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Original Article

Glycated haemoglobin and the risk of postoperative complications in people without diabetes: a prospective population-based study in UK Biobank

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Summary
The aim of our study was to clarify the association between glycated haemoglobin (HbA_{1c}) and postoperative outcomes in people without an existing diagnosis of diabetes. Half a million adults were recruited into the UK Biobank prospective cohort study between March 2006 and October 2010. We divided participants into three groups: no diagnosis of diabetes and $HbA_{1c} < 42$ mmol.mol^{-1}; no diagnosis of diabetes and elevated HbA_{1c} (≥ 42 mmol.mol^{-1} with no upper limit); and prevalent diabetes (regardless of HbA_{1c} concentration) at recruitment. We followed up participants by linkage with routinely collected hospital data to determine any surgical procedures undertaken after recruitment and the associated postoperative outcomes. Our main outcome measure was a composite primary outcome of 30-day major postoperative complications and 90-day all-cause mortality. We used logistic regression to estimate the odds of the primary outcome by group. We limited analyses to those who underwent surgery within one year of recruitment (n = 26,653). In a combined effects logistic regression model, participants not known to have diabetes with $HbA_{1c} \geq 42$ mmol.mol^{-1} had increased odds of the primary outcome (OR [95% CI] 1.43 [1.02–2.02]; p = 0.04), when compared with those without diabetes and $HbA_{1c} < 42$ mmol.mol^{-1}. This effect was attenuated and no longer statistically significant in a direct effects model with adjustment for hyperglycaemia-related comorbidity (OR [95% CI] 1.37 [0.97–1.93]; p = 0.07). Elevated pre-operative HbA_{1c} in people without diabetes may be associated with an increased risk of complications, but the association is likely confounded by end-organ comorbidity. In contrast to previous evidence, our findings suggest that to prevent adverse postoperative outcomes, optimisation of pre-existing morbidity should take precedence over reducing HbA_{1c} in people without diabetes.

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Introduction

The prevalence of diabetes in the UK is estimated to be 7% in the adult population [1]. People with diabetes undergoing surgery are at increased risk of postoperative complications, with roughly double the risk of mortality compared with people without the condition [2, 3]. Of concern is the potentially large number of surgical patients who have pre-diabetes (also known as non-diabetic hyperglycaemia) or undiagnosed, and therefore untreated, diabetes. Pre-diabetes is defined by a glycated haemoglobin

(HbA_{1c}) of 42–47 mmol.mol^{-1} (6.0–6.4%) and undiagnosed diabetes by HbA_{1c} of ≥48 mmol.mol^{-1} (6.5%) without a formal diagnosis of diabetes [4]. Public Health England has estimated the prevalence of pre-diabetes in the general population to be 10.7% and undiagnosed diabetes to be 2.3% [5].

Poor pre-operative glycaemic control, measured using either serum glucose or a marker of plasma glucose (HbA_{1c}) over the preceding three months has been shown to be associated with adverse postoperative outcomes including: higher rates of infection; acute renal failure; myocardial infarction; increased length of stay; and higher mortality [2]. The risk of complications is particularly high in those not previously known to have diabetes, with observational data suggesting that morbidity risk is doubled in such patients [3] and mortality increased by a factor of up to 12 when compared with those without diabetes who maintain normal glucose concentrations [2]. Such work potentially highlights an important at-risk group in whom improving glycaemic control could improve postoperative outcomes. However, there are significant limitations to these previous data due to insufficient sample sizes and the potential effects of confounding due to chronic hyperglycaemia-related comorbidity. This may explain why short-term correction of blood glucose in the peri-operative period has not been consistently equated with reduced postoperative complications in randomised controlled trials [6]. As such, the National Institute for Health and Care Excellence (NICE) does not currently recommend measuring HbA_{1c} in those without diabetes before surgery [7].

To clarify the association between HbA_{1c} and postoperative outcomes in people without diabetes across all major surgical specialties, we sought to use a large prospective cohort study design with adequate control of potential confounding factors.

Methods

Our study is reported in accordance with the STROBE statement [8]. Over 500,000 participants aged between 37 and 73 y were enrolled in the UK Biobank from March 2006 to October 2010 from 22 assessment centres across England, Wales and Scotland. Baseline assessments consisted of a self-administered touchscreen questionnaire followed by an interview, physical measurements and biological sample collection [9].

Primary characteristics; socio-economic factors; self-reported medical conditions; risk-factors (including smoking, alcohol consumption and levels of physical activity); physical measures (including weight, height and waist circumference); and biological samples were obtained and measured using standardised methods. Glycated haemoglobin was measured by high-performance liquid chromatography analysis on a Bio-Rad VARIANT-2 Turbo (Bio-Rad Laboratories Ltd, Hertfordshire, UK) on 467,898 participants and reported in mmol.mol^{-1} [10]. For this study, we obtained the data by application to UK Biobank, with access granted on 10 August 2020. The UK Biobank is linked to national databases for routinely collected hospital data: Hospital Episode Statistics for England (HES); Scottish Morbidity Record (SMR); and Patient Episode Database for Wales (PEDW). Routinely collected hospital data captured procedures and surgical operations using Classification of Interventions and Procedures version 4 (OPCS-4) and diagnoses made during hospital attendances using International Classification of Diseases, version 10, 2016 (ICD-10).

We defined prevalent diabetes as either self-reported or a hospital admission diagnosis of diabetes using ICD-9, '250' and ICD-10, 'E10 to E14' codes, with a diagnosis date before the assessment centre attendance date (regardless of baseline HbA_{1c}). Participants with normal HbA_{1c} were identified by a baseline HbA_{1c} of <42 mmol.mol^{-1} without prevalent diabetes. Participants with elevated HbA_{1c} (≥ 42 mmol.mol^{-1}) included those with pre-diabetes (HbA_{1c} ≥ 42 to 47 mmol.mol^{-1}) and undiagnosed diabetes (HbA_{1c} ≥ 48 mmol.mol^{-1}) [4]. Grouping of pre-diabetes and undiagnosed diabetes was necessary due to small numbers in the latter group (n = 181). We identified prevalent comorbidity using self-reported diagnoses at baseline and ICD-10 codes (online Supporting Information Table S1) based on the Charlson Comorbidity Index Definitions [11]. All surgical procedures which occurred within one year of the date of recruitment were included and grouped by specialty (online Supporting Information Appendix S1). Endoscopic, transluminal, percutaneous and endovascular procedures (apart from specific vascular procedures) were excluded, as were procedures mostly performed in a clinic setting. If participants had more than one procedure within one year of recruitment, a criterion was used to decide on the index procedure for study inclusion (online Supporting Information Table S2). Participants who underwent surgery were followed from baseline to 90 days after the date of their surgical operation, unless the following occurred first: death; a postoperative complication; or the date of last data linkage with hospital inpatient data (31 March 2017 for England, 31 October 2016 for Scotland and 29 February 2016 for Wales).

We defined a major postoperative complication as follows: cardiac (arrhythmia, myocardial infarction,

congestive cardiac failure and cardiac arrest); pulmonary (pneumonia, respiratory arrest and acute respiratory disease syndrome); neurological (stroke, transient ischaemic attack); thrombo-embolic (deep vein thrombosis and pulmonary embolism); renal (acute renal failure); sepsis; and shock/systemic inflammatory response syndrome/ disseminated intravascular coagulation. All complications were identified from routinely collected hospital data using ICD-10 codes (online Supporting Information Appendix Table S3) and included if they occurred within 30 days after the date of surgery. Mortality was defined as all-cause mortality occurring within 90 days of the date of surgery and identified via linkage to death registries [12]. Our primary outcome measure was a composite of 30-day major postoperative complications and 90-day mortality.

As this was a non-interventional observational study, sample size was not predetermined, but we aimed to include all eligible participants who had complete case data. We undertook the primary analyses on participants who underwent major surgery within one year of recruitment. Baseline characteristics were described after stratification by disease status.

To examine the associations between HbA_{1c} and postoperative complications, we divided participants into three groups based on diabetes status and baseline HbA_{1c} as follows: no diagnosis of diabetes and HbA_{1c} < 42 $mmol.mol^{-1}$, henceforth referred to as the 'reference group'; no diagnosis of diabetes and elevated $HbA_{1c} \geq 42$ $mmol.mol^{-1}$ (with no upper limit), referred to as the 'elevated HbA_{1c}' group; and prevalent diabetes (regardless of HbA_{1c} concentration), referred to as the 'prevalent diabetes' group. We used logistic regression models to estimate the odds of the composite primary outcome by group, using the reference group as the comparator. These models were adjusted for the following variables: age (continuous); sex (binary); BMI (continuous); ethnicity (white, mixed, Asian, Black, other); alcohol frequency (daily, 3–4 times/week, 1–2 times/week, 1–3 times/month, rarely and never); smoking status (never, former and current); social deprivation (Townsend deprivation index (levels 1–5)); levels of physical activity (International Physical Activity Index (low, moderate and high)); and comorbidity burden (myocardial infarction, congestive cardiac failure, peripheral vascular disease, cancer, cerebral vascular disease and liver disease (binary)), taking into account the location of assessment centre. We calculated an age- and sex-adjusted model as well as total effects and direct effects models based on a directed acyclic graph [13] (Fig. 1), which was used to estimate the plausible causal pathway. All analyses were done using STATA version 16.0 for Windows (StataCorp LLC, College Station, TX, USA).

Results

Between 13 March 2006 and 1 October 2010, 502,493 participants were enrolled in UK Biobank, of whom 26,653 had a full set of variables of interest, underwent surgery within one year of recruitment and had full follow-up data (online Supporting Information Figure S1). Table 1 presents baseline characteristics of participants stratified by HbA_{1c} and disease status. Prevalent diabetes was present in 2093 participants (7.8%). In total, 1305 (4.9%) had an elevated HbA_{1c} ($\geq$ 42 $mmol.mol^{-1}$). Within this elevated HbA_{1c} group, 1124 (4.2%) had pre-diabetes or non-diabetic hyperglycaemia (HbA_{1c} of 42–47 $mmol.mol^{-1}$) and 181 (0.7%) had undiagnosed diabetes ($HbA_{1c} \geq 48$ $mmol.mol^{-1}$).

Comparing the group with elevated HbA_{1c} with the reference group, participants were older (mean (SD) 61 (7) vs. 58 (8) y), with a higher proportion of males (45% vs. 41%) and higher BMI (mean (SD) 30.9 (5.7) vs. 27.6 (4.7) $kg.m^{-2}$). On comparing measured biomarkers, high-density lipoprotein cholesterol concentrations were lower (median (IQR [range]) 1.2 (1.1–1.5 [0.6–2.7]) vs. 1.4 (1.2–1.7 [0.5–4.0]) $mmol.l^{-1}$), whereas triglyceride concentrations (median (IQR [range]) 2.0 (1.4–2.7 [0.5–9.6]) vs. 1.5 (1.1–2.2 [0.3–10.8]) $mmol.l^{-1}$); total white cell count (median (IQR [range]) 7.5 (6.3–8.9 [1.3–46.3]) vs. 6.7 (5.7–7.9 [1.2–104.9]) x $10^9.l^{-1}$; and C-reactive protein levels (median (IQR [range]) 3.1 (1.4–6.2 [0.2–77.1]) vs. 1.5 (0.7–3.2 [0.1–74.8]) $mg.l^{-1}$), were higher. On further comparison with the reference group, the elevated HbA_{1c} group contained a greater proportion of current smokers (16% vs. 11%), a greater proportion with low levels of physical activity (19% vs. 16%), total household income < £18,000 (32% vs. 23%) and a lesser number of participants with degree level education (26% vs. 38%). Finally, comorbid disease was more prevalent, with approximately double the number of individuals with prevalent peripheral vascular (2.5% vs. 1.3%), cerebrovascular (5.7% vs. 2.6%) or renal disease (1.5% vs. 0.8%) and triple the number with myocardial infarction (8.2% vs. 2.6%) or congestive cardiac failure (1.8% vs. 0.6%).

A total of 6653 participants underwent surgery across 12 surgical specialties within one year of recruitment (Table 2). The most common surgical operations were orthopaedic and plastic (n = 9626), lower gastro-intestinal (n = 3395), ophthalmic (n = 3265) and gynaecological (n = 2069). A full list of the surgical operations is included as online Supporting Information Appendix S1.

Across all surgical specialties (Table 2), 30-day major postoperative morbidity occurred in the reference group in

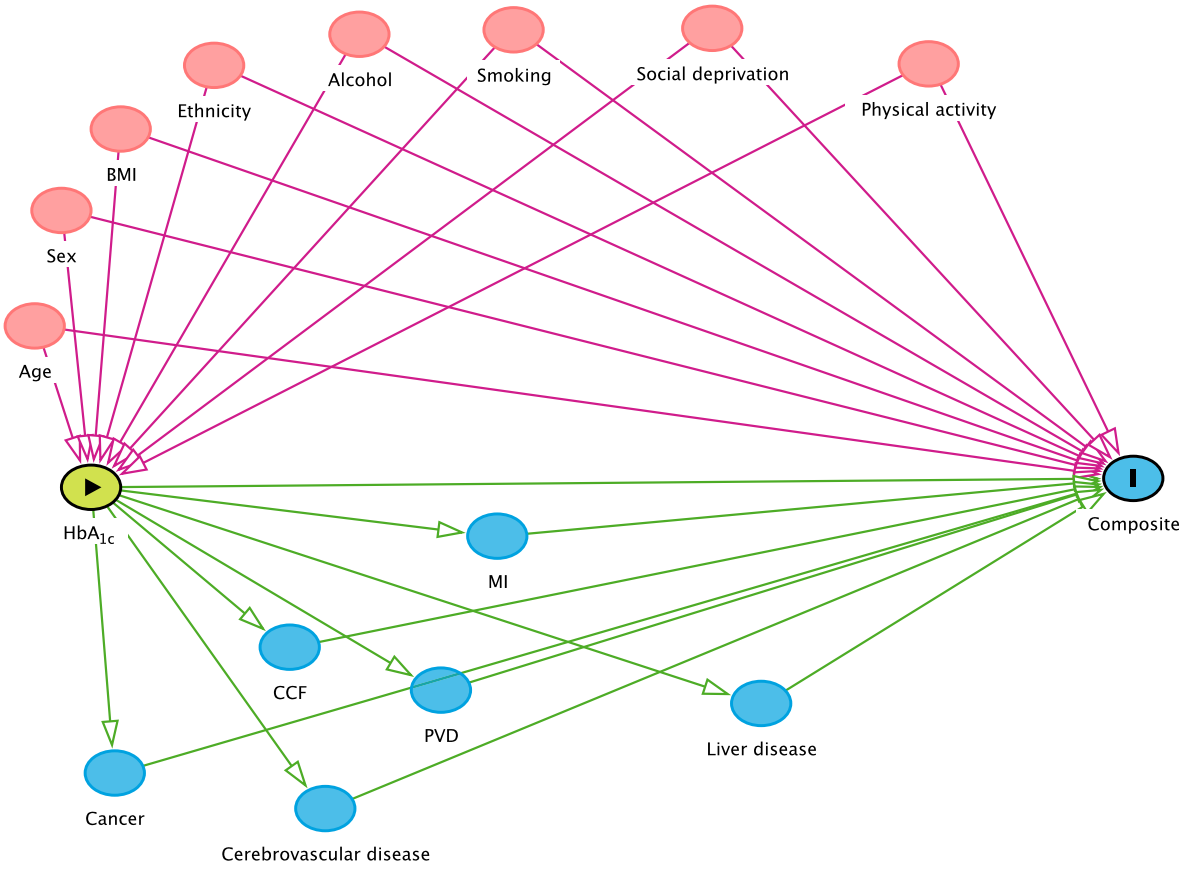

Figure 1 Directed acyclic graph representing the casual relationship between HbA_{1c} and postoperative complications. HbA_{1c}, glycated haemoglobin; MI, myocardial infarction; CCF, congestive cardiac disease; PVD, peripheral vascular disease; and Composite, 30-day major postoperative complication and 90-day all-cause mortality. The green line from HbA_{1c} to the composite outcome represents the direct casual pathway of HbA_{1c} (direct effect). The blue risk factors represent mediators through which HbA_{1c} also acts. If, after adjustment of mediators, an association is found between HbA_{1c} and the composite outcome, this would suggest that HbA_{1c} is not dependent on the mediators, that is, has a direct effect on the composite outcome. A direct effect would support optimisation of HbA_{1c} before surgery. No direct effect would support optimisation of the mediators before surgery.

2.6% of participants, 90-day all-cause mortality in 0.3% and the composite outcome measure (both morbidity and mortality) in 2.9%. In the elevated HbA_{1c} group (vs. reference group), morbidity and mortality increased by a factor of 1.6 and 2.0, respectively. In those with prevalent diabetes (vs. reference group), morbidity and mortality increased by a factor of 2.5 and 3.0, respectively. Within individual specialties, the highest differences in these outcome rates by group category occurred in upper gastro-intestinal surgery, orthopaedics, lower gastro-intestinal surgery and head and neck surgery.

Table 3 presents the effect sizes for the estimates of three logistic regression models using participants without diabetes and $HbA_{1c} < 42$ mmol.mol^{-1} as the reference group. In an age- and sex-adjusted model, those with elevated HbA_{1c} (without diabetes with $HbA_{1c} \geq 42$ mmol.mol^{-1}) had increased odds of the primary composite outcome (OR [95% CI] 1.49 [1.10–2.01]; p = 0.01). When adjusting for risk-factors which were not assumed to lie along the causal pathway (age; sex; BMI; ethnicity; alcohol; smoking; social deprivation; and physical activity levels (Fig. 1)), the effect size was only moderately attenuated (OR [95% CI] 1.43 [1.02–2.02]; p = 0.04); this estimate reflects the total effects of elevated HbA_{1c} on postoperative risk. In a direct effects model with adjustment for comorbid factors presumed to lie along the causal pathway (myocardial infarction; congestive cardiac failure; peripheral vascular disease; cerebrovascular disease; cancer; and liver disease), the effect size still suggested an association between elevated HbA_{1c} and adverse outcomes but was no longer statistically significant (OR [95% CI] 1.37 [0.97–1.93]; p = 0.07). Such an adjusted estimate suggests that elevated pre-operative HbA_{1c} in people without diabetes is associated with an increased risk of adverse

Table 1 Baseline characteristics of study participants who underwent surgery within one year of recruitment. Stratified according to baseline HbA_{1c} and formal diagnosis of diabetes. Values are number (proportion), mean (SD) or median (IQR [range]).

	No diagnosis of diabetes		**Prevalent diabetes**
	HbA_{1c} < 42 mmol.mol^{-1} n = 23,255 (87.3%)	**HbA_{1c} ≥ 42 mmol.mol^{-1} n = 1305 (4.9%)**	**n = 2093 (7.8%)**
Male sex	9490 (40.8%)	586 (44.9%)	1208 (57.7%)
Age at recruitment; y	58 (8)	61 (7)	61 (7)
HbA_{1c}; mmol.mol^{-1}	35.1 (32.8–37.4 [15.3–41.9])	43.8 (42.7–45.8 [42.0–122.3])	49.5 (42.4–59.9 [21.2–132.2])
Non-fasted serum glucose; mmol.l^{-1}	4.9 (4.6–5.3 [2.2–10.8])	5.4 (4.9–6.0 [2.9–24.0])	6.4 (5.2–8.8 [2.1–30.1])
Cholesterol; mmol.l^{-1}	5.7 (5.0–6.5 [2.0–12.5])	5.5 (4.7–6.4 [2.3–10.0])	4.4 (3.8–5.1 [1.8–11.4])
HDL cholesterol; mmol.l^{-1}	1.4 (1.2–1.7 [0.5–4.0])	1.2 (1.1–1.5 [0.6–2.7])	1.2 (1.0–1.4 [0.3–3.7])
LDL cholesterol; mmol.l^{-1}	3.5 (3.0–4.1 [1.0–7.4])	3.5 (2.8–4.1 [1.2–6.8])	2.6 (2.2–3.1 [0.8–7.1])
Triglycerides; mmol.l^{-1}	1.5 (1.1–2.2 [0.3–10.8])	2.0 (1.4–2.7 [0.5–9.6])	1.8 (1.3–2.6 [0.3–10.5])
White cell count; 10^9.l^{-1}	6.7 (5.7–7.9 [1.2–104.9])	7.5 (6.3–8.9 [1.3–46.3])	7.6 (6.3–8.9 [2.4–59.4])
C-reactive protein; mg.l^{-1}	1.5 (0.7–3.2 [0.1–74.8])	3.1 (1.4–6.2 [0.2–77.1])	2.2 (1.1–4.7 [0.1–73.0])
Systolic blood pressure; mmHg	138 (126–153 [80–236])	143 (130–156 [94–210])	143 (131–156 [80–221])
BMI; kg.m^{-2}	27.6 (4.7)	30.9 (5.7)	31.8 (6.1)
Smoking status; current	2480 (10.7%)	211 (16.2%)	242 (11.6%)
Alcohol; daily/almost daily	4549 (19.6%)	184 (14.1%)	278 (13.3%)
IPAQ activity group; low level	3623 (15.6%)	250 (19.2%)	492 (23.5%)
College or university degree	8714 (37.5%)	340 (26.1%)	572 (27.3%)
Average household income (< £18 k)	5393 (23.2%)	411 (31.5%)	722 (34.5%)
Townsend deprivation index 5 (lowest)	2480 (10.7%)	211 (16.2%)	242 (11.6%)
Family history of diabetes	4683 (20.1%)	401 (30.7%)	919 (43.9%)
White ethnicity	22,222 (95.6%)	1141 (87.4%)	1826 (87.2%)
Asian ethnicity	304 (1.3%)	49 (3.8%)	134 (6.4%)
Comorbidities			
Myocardial infarction	601 (2.6%)	107 (8.2%)	211 (10.1%)
Congestive cardiac failure	146 (0.6%)	24 (1.8%)	74 (3.5%)
Peripheral vascular disease	291 (1.3%)	33 (2.5%)	94 (4.5%)
Cerebrovascular disease	609 (2.6%)	75 (5.7%)	134 (6.4%)
Renal disease	184 (0.8%)	19 (1.5%)	91 (4.3%)
COPD	1898 (8.2%)	187 (14.3%)	297 (14.2%)
Liver disease	279 (1.2%)	25 (1.9%)	67 (3.2%)
Cancer (previous or current)	1813 (7.8%)	117 (9.0%)	162 (7.7%)

HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IPAQ, international physical activity index; COPD, chronic obstructive pulmonary disease.

postoperative outcomes but the association may be confounded by end-organ comorbidity.

Those with prevalent diabetes had increased odds of the composite outcome in both a total effects (OR [95% CI] [1.53–2.54]; $p < 0.0001$) and a direct effects model (OR [95% CI] 1.79 [1.37–2.31]; $p < 0.0001$) when compared with the reference group.

Discussion

Our data confirms previous work suggesting a statistically significant causal relationship between prevalent diabetes and adverse postoperative outcomes. Our study also found an association between elevated HbA_{1c} and increased postoperative risk in people who are not known to have diabetes. However, the strength of this relationship was reduced and no longer significant after adjustment for comorbid disease. The findings of our study suggest that more focus should be given to pre-operative optimisation of both potential and present comorbidities in this population rather than short-term glycaemic optimisation.

Multiple previous observational studies, the vast majority of which were retrospective, have examined the association between HbA_{1c} and postoperative outcome

Table 2 Complication rates of study participants who underwent surgery within one year of recruitment by surgical specialty. Stratified according to baseline HbA_{1c} and formal diagnosis of diabetes. Values are number (proportion).

	No diagnosis of diabetes		
	HbA_{1c} < 42 mmol.mol^{-1}	**HbA_{1c} ≥ 42 mmol.mol^{-1}**	**Prevalent diabetes**
Upper gastro-intestinal (n = 1240)	1041 (84.0%)	74 (6.0%)	125 (10.1%)
30-day significant morbidity	50 (4.8%)	7 (9.5%)	15 (12.0%)
90-day all-cause mortality	8 (0.8%)	1 (1.4%)	3 (2.4%)
Composite outcome	56 (5.4%)	7 (9.5%)	17 (13.6%)
Lower gastro-intestinal (n = 3395)	3016 (88.8%)	163 (4.8%)	216 (6.4%)
30-day significant morbidity	106 (3.5%)	11 (6.7%)	19 (8.8%)
90-day all-cause mortality	22 (0.7%)	3 (1.8%)	4 (1.9%)
Composite outcome	119 (3.9%)	13 (8.0%)	21 (9.7%)
Cardiothoracic (n = 516)	401 (77.7%)	38 (7.4%)	77 (14.9%)
30-day significant morbidity	82 (20.4%)	10 (26.3%)	28 (36.4%)
90-day all-cause mortality	10 (2.5%)	2 (5.3%)	1 (1.3%)
Composite outcome	88 (21.9%)	10 (26.3%)	28 (36.4%)
Spinal (1090)	939 (86.1%)	74 (6.8%)	77 (7.1%)
30-day significant morbidity	19 (2.0%)	2 (2.7%)	2 (2.6%)
90-day all-cause mortality	8 (0.9%)	0	1 (1.3%)
Composite outcome	25 (2.7%)	2 (2.7%)	3 (3.9%)
Urology (1241)	1065 (85.8%)	58 (4.7%)	118 (9.5%)
30-day significant morbidity	35 (3.3%)	3 (5.2%)	10 (8.5%)
90-day all-cause mortality	5 (0.5%)	0	1 (0.8%)
Composite outcome	40 (3.8%)	3 (5.2%)	10 (8.5%)
Gynaecology (2069)	1890 (91.3%)	85 (4.1%)	94 (4.5%)
30-day significant morbidity	72 (3.8%)	1 (1.2%)	3 (3.2%)
90-day all-cause mortality	1 (0.1%)	0	0
Composite outcome	73 (3.9%)	1 (1.2%)	3 (3.2%)
Orthopaedics and plastic (9626)	8518 (88.5%)	447 (4.6%)	660 (6.9%)
30-day significant morbidity	98 (1.2%)	8 (1.8%)	21 (3.2%)
90-day all-cause mortality	7 (0.1%)	2 (0.4%)	2 (0.3%)
Composite outcome	104 (1.2%)	10 (2.2%)	22 (3.3%)
Vascular (570)	459 (80.5%)	34 (6.0%)	77 (13.5%)
30-day significant morbidity	46 (10.0%)	6 (17.7%)	13 (16.9%)
90-day all-cause mortality	7 (1.5%)	0	5 (6.5%)
Composite outcome	50 (10.9%)	6 (17.7%)	16 (20.8%)
Head and neck (1915)	1707 (81.9%)	87 (4.5%)	121 (6.3%)
30-day significant morbidity	33 (1.9%)	4 (4.6%)	8 (6.6%)
90-day all-cause mortality	1 (0.1%)	0	1 (0.8%)
Composite outcome	34 (2.0%)	4 (4.6%)	8 (6.6%)
Neurosurgery (417)	368 (88.8%)	13 (3.1%)	36 (8.6%)
30-day significant morbidity	36 (9.8%)	2 (15.4%)	2 (5.6%)
90-day all-cause mortality	9 (2.4%)	0	0
Composite outcome	40 (10.9%)	2 (15.4%)	2 (5.6%)
Breast (1309)	1188 (90.8%)	53 (4.0%)	68 (5.2%)
30-day significant morbidity	24 (2.0%)	0	0
90-day all-cause mortality	3 (0.3%)	0	0

(continued)

Table 2 (*continued*)

	No diagnosis of diabetes		
	HbA_{1c} < 42 mmol.mol^{-1}	**HbA_{1c} ≥ 42 mmol.mol^{-1}**	**Prevalent diabetes**
Composite outcome	26 (2.2%)	0	0
Ophthalmology (3265)	2663 (81.6%)	179 (5.5%)	423 (13.0%)
30-day significant morbidity	9 (0.3%)	0	12 (2.8%)
90-day all-cause mortality	2 (0.1%)	0	0
Composite outcome	11 (0.4%)	0	12 (2.8%)
All surgical specialties (26,653)	23,255 (87.3%)	1305 (4.9%)	2093 (7.9%)
30-day significant morbidity	610 (2.6%)	54 (4.1%)	133 (6.4%)
90-day all-cause mortality	83 (0.3%)	8 (0.6%)	18 (0.9%)
Composite outcome	666 (2.9%)	58 (4.4%)	142 (6.8%)

Table 3 Logistic regression analyses to estimate the odds of the composite primary outcome (major 30-day postoperative complications and 90-day mortality) by disease status for study participants who underwent surgery within one year of recruitment according to baseline HbA_{1c} and formal diagnosis of diabetes.

	Age- and sex-adjusted OR [95% CI]	**Adjusted for total effect OR [95% CI]**	**Adjusted for direct effect OR [95% CI]**
No diagnosis of diabetes HbA_{1c} < 42 mmol.mol^{-1}	reference	reference	reference
No diagnosis of diabetes HbA_{1c} ≥ 42 mmol.mol^{-1}	1.49 [1.10–2.01]; p = 0.01	1.43 [1.02–2.02]; p = 0.04	1.37 [0.97–1.93]; p = 0.07
Prevalent diabetes	2.21 [1.80–2.72]; p < 0.0001	2.00 [1.53–2.54]; p < 0.0001	1.79 [1.37–2.31]; p < 0.0001

Total effect adjustment: age; sex; BMI (continuous); ethnicity (white, mixed, Asian, Black, other); alcohol frequency (daily, 3–4 times/week, 1–2 times/week, 1–3 times/month, rarely and never); smoking status (never, former, current); Townsend deprivation index (1–5); International Physical Activity Index (low, moderate and high); and assessment centre location.
Direct affects adjustment = as per total effect model + comorbidity (myocardial infarction; congestive cardiac failure; peripheral vascular disease; cancer; cerebrovascular disease; and liver disease).

[14]. However, in the study analyses, authors have rarely divided subjects into those with and without diabetes. For example, of the seven observational studies in orthopaedic surgery published in the last decade that examined hyperglycaemia and postoperative outcome in people with and without diabetes, all analysed those with and without the condition together. These types of analyses are also present in all studies in head and neck [15], thoracic [16], hepatobiliary [17–19] and neurosurgery [20, 21] and in the majority of papers in cardiac [22–31], lower [32–34] and upper [34, 35] gastro-intestinal surgery. People with diabetes have increased risk of cardiovascular, renal, ophthalmic and neurological morbidities. Studies which stratify only by HbA_{1c} will likely report a confounded association by identifying individuals with diabetes (who will have higher serum HbA_{1c}) and therefore have a greater risk of poor postoperative outcomes.

Where studies do stratify by diabetes status, adequate control for comorbidity must be included in statistical models (if a direct causal association between peri-operative glycaemic control and risk is sought), yet this is frequently poorly done [36]. Such a causal association, if present, is enticing because tight glycaemic control in the peri-operative period would potentially reduce the risks of complications in surgical patients. However, a confounded association could mean that a focus on addressing known and unknown comorbid risks may be neglected.

The strengths of our study include a large prospective cohort design, inclusion of all surgical specialties, and adequate adjustment for potential confounding factors informed by a directed acyclic graph (Fig. 1). Our study has several important limitations. Measurement error may have occurred in the use of routinely collected hospital data. There are data quality concerns regarding routinely collected data, particularly for older data extracts. In 2001, a systematic review on the accuracy of data routinely collected in the UK estimated 84% accuracy for diagnostic codes [37]. However, the accuracy of clinical coding is improving year-on-year with a 2010 Audit Commission report for NHS England finding improvements in the

accuracy of coding for diagnoses and procedures from 84% in 2008 to 88.7% in 2010 [38]. A 2012 systematic review reported that following the introduction of Payment by Results in 2002, the accuracy of diagnoses improved from a median (IQR) of 73.8 (59.3–92.1)% (full range not reported in original data) to 96.0 (89.3–96.3)%; p = 0.02 [39]. Because recruitment into UK Biobank occurred between 2006 and 2010, we anticipated that measurement errors would be less problematic than data that go further back. We would also expect such errors to be non-differential and therefore lead to dilution of our effect sizes rather than false inflation.

Glycated haemoglobin reflects the average plasma glucose levels that the haemoglobin molecule has been exposed to over the preceding three months. In a pragmatic approach to increase power, we used HbA_{1c} measured within one year of surgery. In our dataset, the median time between date of surgery and baseline HbA_{1c} measurement was 6.3 (3.2–9.1 [0.1–11.9]) months. Of note, a total of 7336 participants within UK Biobank had a repeat centre assessment visit (data not used in our analyses) with HbA_{1c} measurements more than three months after baseline value, at a median of 5 (3.1–7.6 [3.0–26.9]) months. Mean HbA_{1c} at baseline was 35.7 $mmol.mol^{-1}$, rising to 36.6 $mmol.mol^{-1}$ at follow-up (mean difference of −0.8 $mmol.mol^{-1}$; R = 0.76). We would, therefore, expect our use of HbA_{1c} (within one year) to introduce dilution towards non-significance. Such measurement bias is a recognised limitation of prospective cohort studies, where variables are usually measured only at baseline and presumed to remain fixed throughout time. As we were only able to use HbA_{1c} within one year, our analyses were limited to patients operated on within one year from recruitment (between 2006 and 2010). We acknowledge that both disease detection and treatment may have changed since that time, limiting the generalisability of our findings.

Previous work has shown that people with diabetes are more likely to be referred for surgery than people without diabetes [40]. Our data also suggests that people with diabetes are more likely to have a surgical operation compared with the background population prevalence. It may well be that individuals with raised HbA_{1c} undergo a greater number of high-risk surgical procedures than people with normal glycaemic indices. To address this, we added surgical specialty as a variable in a further multiple regression model. Results showed only very modest attenuation of the effect sizes (online Supporting Information Table S4).

People with diabetes are at higher risk of adverse postoperative outcomes. In addition, having an HbA_{1c} concentration of ≥42 $mmol.mol^{-1}$ without a diagnosis of diabetes (measured up to one year before a surgical procedure) was associated with an increased risk of developing postoperative complications. Such people may be at increased risk due to underlying comorbidities, with HbA_{1c} acting as marker of this risk. Measurement of HbA_{1c} may aid peri-operative risk stratification. However, the optimisation of potential and diagnosed comorbid disease in the peri-operative period may be preferable. We suggest the wider use of pre-operative HbA_{1c} measurement to inform wider peri-operative care, particularly in those with risk-factors for developing diabetes.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. OPCS-4 operation codes.

Figure S1. Study flow diagram

Table S1. Prevalent comorbidity coding.

Table S2. Index procedure criteria.

Table S3. 30-day postoperative complication coding.

Table S4. Logistic regression analysis to estimate odds of primary composite outcome (major 30-day postoperative complications and 90-day mortality).

