symptoms are recorded using Read codes<sup>18</sup>. Patients are  
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33 106 broadly representative of the UK population and the data have been validated for a wide  
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35 107 range of outcomes<sup>19-21</sup>. The HES database contains patient data from hospital admissions to  
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37 108 English hospitals within the National Health Service<sup>22</sup>. For each hospital admission, the  
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39 109 diagnoses are recorded using standardised codes of the International Classification of  
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41 110 Diseases, Tenth Revision (ICD-10)<sup>23 24</sup>. Data from 70% of CPRD practices in England has been  
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43 111 linked at patient level with HES admission data thus allowing the combined analysis of data  
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45 112 from primary and acute hospital care for a subset of patients<sup>19</sup>.  
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53 114 **Cohort design and propensity matching**  
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3 115 A detailed description of how the cohort was constructed is described elsewhere<sup>7</sup>. In brief,  
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5 116 records of patients who underwent bariatric surgery (n=3,882) between 1997 and 2015  
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7 117 were matched to individuals who did not undergo surgery (n=3,882) using propensity  
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9 118 scores.

11 119 Study population matching and the propensity score incorporated information on age, sex,  
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13 120 calendar period, history of T2DM, hypertension, coronary heart disease, cerebrovascular  
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15 121 disease, peripheral vascular disease, other atheroma, use of insulin, use of oral antidiabetic  
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17 122 medication, use of statins, smoking status, and alcohol consumption.

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19 123 Patients with bariatric surgery were identified using Read codes for surgery in the CPRD  
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21 124 database (S1 Appendix) and were included in the study if they had been registered in the  
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23 125 CPRD  $\geq 12$  months prior to the intervention. We excluded those with a record of prior  
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25 126 bariatric surgery reversal.

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27 127 For the comparison group, the inclusion criteria were to have at least one BMI  
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29 128 measurement  $\geq 40$  kg/m<sup>2</sup> during their CPRD registration, which could span 10 years or more,  
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31 129  $\geq 12$  months of follow-up prior to the index date in the database, and no prior record of  
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33 130 bariatric surgery or bariatric surgery reversal. Based on this, it is therefore possible that the  
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35 131 BMI recorded closest to the index date was lower than 40 kg/m<sup>2</sup>.

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37 132 The study sample was restricted to eligible patients registered at practices linked to the HES  
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39 133 database and information on AKI events was obtained, resulting in a final cohort comprising  
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41 134 2,643 patients who underwent bariatric surgery, and 2,595 patients who did not.

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43 135 Follow-up started on the day of surgery for those with bariatric surgery, and for the  
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45 136 comparison group who did not undergo bariatric surgery, on the surgery date of their  
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47 137 matched case. Patient records were censored at the earliest of: AKI, death, leaving the

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3 138 practice, latest data collection from current practice, or end of linkage period to the HES  
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5 139 database.

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14 143 **Outcomes and covariates**

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16 144 The primary outcome of this study was the incidence rate of the first AKI episode during  
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18 145 follow-up in patients with and without bariatric surgery. AKI episodes were obtained from  
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20 146 the HES database using ICD-10 codes: N17.0 (“Acute kidney failure with tubular necrosis”),  
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22 147 N17.1 (“Acute renal failure with acute cortical necrosis), N17.2 (“Acute renal failure with  
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24 148 medullary necrosis”), N17.8 (“Other acute renal failure”), N17.9 (“Acute kidney failure,  
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26 149 unspecified”), and N19 (“Unspecified kidney failure”). In this cohort, events coded with  
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28 150 N17.1, N17.2, and N17.8 were not found. AKI events that occurred before the start of  
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30 151 follow-up were recorded as a binary variable “history of AKI”, while AKI events occurring  
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32 152 during follow-up were used to analyse AKI incidence.

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35 153 Recorded serum creatinine values from the CPRD database were not routinely standardised  
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37 154 with isotope-dilution mass spectrometry before 2013. Thus, we assumed all measurements  
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39 155 to be unstandardized and multiplied the creatinine measures with the factor 0.95 before  
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41 156 calculating the estimated glomerular filtration rate (eGFR) using the “Chronic Kidney Disease  
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43 157 Epidemiology Collaboration” (CKD-EPI) equation<sup>25</sup>. Ethnicity was not considered in the eGFR  
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45 158 calculation due to incomplete recording in the database and the low proportion of Afro-  
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47 159 Caribbean people in the population. CKD stages were defined according to eGFR values in  
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49 160 ml/min/1.73m<sup>2</sup> according to current guidelines<sup>26</sup>: eGFR ≥60 = no known CKD; eGFR 45-59 =  
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51 161 stage 3a; eGFR 30-44 = stage 3b; eGFR 15-29 = stage 4; eGFR <15 = stage 5. Baseline CKD

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3 162 status was derived from eGFR measurements in the year prior to start of follow-up by: 1)  
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5 163 taking the last two measurements before the index date  $\geq 90$  days apart – with the higher  
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7 164 eGFR value corresponding to the CKD baseline status, or 2) taking the most recent serum  
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9 165 creatinine result if only one suitable test result was available. Since serum creatinine is more  
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11 166 likely to be tested in the acutely unwell or in people who are routinely monitored as part of  
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13 167 incentivised programs (e.g. people with diabetes), patients without measurements of CKD  
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15 168 baseline status were assumed to have no CKD<sup>27</sup> and were analysed as such.  
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### 23 171 **Statistical Analysis**

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25 172 Though propensity score matching was employed to minimise confounding, we compared  
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27 173 the distribution of baseline characteristics between the exposed and unexposed groups to  
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29 174 check for any imbalances that may be relevant to the outcome of AKI. The baseline  
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31 175 distribution of categorical variables was analysed using percentages and  $\chi^2$ -tests.  
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33 176 Continuous variables were analysed as means with standard deviations for normally  
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35 177 distributed variables and medians with interquartile ranges for non-normally distributed  
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37 178 variables. Differences in continuous variables were analysed with Student's t-tests or  
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39 179 Wilcoxon rank sum tests for normally and non-normally distributed data, respectively.  
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44 180 The association between bariatric surgery and AKI was analysed using a Poisson regression  
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46 181 model with a time to first event analysis. P-values were calculated using Wald tests. In order  
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48 182 to separate short-term effects of the surgery from potential long-term effects, we analysed  
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50 183 the association separately for: a) events within the first 30 days, and b) events after 30 days.  
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52 184 When the cohort was initially constructed, propensity score matching was used to deal with  
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54 185 confounding<sup>7</sup>. This study uses a subset of this cohort since patients from practices without  
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3 186 linkage between the CPRD and HES databases had to be excluded (as AKI was assessed using  
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5 187 hospital admission data). To identify variables for the multivariable model, potential  
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7 188 confounders that were not deemed to be on the causal pathway were added individually to  
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9 189 the univariable model. If the addition changed the effect estimate  $\geq 10\%$  these variables  
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11 190 were included in the multivariable model. Consequently, history of AKI, history of taking oral  
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13 191 antidiabetics, and BMI at baseline were included (S2 Appendix). In addition, age at baseline,  
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15 192 sex, calendar period (1997-2005, 2006-2010, 2011-2015), and CKD status at baseline were  
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17 193 selected *a priori* as forced variables. For models with <40 outcomes, only age and sex were  
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19 194 included in the multivariable model due to data sparsity.

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21 195 The 5% bands of patients with the highest and lowest propensity scores were excluded from  
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23 196 the primary analysis ("trimming") since these contain patients that are treated in stark  
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25 197 contrast to their health status, potentially causing bias<sup>28</sup>.

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27 198 Heterogeneity of effect estimates between the calendar periods was tested with a  
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29 199 Likelihood Ratio Test.

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31 200 The analysis was performed for all patients with bariatric surgery and also further stratified  
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33 201 by type of surgery. Patients with stage 5 CKD (baseline eGFR < 15 ml/min/1.73m<sup>2</sup>) were  
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35 202 excluded from the analyses since this constitutes end-stage renal failure (ESRD). In addition,  
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37 203 patients with missing data in  $\geq 1$  variable of the multivariable model were excluded from  
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39 204 both uni- and multivariable analyses.

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41 205 All analyses were performed with Stata 14.1.

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### 44 207 **Subgroup analyses**

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46 208 Several planned sensitivity analyses were undertaken: 1) To determine the net effect of the  
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48 209 intervention we calculated the risk of AKI over the whole period of follow-up; 2) The

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3 210 prevalence of decreased kidney function in the CPRD database was similar to that in a  
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5 211 nationally representative kidney disease registry <sup>27</sup> indicating that patients with missing  
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7 212 eGFR measurements are unlikely to have CKD. To identify potential differences in the effect  
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9 213 between patients with known and unknown eGFR measurements, we restricted the analysis  
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11 214 to a) patients known to have no CKD at baseline (baseline eGFR  $\geq$  60 ml/min/1.73m<sup>2</sup>), b)  
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13 215 patients without known CKD at baseline (as above but including patients with missing  
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15 216 creatinine values at baseline and assuming these individuals to have no CKD), and c)  
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17 217 patients with known CKD at baseline.<sup>27</sup>; 3) Moreover, to investigate the effect in a group of  
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19 218 particular interest which is under more scrutiny for measuring kidney function we restricted  
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21 219 the analysis to patients with: a) T2DM, and b) a history of taking insulin; 4) To avoid  
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23 220 misclassification of low eGFR values as AKI <sup>29</sup> we excluded patients with stage 4 CKD at  
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25 221 baseline; 5) We restricted the analysis to ICD-10 codes N17.0 and N17.9, which have a high  
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27 222 positive predictive value for AKI <sup>24</sup>; 6) We increased the immediate post-surgery time span  
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29 223 from 30 to 60 days; 7) We included people with extreme propensity scores; and 8) We  
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31 224 excluded patients with a BMI < 35 kg/m<sup>2</sup> at baseline.  
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## 226 **Ethical approval**

227 This study was approved by the London School of Hygiene & Tropical Medicine ethics  
228 committee (LSHTM MSc Ethics Ref: 11065) and the Independent Scientific Advisory  
229 Committee on Medicines & Healthcare Products Regulatory Agency database research  
230 (approval number: 16\_106R).



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3 231 **RESULTS**  
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5 232 Since linkage to the HES-database was only possible for patients whose GPs had agreed for  
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7 233 their practice data to be linked to HES (S3 Appendix), there were 2,643 patients with  
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9 234 bariatric surgery and 2,595 people without surgery resulting in a cohort of overall 5,238  
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11 235 people with a median follow-up of 2.9 years (Table 1). The median follow-up prior to  
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13 236 baseline was similar between the groups: 8.8 years (IQR: 8.1 years) for patients with  
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15 237 bariatric surgery and 9.3 years (IQR: 8.0 years) for people without surgery.  
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238 *Table 1: Baseline data for CPRD/HES-linked cohort study of people with bariatric surgery and*  
 239 *the corresponding propensity score-matched\* comparison cohort*  
 240 *(data are n (%) unless otherwise specified)*

	Bariatric Surgery (n = 2,643)	Matched Comparison group without surgery (n = 2,595)	p-value <sup>1</sup>
<b>Follow-up (years), median (IQR)</b>	2.9 (3.2)	2.9 (3.4)	0.616
<b>Age (years), mean (SD)</b>	45.2 (10.7)	45.0 (10.8)	0.417
17 – 39, n (%)	818 (31.0)	826 (31.8)	
40 – 49, n (%)	945 (35.8)	928 (35.8)	0.727
50 – 85, n (%)	880 (33.3)	841 (32.4)	
<b>BMI at baseline, mean (SD)</b>	44.9 (8.9)	42.2 (6.5)	<0.001
13 – 34, n (%)	297 (11.2)	287 (11.1)	
35 – 39, n (%)	448 (17.0)	456 (17.6)	
40 – 44, n (%)	625 (23.7)	1,118 (43.1)	<0.001
45 – 49, n (%)	571 (21.6)	438 (16.9)	
50 – 94, n (%)	667 (25.2)	253 (9.8)	
Missing, n (%)	35 (1.3)	43 (1.7)	
<b>Female</b>	2,131 (80.6)	2,131 (82.1)	0.166
<b>History of</b>			
<b>Cerebrovascular disease</b>	37 (1.4)	26 (1.0)	0.186
<b>Coronary heart disease</b>	104 (3.9)	82 (3.2)	0.130
<b>Peripheral vascular disease</b>	11 (0.4)	15 (0.6)	0.405
<b>Other atheroma</b>	0	<5 <sup>2</sup>	0.313
<b>T2DM</b>	900 (34.1)	853 (32.9)	0.365
<b>Taking oral antidiabetic</b>	571 (21.6)	455 (17.5)	<0.001
<b>Taking insulin</b>	180 (6.8)	156 (6.0)	0.238
<b>Hypertension</b>	890 (33.7)	869 (33.5)	0.886
<b>Statin use</b>	699 (26.4)	640 (24.7)	0.139
<b>AKI</b>	30 (1.1)	11 (0.4)	0.003
<b>Alcohol status</b>			
<b>Non-drinker</b>	435 (16.5)	397 (15.3)	
<b>Ex-drinker</b>	278 (10.5)	236 (9.1)	
<b>Current drinker (amount unknown)</b>	15 (0.6)	13 (0.5)	
<2 units/day	659 (24.9)	644 (24.8)	0.366
3-6 units/day	862 (32.6)	909 (35.0)	
>6 units/day	170 (6.4)	164 (6.3)	
<b>Unknown</b>	224 (8.5)	232 (8.9)	
<b>Smoking status</b>			
<b>Non-smoker</b>	1,126 (42.6)	1,151 (44.4)	
<b>Current smoker</b>	403 (15.3)	345 (13.3)	0.093
<b>Ex-smoker</b>	1,112 (42.1)	1,099 (42.4)	
<b>Unknown</b>	<5 <sup>2</sup>	0	
<b>CKD at baseline</b>			
<b>Baseline CKD status absent</b>	1,119 (42.3)	1,299 (50.1)	
<b>No CKD</b>	1,470 (55.6)	1,242 (47.9)	
<b>Stage 3a</b>	27 (1.0)	37 (1.4)	<0.001
<b>Stage 3b</b>	16 (0.6)	10 (0.4)	
<b>Stage 4</b>	10 (0.4)	5 (0.2)	
<b>Stage 5</b>	<5 <sup>2</sup>	<5 <sup>2</sup>	
<b>Type of bariatric surgery</b>			
<b>Gastric band</b>	1,193 (45.1)		
<b>Sleeve gastrectomy</b>	364 (13.8)		
<b>Gastric bypass</b>	1,075 (40.7)		
<b>Other</b>	11 (0.4)		
<b>ICD-10 code for AKI during follow-up</b>	<b>n = 44</b>	<b>n = 62</b>	
<b>N17.0 (Acute kidney failure with tubular necrosis)</b>	<5 <sup>2</sup>	<5 <sup>2</sup>	
<b>N17.9 (Acute kidney failure, unspecified)</b>	38 (86.4)	52 (83.9)	0.927
<b>N19 (Unspecified kidney failure)</b>	5 (11.4)	8 (12.9)	

<sup>1</sup> categorical variables:  $\chi^2$ -test; continuous variables: t-test + SD if normally distributed, rank sum test + IQR if non-normally distributed

<sup>2</sup>cell counts <5 have been suppressed to ensure anonymity

\*In the original study, each surgery patient was matched 1:1 to the person without surgery with the closest propensity score, choosing matches at random where more than one possible match had the same score<sup>7</sup>

AKI = acute kidney injury, BMI = body mass index, CKD = chronic kidney disease, ICD-10 = International Classification of Diseases, Tenth Revision, IQR = interquartile range, SD = standard deviation, T2DM = type 2 diabetes mellitus

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3 242 This cohort was comparable to the cohort from the original study regarding sex, mean age,  
4  
5 243 mean BMI, history of T2DM, type of bariatric surgery and the imbalance of BMI at baseline  
6  
7 244 <sup>7</sup>. More patients in the intervention group had a history of AKI compared to the comparison  
8  
9 245 group (1.1% vs. 0.4%). Of the 106 included events during follow-up, 84.9% were classified  
10  
11 246 with the ICD-10 code N17.9 (“acute kidney failure, unspecified”), 12.3% were coded as N19  
12  
13 247 (“unspecified kidney failure”), and 2.8% had a code of N17.0 (“Acute kidney failure with  
14  
15 248 tubular necrosis”). CKD status at baseline was unknown for about half of the patients in  
16  
17 249 each group with a slightly higher proportion in the unexposed group (50.1% vs. 42.3%). The  
18  
19 250 majority of the patients with creatinine tests at baseline did not have CKD (96.2 %).  
20  
21 251 The number of AKI events recorded in the first 30 days of follow-up was low. All five events  
22  
23 252 happened in patients with bariatric surgery and none were recorded in the control group,  
24  
25 253 which is consistent with the possibility of an increased risk of AKI directly after surgery  
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30 254 (Table 2).  
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255 *Table 2: Association of bariatric surgery with first incident AKI, stratified by length of follow-*  
 256 *up. Unexposed refers to the propensity matched comparison group*

	PY	Events	Rate per 1000 PY (95% CI)	Crude RR (95% CI) <sup>1</sup>	p-value <sup>2</sup>	Adjusted RR (95% CI) <sup>3</sup>	p-value <sup>2</sup>
<b>All patients</b>							
<b>Day 1-30</b>							
Unexposed	203	0	0	-			
Bariatric surgery	199	5	25.1 (10.5, 60.4)	-			
<b>&gt; Day 30</b>							
Unexposed	7,882	54	6.9 (5.2, 8.9)	-			
Bariatric surgery	8,061	34	4.2 (3.0, 5.9)	0.62 (0.40, 0.95)	0.027	0.37 (0.23, 0.61)	<0.001
<b>All patients analysed by type of surgery<sup>4</sup></b>							
<b>Day 1-30</b>							
Unexposed							
Gastric band							
Sleeve gastrectomy							
Gastric bypass							
Other							
<b>&gt; Day 30</b>							
Unexposed	7,882	54	6.9 (5.2, 8.9)	-			
Gastric band	4,614	17	3.7 (2.3, 5.9)	0.54 (0.31, 0.93)	0.026		
Sleeve gastrectomy	728	<5 <sup>5</sup>	5.5 (2.1, 14.6)	0.80 (0.29, 2.21)	0.670		
Gastric bypass	2,655	13	4.9 (2.8, 8.4)	0.71 (0.39, 1.31)	0.277		
Other	63	0	-	-			
<b>All patients over whole period of follow-up</b>							
Unexposed	8,085	54	6.7 (5.1, 8.7)	-			
Bariatric surgery	8,259	39	4.7 (3.5, 6.5)	0.71 (0.47, 1.07)	0.099	0.45 (0.28, 0.72)	0.001

<sup>1</sup> Poisson regression model

<sup>2</sup> Wald test

<sup>3</sup> Poisson regression model adjusted for age at baseline, sex, calendar time, CKD at baseline, history of AKI, history of taking oral antidiabetics, and BMI at baseline

<sup>4</sup> No analysis for day 1-30 owing to sparse data

<sup>5</sup> Cell counts <5 have been suppressed to ensure anonymity

AKI = acute kidney injury, CKD = chronic kidney disease, PY = person-years, RR = rate ratio

257  
 258 From 30 days onwards, bariatric surgery had a protective association with AKI risk (crude RR  
 259 = 0.62, 95% CI 0.40, 0.95). The effect estimate of the multivariable model indicated an even  
 260 stronger protective effect associated with bariatric surgery (RR = 0.37, 95% CI 0.23, 0.61),  
 261 largely due to the confounding by AKI prior to baseline.  
 262 The analysis by type of surgery yielded protective effect estimates for all types but the  
 263 confidence intervals were wide and no comparison between individual procedures was  
 264 feasible. Sensitivity analyses yielded similar results (S4 Appendix). A sensitivity analysis  
 265 restricted to patients with known CKD at baseline could not be done owing to sparse data.  
 266 Investigation of the effect of bariatric surgery over the whole follow-up period resulted in a  
 267 protective net effect associated with the intervention in univariable (RR = 0.71, 95% CI 0.47,  
 268 1.07) and multivariable (RR = 0.45, 95% CI 0.28, 0.72) analyses.

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3 269 **DISCUSSION**  
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5 270 In this study using prospectively recorded routine healthcare data from a representative  
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7 271 sample in the UK, bariatric surgery was associated with a potentially increased risk of AKI  
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9 272 within the first 30 days after surgery (5 events in patients with bariatric surgery, no events in  
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11 273 control patients) but a strongly protective association thereafter (adjusted RR = 0.37, 95% CI  
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13 274 0.23, 0.61). The association was consistent across subgroups and sensitivity analyses. To the  
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15 275 best of our knowledge, this is the first study to describe long-term effects of bariatric  
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17 276 surgery on AKI.

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19 277 AKI has been described as a perioperative event for bariatric surgery<sup>12 13 15 16</sup>. Our results  
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21 278 are consistent with an increased risk in the early stages after surgery, however our analysis  
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23 279 lacked enough early events to rule out chance as a reason for the results observed. Since  
24  
25 280 patients do not have kidney function measures routinely checked by their family physician  
26  
27 281 after bariatric surgery, many events could remain unnoticed. Patients with known CKD are  
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29 282 more thoroughly checked for AKI and are a valuable subgroup to investigate, but the  
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31 283 numbers in this dataset were too low to analyse.

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33 284 This study uses high quality data from routine medical care in the UK. The healthcare system  
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35 285 allows universal patient access to primary and secondary care so that the data is  
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37 286 representative of the population. Patients are followed continuously while they are  
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39 287 registered with a general practitioner allowing prospective data capture over long  
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41 288 observation periods and avoiding problems with reverse causality.

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43 289 Some limitations need to be considered. Even though the data is taken from a  
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45 290 representative sample of the UK population, the baseline data indicate that patients who  
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47 291 undergo bariatric surgery are mostly female, of middle age, and with a history of T2DM.  
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49 292 While the results were adjusted for age and sex they might not be applicable for other  
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3 293 groups suffering from obesity like adolescents. Linkage between the CPRD and HES  
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5 294 databases was restricted to England. However, there is no cogent reason why the results  
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7 295 should not be applicable to regions with similar healthcare systems, both in the UK and  
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9 296 internationally. We had insufficient data to determine whether the association with AKI  
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11 297 varied between different types of bariatric surgery; we found a protective effect for gastric  
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13 298 band but results were inconclusive for sleeve gastrectomy and gastric bypass.

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16 299 Of all AKI episodes identified in the HES database, the ICD-10 codes N17.0 and N17.9  
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18 300 comprised 87.7% of all events and have previously been shown to accurately identify AKI in  
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20 301 a single centre study<sup>24</sup>. However, there are no ICD-10 codes for grades of AKI severity. Thus,  
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22 302 we were not able to investigate whether there was an association between bariatric surgery  
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24 303 and AKI severity. In general, AKI diagnosed during hospitalisation is likely to represent more  
25  
26 304 serious AKI events and therefore may underestimate AKI incidence. Thus, the conclusions  
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28 305 drawn from this study may only be applicable to severe AKI diagnosed during  
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30 306 hospitalisation, however, we would argue these are the most clinically relevant outcomes.  
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32 307 Moreover, a patient who experienced a previous AKI episode might be under more scrutiny  
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34 308 for detection of future episodes. Since more patients in the bariatric surgery group had a  
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36 309 history of AKI they might have a higher chance of detection of an AKI episode during follow-  
37  
38 310 up, which we adjusted for in our analyses.

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44 311 Misclassification of diagnostic codes is likely non-differential between the bariatric surgery  
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46 312 patients and the matched comparison group and would bias the effect towards the null  
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48 313 value. However, it is also conceivable during the immediate post-operative period those  
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50 314 undergoing bariatric surgery might have been under more scrutiny to detect potential AKI  
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52 315 events than people without surgery. In this case our current relative risk estimate for the  
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54 316 immediate postoperative period would be an overestimate. Another problem of primary

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3 317 care data is that not every patient is routinely checked for their kidney function, as  
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5 318 incentives of testing apply primarily for those at risk of kidney disease due to diabetes and  
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7 319 hypertension. The study relied on AKI events recorded in HES as part of a hospital admission  
8  
9 320 and over time, the awareness of the importance of AKI has likely changed resulting in  
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11 321 secular changes in recording of AKI<sup>30</sup>; analyses have adjusted for calendar period to account  
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13 322 for this<sup>23 31</sup>. Future studies with hospital creatinine data should compare the AKI severity  
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15 323 between the groups to investigate this issue.  
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18 324 In addition, CKD status at baseline was missing in almost half of the patient population.  
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20 325 However, a recent study indicated that the prevalence of CKD in the CPRD database was  
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22 326 comparable to that found in nationally representative registry studies<sup>27</sup>. This indicates that  
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24 327 patients without a GP record of eGFR-measurements at baseline are unlikely to have CKD. In  
25  
26 328 addition, sensitivity analyses investigating the effect in patients with known or unknown  
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28 329 CKD status at baseline yielded comparable results.  
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31 330 Since access to bariatric surgery is restricted within the UK healthcare system, some  
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33 331 patients might have funded their operation privately, resulting in selection bias. In a recent  
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35 332 analysis about 40% of bariatric surgery operations in the UK were privately funded<sup>32</sup>. Thus,  
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37 333 the intervention group might have a higher socioeconomic status than the non-exposed  
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39 334 group, in which similar patients would not be able to afford surgery. Since the  
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41 335 socioeconomic background is an important determinant of health outcomes and was an  
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43 336 unmeasured potential confounder not considered in the matching process, this could have  
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45 337 led to more positive health outcomes in the intervention group irrespective of surgery and  
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47 338 to an overestimation of the effect. In this study setting it was not possible to determine  
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49 339 which patients had privately funded surgery.  
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3 340 Even though most baseline variables were evenly distributed due to the matching process  
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5 341 this does not guarantee that unmeasured variables are evenly distributed as well, which can  
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7 342 constitute residual confounding. Incorrect, imprecise, or missing measurements of  
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9 343 covariates could also have led to residual confounding. For the multivariable model,  
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11 344 adjusting for history of AKI led to the strongest change of the effect estimate. AKI events are  
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13 345 likely under-recorded in the HES database, for reasons described above, and thus residual  
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15 346 confounding is possible. Since adjusting for AKI history led to a stronger effect estimate, the  
16  
17 347 protective effect we report here may be an underestimate if AKI history is missing to the  
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19 348 same degree in surgery and non-surgery patients.  
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23 349 This study adds to the evidence of long term effects of bariatric surgery, and appears to be  
24  
25 350 the first study to quantify a long-term beneficial effect on AKI. Future studies with higher  
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27 351 patient numbers may be able to determine differences in effect between types of surgery,  
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29 352 investigate the effect in patients with CKD, and elucidate mechanisms of the association  
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31 353 between bariatric surgery and AKI.  
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3 355 **SUPPLEMENTARY INFORMATION**  
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5 356 Supplementary information is available at the *BMJ open* website.  
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17

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25

26 366 analysis, the writing of the report, or the decision to submit the paper for publication.  
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32 368 **CONFLICT OF INTEREST**  
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34 369 The authors have no conflicts of interest to disclose.  
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39 371 **DATA SHARING**  
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41 372 The data were obtained from the Clinical Practice Research Datalink (CPRD). CPRD data  
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43 373 governance does not allow us to distribute patient data to other parties. Researchers may  
44

45 374 apply for data access at [www.CPRD.com](http://www.CPRD.com). The codes used to produce the data for this study  
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47 375 are provided in the Supporting Information.  
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3 379 **CONTRIBUTIONS**  
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5 380 UK, DN, RLB, IJD, and LS were responsible for conceptualisation of the study and formulate  
6  
7 381 the research goals and aims. UK, DN, KEM, RM, KB, RLB, LS, and IJD developed the  
8  
9 382 methodology and models. UK, KEM, KB, IJD, and RM worked on the data curation. UK  
10  
11 383 performed the statistical analysis and wrote the original draft. UK, DN, KEM, RM, KB, RLB,  
12  
13  
14 384 LS, and IJD reviewed and commented the draft and gave input on editing.  
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- 3 1 **Long-term effects of bariatric surgery on acute kidney injury: A propensity-matched**
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- 6 2 **cohort in the United Kingdom Clinical Practice Research Datalink**
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- 10 4 **Supporting Information**
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- 13 5
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- 15 6 **Overview**
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- 18 7 S1 Appendix – Code List for Identification of patients with bariatric surgery
- 19
- 20 8 S2 Appendix – Association of potential confounders with bariatric surgery and AKI
- 21
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- 23 9 S3 Appendix – Patient selection from the original cohort
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- 25 10 S4 Appendix – Sensitivity Analyses
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11 **S1 Appendix**

12 *Appendix 1: Code List for identification of patients with bariatric surgery from the CPRD database as*  
13 *published by Douglas et al. [7]*

14	<i>Read code</i>	<i>description</i>
15	76132.00	Laparoscopic adjustable gastric banding
16	76134.00	Partitioning of stomach using staples
17	76131.11	Mason vertical banded gastroplasty
18	76133.00	Partitioning of stomach using band
19	76116.00	Laparoscopic sleeve gastrectomy
20	76115.00	Sleeve gastrectomy NEC
21	76425.00	Duodenal switch
22	76135.00	Partitioning of stomach NEC
23	76114.00	Sleeve gastrectomy and duodenal switch
24	76166.00	Laparoscopic gastric bypass

25 **S2 Appendix**

26 *Appendix 2: Identification of potential confounders in the association of bariatric surgery (exposure)*  
 27 *and the endpoint of incident AKI (outcome) in patients of the linked CPRD/HES cohort*

	RR (95%CI)	Change in %	Selection for multivariable model
<b>Crude effect estimate</b>	0.62 (0.40, 0.95)		
<b>Effect estimates when individually adjusting for</b>			
<b>Age</b>	0.62 (0.40, 0.95)	0.2 %	yes (a priori)
<b>Sex</b>	0.60 (0.39, 0.92)	2.7 %	yes (a priori)
<b>Calendar Time</b>	0.61 (0.40, 0.94)	0.9%	yes (a priori)
<b>CKD status at baseline</b>	0.59 (0.38, 0.91)	4.4 %	yes (a priori)
<b>BMI at baseline</b>	0.53 (0.34, 0.83)	13.9 %	yes
<b>Alcohol Status</b>	0.61 (0.40, 0.93)	1.3 %	no
<b>Smoking Status</b>	0.61 (0.40, 0.94)	0.3 %	no
<b>History of cerebrovascular disease</b>	0.61 (0.40, 0.94)	0.6 %	no
<b>History of coronary heart disease</b>	0.60 (0.39, 0.91)	3.3 %	no
<b>History of peripheral vascular disease</b>	0.64 (0.41, 0.98)	3.2 %	no
<b>History of other atheroma</b>	0.62 (0.40, 0.95)	0.0 %	no
<b>History of diabetes</b>	0.60 (0.39, 0.92)	2.7%	no
<b>History of taking oral antidiabetics</b>	0.55 (0.36, 0.85)	10.4%	yes
<b>History of taking insulin</b>	0.57 (0.37, 0.87)	7.9 %	no
<b>History of hypertension</b>	0.61 (0.40, 0.94)	1.1 %	no
<b>History of statin use</b>	0.58 (0.38, 0.89)	5.5 %	no
<b>History of AKI</b>	0.42 (0.26, 0.67)	31.9 %	yes

Variables were added individually to the univariable model testing the association between bariatric surgery and AKI. If the addition of the respective variable changed the model  $\geq 10\%$  then the variable was selected to be included in the multivariable model.

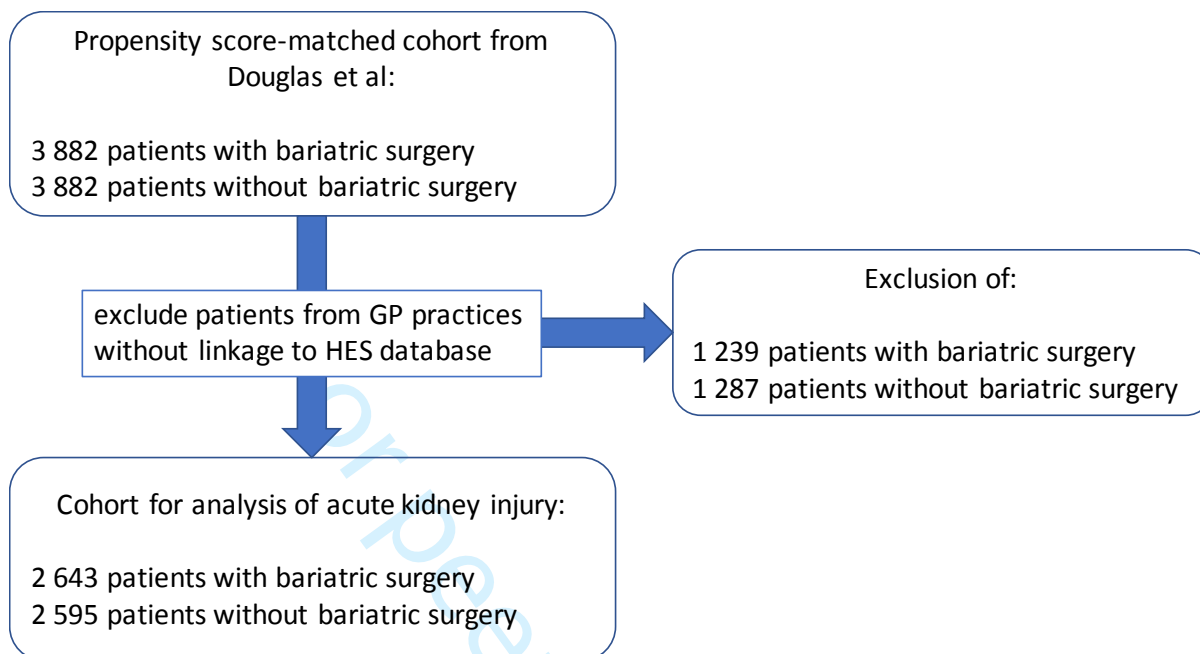
AKI = acute kidney injury, BMI = body mass index, CKD = chronic kidney disease

28

29 **S3 Appendix**

30 *Appendix 3: Patient selection from the original cohort as described in Douglas et al [7]*

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32  
33



34 **S4 Appendix**35 *Appendix 4: Sensitivity analyses for the association of bariatric surgery with acute kidney injury*

	PY	Events	Rate per 1000 PY (95% CI)	Crude RR (95% CI) <sup>1</sup>	p-value <sup>2</sup>	Adjusted RR (95% CI) <sup>3</sup>	p-value <sup>2</sup>
<b>Restricted to patients without CKD at baseline (available serum creatinine measures + eGFR ≥60)</b>							
<b>Day 1-30</b>							
Unexposed	98	0	0	-			
Bariatric surgery	111	<5 <sup>b</sup>	36.2 (13.6, 96.3)	-			
<b>&gt;Day 30</b>							
Unexposed	3,550	27	7.6 (5.2, 11.1)	-			
Bariatric surgery	4,311	22	5.1 (3.4, 7.7)	0.67 (0.38, 1.18)	0.165	0.53 (0.29, 1.00)	0.050
<b>Restricted to patients without known CKD at baseline (available serum creatinine measures + eGFR ≥60 or missing eGFR at baseline)</b>							
<b>Day 1-30</b>							
Unexposed	199	0	0	-			
Bariatric surgery	195	<5 <sup>b</sup>	20.5 (7.7, 54.7)	-			
<b>&gt;Day 30</b>							
Unexposed	7,735	42	5.4 (4.0, 7.3)	-			
Bariatric surgery	7,930	27	3.4 (2.3, 5.0)	0.63 (0.39, 1.02)	0.058	0.42 (0.25, 0.73)	0.002
<b>Excluding patients with CKD stage 4</b>							
<b>Day 1-30</b>							
Unexposed	203	0	0	-			
Bariatric surgery	198	5	25.2 (10.5, 60.6)	-			
<b>&gt; Day 30</b>							
Unexposed	7,875	52	6.6 (5.0, 8.7)	-			
Bariatric surgery	8,037	32	4.0 (2.8, 5.6)	0.60 (0.39, 0.94)	0.024	0.35 (0.21, 0.59)	<0.001
<b>Restricted to patients with T2DM</b>							
<b>Day 1-30</b>							
Unexposed	65	0	0	-			
Bariatric surgery	69	<5 <sup>b</sup>	43.6 (14.1, 135.1)	-			
<b>&gt;Day 30</b>							
Unexposed	2,325	33	14.2 (10.1, 20.0)	-			
Bariatric surgery	2,548	18	7.1 (4.5, 11.2)	0.50 (0.28, 0.88)	0.017	0.25 (0.13, 0.51)	<0.001
<b>Restricted to patients with a history of taking insulin</b>							
<b>Day 1-30</b>							
Unexposed	11	0	0	-			
Bariatric surgery	13	0	0	-			
<b>&gt;Day 30</b>							
Unexposed	321	11	34.3 (19.0, 61.9)	-			
Bariatric surgery	502	9	17.9 (9.3, 34.5)	0.52 (0.22, 1.26)	0.150	0.22 (0.08, 0.64)	0.005
<b>Restricted to ICD-10 codes N17.0 and N17.9</b>							
<b>Day 1-30</b>							
Unexposed	202	0	0	-			
Bariatric surgery	199	5	25.2 (10.5, 60.5)	-			
<b>&gt;Day 30</b>							
Unexposed	7,871	48	6.1 (4.6, 8.1)	-			
Bariatric surgery	8,055	31	3.8 (2.7, 5.5)	0.63 (0.40, 0.99)	0.046	0.40 (0.24, 0.67)	<0.001
<b>Having an initial post-surgery time span of 60 days instead of 30</b>							
<b>Day 1-60</b>							
Unexposed	403	<5 <sup>b</sup>	2.5 (0.3, 17.6)	-			
Bariatric surgery	395	6	15.2 (6.8, 33.8)	6.11 (0.74, 50.8)	0.094	<sup>4</sup>	
<b>&gt; Day 60</b>							
Unexposed	7,682	53	6.9 (5.3, 9.0)	-			
Bariatric surgery	7,864	33	4.2 (3.0, 5.9)	0.61 (0.39, 0.94)	0.025	0.38 (0.23, 0.63)	<0.001
				Test for interaction <sup>5</sup>	0.011		

Including patients with extreme propensity scores								
<b>Day 1-30</b>								
Unexposed	208	0	0	-				
Bariatric surgery	206	5	24.3 (10.1, 58.3)	-				
<b>&gt; Day 30</b>								
Unexposed	8,054	59	7.3 (5.7, 9.5)	-				
Bariatric surgery	8,324	34	4.1 (2.9, 5.7)	0.56 (0.37, 0.85)	0.007	0.33 (0.20, 0.54)	<0.001	
Excluding patients with BMI < 35 kg/m <sup>2</sup> at baseline								
<b>Day 1-30</b>								
Unexposed	180	0	0	-				
Bariatric surgery	175	<5 <sup>6</sup>	22.8 (8.6, 60.9)	-				
<b>&gt; Day 30</b>								
Unexposed	6,714	48	7.1 (5.4, 9.5)	-				
Bariatric surgery	7,100	32	4.5 (3.2, 6.4)	0.63 (0.40, 0.99)	0.043	0.39 (0.23, 0.65)	<0.001	

<sup>1</sup> Poisson regression model

<sup>2</sup> Wald test for RR, Likelihood-Ratio Test for interaction

<sup>3</sup> Poisson regression model adjusted for age at baseline, sex, calendar time, CKD at baseline, history of AKI, history of taking oral antidiabetics, and BMI at baseline

<sup>4</sup> No analysis for day 1-30 owing to sparse data

<sup>5</sup> Test for interaction of the effect estimate with the time periods 1-30 days and >30 days

<sup>6</sup> cell counts <5 have been suppressed to ensure anonymity

AKI = acute kidney injury, CKD = chronic kidney disease, PY = person-years, RR = rate ratio

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**Supporting Information:****STROBE statement checklist to ensure appropriate reporting of study information of long-term effects of acute kidney injury for the propensity-matched cohort study of patients with and without bariatric surgery**

	Item No	Report
<b>Title and abstract</b>	1	<p>(a) Indicate the study's design with a commonly used term in the title or the abstract</p> <p>“Long-term effects of bariatric surgery on acute kidney injury: A propensity-matched cohort in the United Kingdom Clinical Practice Research Datalink”</p> <p>b) Provide in the abstract an informative and balanced summary of what was done and what was found</p> <p>Abstract: on page 2 containing Background, Methods, Results and Conclusions</p>
<b>Introduction</b>		
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported</p> <p>See page 4 for description of background; Rationale (p4): “To the best of our knowledge, no studies have been published examining the long-term effects of bariatric surgery on AKI.”</p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses</p> <p>Page 4: “In this study, we investigate the long-term effects of bariatric surgery on AKI to see whether the expected reduction in BMI has any impact on subsequent renal health.”</p>
<b>Methods</b>		
Study design	4	<p>Present key elements of study design early in the paper</p> <p>See page 5: “We undertook a matched cohort study using prospectively collected data from CPRD patients registered before 31st December 2014 linked to the Hospital Episodes Statistics (HES) database to investigate long-term effects of bariatric surgery on AKI.”</p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</p> <p>Page 5: “The CPRD database contains anonymised, routinely collected data on approximately 10 million patients in participating primary care practices in the UK, including demographic characteristics, current and previous diagnoses, prescribing, test results, and lifestyle factors. [...] The HES database contains patient data from hospital admissions to English hospitals within the National Health Service [...]. Data from 70% of CPRD practices in England has been linked at patient level with HES admission data thus allowing the combined analysis of data from primary and acute hospital care for a subset of patients.”</p> <p>“A detailed description of how the cohort was constructed is described elsewhere. In brief, records of patients who underwent bariatric surgery (n=3,882) between 1997 and 2015 were matched to individuals who did not undergo surgery (n=3,882) using propensity scores.”</p> <p>Page 6: “Follow-up started on the day of surgery for those with bariatric surgery, and for the comparison group who did not undergo bariatric surgery, on the surgery date</p>

		of their matched case. Patient records were censored at the earliest of: AKI, death, leaving the practice, latest data collection from current practice, or end of linkage period to the HES database.”
Participants	6	<p>(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</p> <p>Page 6: “Patients with bariatric surgery were identified using Read codes for surgery in the CPRD database (S1 Appendix) and were included in the study if they had been registered in the CPRD <math>\geq 12</math> months prior to the intervention. We excluded those with a record of prior bariatric surgery reversal.</p> <p>For the comparison group, the inclusion criteria were to have at least one BMI measurement <math>\geq 40</math> kg/m<sup>2</sup>, <math>\geq 12</math> months of follow-up prior to the index date in the database, and no prior record of bariatric surgery or bariatric surgery reversal.”</p> <p>Page 5: “The CPRD database contains anonymised, routinely collected data on approximately 10 million patients in participating primary care practices in the UK, including demographic characteristics, current and previous diagnoses, prescribing, test results, and lifestyle factors. Diagnoses, signs, and symptoms are recorded using Read codes [...]. The HES database contains patient data from hospital admissions to English hospitals within the National Health Service “</p>
		(b) For matched studies, give matching criteria and number of exposed and unexposed
		<p>Page 6: “Study population matching and the propensity score incorporated information on age, sex, calendar period, history of T2DM, hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, other atheroma, use of insulin, use of oral antidiabetic medication, use of statins, smoking status, and alcohol consumption.”</p> <p>“The study sample was restricted to eligible patients registered at practices linked to the HES database and information on AKI events was obtained, resulting in a final cohort comprising 2,643 patients who underwent bariatric surgery, and 2,595 patients who did not.”</p>
Variables	7	<p>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</p> <p>Page 6/7: “AKI episodes were obtained from the HES database using ICD-10 codes: N17.0 (“Acute kidney failure with tubular necrosis”), N17.1 (“Acute renal failure with acute cortical necrosis”), N17.2 (“Acute renal failure with medullary necrosis”), N17.8 (“Other acute renal failure”), N17.9 (“Acute kidney failure, unspecified”), and N19 (“Unspecified kidney failure”). In this cohort, events coded with N17.1, N17.2, and N17.8 were not found. AKI events that occurred before the start of follow-up were recorded as a binary variable “history of AKI”, while AKI events occurring during follow-up were used to analyse AKI incidence.</p> <p>Recorded serum creatinine values from the CPRD database were not routinely standardised with isotope-dilution mass spectrometry before 2013. Thus, we assumed all measurements to be unstandardized and multiplied the creatinine measures with the factor 0.95 before calculating the estimated glomerular filtration rate (eGFR) using the “Chronic Kidney Disease Epidemiology Collaboration” (CKD-EPI) equation.</p>

Ethnicity was not considered in the eGFR calculation due to incomplete recording in the database and the low proportion of Afro-Caribbean people in the population. CKD stages were defined according to eGFR values in ml/min/1.73m<sup>2</sup> according to current guidelines: eGFR ≥60 = no known CKD; eGFR 45-59 = stage 3a; eGFR 30-44 = stage 3b; eGFR 15-29 = stage 4; eGFR <15 = stage 5. Baseline CKD status was derived from eGFR measurements in the year prior to start of follow-up by: 1) taking the last two measurements before the index date ≥90 days apart – with the higher eGFR value corresponding to the CKD baseline status, or 2) taking the most recent serum creatinine result if only one suitable test result was available. Since serum creatinine is more likely to be tested in the acutely unwell or in people who are routinely monitored as part of incentivised programs (e.g. people with diabetes), patients without measurements of CKD baseline status were assumed to have no CKD and were analysed as such.”

Page 6: “Study population matching and the propensity score incorporated information on age, sex, calendar period, history of T2DM, hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, other atheroma, use of insulin, use of oral antidiabetic medication, use of statins, smoking status, and alcohol consumption.”

Page 8: “When the cohort was initially constructed, propensity score matching was used to deal with confounding. This study uses a subset of this cohort since patients from practices without linkage between the CPRD and HES databases had to be excluded (as AKI was assessed using hospital admission data). To identify variables for the multivariable model, potential confounders that were not deemed to be on the causal pathway were added individually to the univariable model. If the addition changed the effect estimate ≥10% these variables were included in the multivariable model. Consequently, history of AKI, history of taking oral antidiabetics, and BMI at baseline were included (S2 Appendix). In addition, age at baseline, sex, calendar period (1997-2005, 2006-2010, 2011-2015), and CKD status at baseline were selected a priori as forced variables.”

Page 8: “In order to separate short-term effects of the surgery from potential long-term effects, we analysed the association separately for: a) events within the first 30 days, and b) events after 30 days.”

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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
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Page 5: “The CPRD database contains anonymised, routinely collected data on approximately 10 million patients in participating primary care practices in the UK, including demographic characteristics, current and previous diagnoses, prescribing, test results, and lifestyle factors. Diagnoses, signs, and symptoms are recorded using Read codes [...] The HES database contains patient data from hospital admissions to English hospitals within the National Health Service. For each hospital admission, the diagnoses are recorded using standardised codes of the International Classification of Diseases, Tenth Revision (ICD-10). Data from 70% of CPRD practices in England has been linked at patient level with HES admission data thus allowing the combined analysis of data from primary and acute hospital care for a subset of patients.”

Page 5: “Patients with bariatric surgery were identified using Read codes for surgery in the CPRD database (S1 Appendix) and were included in the study if they had been

registered in the CPRD  $\geq 12$  months prior to the intervention. We excluded those with a record of prior bariatric surgery reversal.”

Page 6/7: “AKI episodes were obtained from the HES database using ICD-10 codes: N17.0 (“Acute kidney failure with tubular necrosis”), N17.1 (“Acute renal failure with acute cortical necrosis”), N17.2 (“Acute renal failure with medullary necrosis”), N17.8 (“Other acute renal failure”), N17.9 (“Acute kidney failure, unspecified”), and N19 (“Unspecified kidney failure”).”

Bias	9	Describe any efforts to address potential sources of bias
		Page 9: “The 5% bands of patients with the highest and lowest propensity scores were excluded from the primary analysis (“trimming”) since these contain patients that are treated in stark contrast to their health status, potentially causing bias.”
Study size	10	Explain how the study size was arrived at
		Pages 5/6: “A detailed description of how the cohort was constructed is described elsewhere. In brief, records of patients who underwent bariatric surgery (n=3,882) between 1997 and 2015 were matched to individuals who did not undergo surgery (n=3,882) using propensity scores.” [...] “The study sample was restricted to eligible patients registered at practices linked to the HES database and information on AKI events was obtained, resulting in a final cohort comprising 2,643 patients who underwent bariatric surgery, and 2,595 patients who did not.”
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
		Page 7: “Recorded serum creatinine values from the CPRD database were not routinely standardised with isotope-dilution mass spectrometry before 2013. Thus, we assumed all measurements to be unstandardized and multiplied the creatinine measures with the factor 0.95 before calculating the estimated glomerular filtration rate (eGFR) using the “Chronic Kidney Disease Epidemiology Collaboration” (CKD-EPI) equation. Ethnicity was not considered in the eGFR calculation due to incomplete recording in the database and the low proportion of Afro-Caribbean people in the population. CKD stages were defined according to eGFR values in ml/min/1.73m <sup>2</sup> according to current guidelines: eGFR $\geq 60$ = no known CKD; eGFR 45-59 = stage 3a; eGFR 30-44 = stage 3b; eGFR 15-29 = stage 4; eGFR $< 15$ = stage 5. Baseline CKD status was derived from eGFR measurements in the year prior to start of follow-up by: 1) taking the last two measurements before the index date $\geq 90$ days apart – with the higher eGFR value corresponding to the CKD baseline status, or 2) taking the most recent serum creatinine result if only one suitable test result was available. Since serum creatinine is more likely to be tested in the acutely unwell or in people who are routinely monitored as part of incentivised programs (e.g. people with diabetes), patients without measurements of CKD baseline status were assumed to have no CKD and were analysed as such.”
		Page 8: “In addition, age at baseline, sex, calendar period (1997-2005, 2006-2010, 2011-2015), and CKD status at baseline were selected a priori as forced variables.”
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		Page 8/9: “The association between bariatric surgery and AKI was analysed using a Poisson regression model with a time to first event analysis. P-values were calculated

1 using Wald tests. In order to separate short-term effects of the surgery from potential  
 2 long-term effects, we analysed the association separately for: a) events within the first  
 3 30 days, and b) events after 30 days. When the cohort was initially constructed,  
 4 propensity score matching was used to deal with confounding. This study uses a  
 5 subset of this cohort since patients from practices without linkage between the CPRD  
 6 and HES databases had to be excluded (as AKI was assessed using hospital admission  
 7 data). To identify variables for the multivariable model, potential confounders that  
 8 were not deemed to be on the causal pathway were added individually to the  
 9 univariable model. If the addition changed the effect estimate  $\geq 10\%$  these variables  
 10 were included in the multivariable model. Consequently, history of AKI, history of  
 11 taking oral antidiabetics, and BMI at baseline were included (S2 Appendix). In  
 12 addition, age at baseline, sex, calendar period (1997-2005, 2006-2010, 2011-2015),  
 13 and CKD status at baseline were selected a priori as forced variables. For models with  
 14  $< 40$  outcomes, only age and sex were included in the multivariable model due to data  
 15 sparsity.

16 The 5% bands of patients with the highest and lowest propensity scores were excluded  
 17 from the primary analysis (“trimming”) since these contain patients that are treated in  
 18 stark contrast to their health status, potentially causing bias.

19 Heterogeneity of effect estimates between the calendar periods was tested with a  
 20 Likelihood Ratio Test.

21 The analysis was performed for all patients with bariatric surgery and also further  
 22 stratified by type of surgery. Patients with stage 5 CKD (baseline eGFR  $< 15$   
 23 ml/min/1.73m<sup>2</sup>) were excluded from the analyses since this constitutes end-stage  
 24 renal failure (ESRD). In addition, patients with missing data in  $\geq 1$  variable of the  
 25 multivariable model were excluded from both uni- and multivariable analyses.”

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26 (b) Describe any methods used to examine subgroups and interactions

27 page 8: “In order to separate short-term effects of the surgery from potential long-term  
 28 effects, we analysed the association separately for: a) events within the first 30 days,  
 29 and b) events after 30 days.”

30 page 9: “Heterogeneity of effect estimates between the calendar periods was tested  
 31 with a Likelihood Ratio Test.”

32 Page 9: “The analysis was performed for all patients with bariatric surgery and also  
 33 further stratified by type of surgery.”

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34 (c) Explain how missing data were addressed

35 page 7: “Since serum creatinine is more likely to be tested in the acutely unwell or in  
 36 people who are routinely monitored as part of incentivised programs (e.g. people with  
 37 diabetes), patients without measurements of CKD baseline status were assumed to  
 38 have no CKD and were analysed as such.”

39 page 9: “In addition, patients with missing data in  $\geq 1$  variable of the multivariable  
 40 model were excluded from both uni- and multivariable analyses.”

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41 (d) If applicable, explain how loss to follow-up was addressed

42 page 6: “Patient records were censored at the earliest of: AKI, death, leaving the  
 43 practice, latest data collection from current practice, or end of linkage period to the

HES database.”

(e) Describe any sensitivity analyses

Pages 9/10: “Several planned sensitivity analyses were undertaken: 1) To determine the net effect of the intervention we calculated the risk of AKI over the whole period of follow-up; 2) The prevalence of decreased kidney function in the CPRD database was similar to that in a nationally representative kidney disease registry indicating that patients with missing eGFR measurements are unlikely to have CKD. To identify potential differences in the effect between patients with known and unknown eGFR measurements, we restricted the analysis to a) patients known to have no CKD at baseline (baseline eGFR  $\geq 60$  ml/min/1.73m<sup>2</sup>), b) patients without known CKD at baseline (as above but including patients with missing creatinine values at baseline and assuming these individuals to have no CKD), and c) patients with known CKD at baseline.; 3) Moreover, to investigate the effect in a group of particular interest which is under more scrutiny for measuring kidney function we restricted the analysis to patients with: a) T2DM, and b) a history of taking insulin; 4) To avoid misclassification of low eGFR values as AKI we excluded patients with stage 4 CKD at baseline; 5) We restricted the analysis to ICD-10 codes N17.0 and N17.9, which have a high positive predictive value for AKI; 6) We increased the immediate post-surgery time span from 30 to 60 days; and 7) We included people with extreme propensity scores.”

## 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  see S3 Appendix  (b) Give reasons for non-participation at each stage  not applicable  (c) Consider use of a flow diagram  see S3 Appendix
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders  page 12: see Table 1  (b) Indicate number of participants with missing data for each variable of interest  page 12: see Table 1  (c) Summarise follow-up time (eg, average and total amount)  page 12: see Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time  page 12: see Table 1
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



1		adjusted for and why they were included
2		
3		page 13: see Table 2
4		(b) Report category boundaries when continuous variables were categorized
5		
6		page 12: see Table 1
7		
8		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
9		meaningful time period
10		
11		not applicable
12		
13	Other analyses	17 Report other analyses done—eg analyses of subgroups and interactions, and
14		sensitivity analyses
15		
16		Page 13: see table 2
17		see S4 Appendix
18		
19	<b>Discussion</b>	
20	Key results	18 Summarise key results with reference to study objectives
21		
22		Page 15: “In this study using prospectively recorded routine healthcare data from a
23		representative sample in the UK, bariatric surgery was associated with a potentially
24		increased risk of AKI within the first 30 days after surgery (5 events in patients with
25		bariatric surgery, no events in control patients) but a strongly protective association
26		thereafter (adjusted RR = 0.37, 95% CI 0.23, 0.61). The association was consistent
27		across subgroups and sensitivity analyses. To the best of our knowledge, this is the
28		first study to describe long-term effects of bariatric surgery on AKI.”
29		
30		
31	Limitations	19 Discuss limitations of the study, taking into account sources of potential bias or
32		imprecision. Discuss both direction and magnitude of any potential bias
33		
34		Pages 15-18: “Some limitations need to be considered. Even though the data is taken
35		from a representative sample of the UK population, the baseline data indicate that
36		patients who undergo bariatric surgery are mostly female, of middle age, and with a
37		history of T2DM. While the results were adjusted for age and sex they might not be
38		applicable for other groups suffering from obesity like adolescents. Linkage between
39		the CPRD and HES databases was restricted to England. However, there is no cogent
40		reason why the results should not be applicable to regions with similar healthcare
41		systems, both in the UK and internationally. We had insufficient data to determine
42		whether the association with AKI varied between different types of bariatric surgery;
43		we found a protective effect for gastric band but results were inconclusive for sleeve
44		gastrectomy and gastric bypass.
45		Any misclassification of diagnostic codes is likely non-differential between the
46		bariatric surgery patients and the matched comparison group and would bias the effect
47		towards the null value. Another problem of primary care data is that not every patient
48		is routinely checked for their kidney function, as incentives of testing apply primarily
49		for those at risk of kidney disease due to diabetes and hypertension. The study relied
50		on AKI events recorded in HES as part of a hospital admission and over time, the
51		awareness of the importance of AKI has likely changed resulting in secular changes in
52		recording of AKI ; analyses have adjusted for calendar period to account for this.
53		Future studies with hospital creatinine data should compare the AKI severity between
54		the groups to investigate this issue. In general, AKI diagnosed during hospitalisation
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60		

is likely to represent more serious AKI events, though we would argue these are the most clinically relevant outcomes. Moreover, a patient who experienced a previous AKI episode might be under more scrutiny for detection of future episodes. Since more patients in the bariatric surgery group had a history of AKI they might have a higher chance of detection of an AKI episode during follow-up. This would bias the estimate towards the null value and could indicate that the association we report is an under-estimate.

In addition, CKD status at baseline was missing in almost half of the patient population. However, a recent study indicated that the prevalence of CKD in the CPRD database was comparable to that found in nationally representative registry studies. This indicates that patients without eGFR-measurements at baseline are unlikely to have CKD. In addition, sensitivity analyses investigating the effect in patients with known or unknown CKD status at baseline yielded comparable results. Since access to bariatric surgery is restricted within the UK healthcare system, some patients might have funded their operation privately, resulting in selection bias. In a recent analysis about 40% of bariatric surgery operations in the UK were privately funded. Thus, the intervention group might have a higher socioeconomic status than the non-exposed group, in which similar patients would not be able to afford surgery. Since the socioeconomic background is an important determinant of health outcomes and was an unmeasured potential confounder not considered in the matching process, this could have led to more positive health outcomes in the intervention group irrespective of surgery and to an overestimation of the effect. In this study setting it was not possible to determine which patients had privately funded surgery. Even though most baseline variables were evenly distributed due to the matching process this does not guarantee that unmeasured variables are evenly distributed as well, which can constitute residual confounding. Incorrect, imprecise, or missing measurements of covariates could also have led to residual confounding. For the multivariable model, adjusting for history of AKI led to the strongest change of the effect estimate. AKI events are likely under-recorded in the HES database, for reasons described above, and thus residual confounding is possible. Since adjusting for AKI history led to a stronger effect estimate, the protective effect we report here may be an underestimate if AKI history is missing to the same degree in surgery and non-surgery patients.“

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
<p>Page 18: “This study adds to the evidence of long term effects of bariatric surgery, and appears to be the first study to quantify a long-term beneficial effect on AKI. Future studies with higher patient numbers may be able to determine differences in effect between types of surgery, investigate the effect in patients with CKD, and elucidate mechanisms of the association between bariatric surgery and AKI.”</p>		
Generalisability	21	Discuss the generalisability (external validity) of the study results
<p>Page 15/16: “Even though the data is taken from a representative sample of the UK population, the baseline data indicate that patients who undergo bariatric surgery are mostly female, of middle age, and with a history of T2DM. While the results were adjusted for age and sex they might not be applicable for other groups suffering from obesity like adolescents. Linkage between the CPRD and HES databases was restricted to England. However, there is no cogent reason why the results should not</p>		

be applicable to regions with similar healthcare systems, both in the UK and internationally.”

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#### Other information

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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
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\*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>.