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1. Title: The impact of preoperative glycated hemoglobin (HbA1c) on postoperative complications after elective major abdominal surgery: a meta-analysis

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The Impact of Preoperative Glycated Hemoglobin (HbA1c) on Postoperative Complications After
Elective Major Abdominal Surgery: A Meta-Analysis

Running title: HbA1c impact on major abdominal surgery

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Abstract

Background: Diabetes is a risk factor for postoperative complications. Prior meta-analyses have shown that elevated glycated hemoglobin (HbA1c) is associated with postoperative complications in various surgical populations. However, no meta-analysis has investigated this association in elective major abdominal surgery patients. This is the first meta-analysis to investigate the association between preoperative HbA1c and postoperative complications in this unique population.

Methods: PRISMA guidelines were adhered to. Six databases were searched up to 1st April 2020. Primary studies investigating the effect of HbA1c on postoperative complications in elective major abdominal surgery patients were included. Risk of bias and quality of evidence assessment of the studies were performed. Data was pooled using a random-effects model. Meta-regression was performed to evaluate the effect of different HbA1c cut-off values.

Results: 12 observational studies (25036 patients) were included. Most studies scored 'good' and 'moderate quality' using NOS and GRADE respectively. Patients with high HbA1c had a higher risk of anastomotic leaks (OR 2.80, 95%CI 1.63-4.83, $p<0.001$), wound infections (OR 1.21, 95%CI 1.08-1.36, $p=0.001$), major complications defined as Clavien-Dindo 3-5 (OR 2.16, 95%CI 1.54-3.01, $p<0.001$), and overall complications defined as Clavien-Dindo 1-5 (OR 2.12, 95%CI 1.48-3.04, $p<0.001$).

Conclusions: This meta-analysis shows that HbA1c 6-7% is associated with higher risks of anastomotic leaks, wound infections, major complications and overall postoperative complications. Guidelines currently using HbA1c thresholds $>7\%$ may therefore be conducting elective surgery on pre-optimised patients. A randomized controlled trial should be conducted to explore if this association is causative before policy changes are made.

Keywords: Diabetes Mellitus; Glycated Hemoglobin A; Postoperative Complications; Elective Surgical Procedures; General Surgery; Surgical Procedures, Operative.

Introduction

Diabetes mellitus is known to be a predisposing factor for postoperative complications such as infections, poor wound healing, anastomotic leaks, cardiac complications, and more. When compared with non-diabetic patients, both in-hospital and long-term mortality are considerably higher[1]. Hence, glycemic control in the perioperative period could serve as a modifiable risk factor and potential target for reducing postoperative complications.

The American Diabetes Association endorses glycated hemoglobin (HbA1c) for monitoring glycemic control among diabetic patients[2]. It is a measure reflecting the three-month average blood glucose level, giving an indirect measurement of how effectively blood glucose is controlled. It has been shown through systematic reviews and meta-analyses that increased levels of preoperative HbA1c is associated with higher rates of postoperative complications and poorer outcomes in surgical specialties such as cardiothoracic[3], bariatric[4], and orthopedic surgery[5].

Major abdominal surgery, defined as a major operation involving the abdominal and/or retroperitoneal compartment, is associated with high postoperative morbidity due to the extensive nature of surgery. Despite the clinical significance of this, there has not been a systematic review or meta-analysis investigating the association between preoperative HbA1c and postoperative complications in this population. Furthermore, there is no consensus on HbA1c threshold at which postponing elective surgery is warranted. Joint British Diabetes Societies for Inpatient Care (JBDS-IP) and The Association of Anaesthetists of Great Britain and Ireland recommend further optimisation

of glycemic control at a HbA1c threshold of 8.5%[6] whilst the US Society for Ambulatory Anesthesia (SAMBA) recommends a threshold of 7.0%[7] and the Australian Diabetes Society recommends a threshold of 9.0%[8]. A HbA1c target set too low may be unrealistic to achieve and delay patients' surgeries unnecessarily, whereas a HbA1c target set too high may be inadequate in risk prognostication and in reducing postoperative complications.

There is thus a gap in research as the association between preoperative HbA1c and postoperative complications in elective major abdominal surgery remains unknown despite the increasing incidence of both diabetes and abdominal surgery. The UK National Diabetes Inpatient Audit showed that 21% of all surgical patients had diabetes, and that general surgery (36%) and colorectal surgery (22%) were the surgical specialties with the highest prevalence[9]. Further insight into the association between preoperative HbA1c and postoperative complications after elective major abdominal surgery could help in risk prognostication and perioperative management.

This is the first meta-analysis which aims to evaluate all evidence on the association between preoperative HbA1c level and postoperative complications in this unique population of patients undergoing elective major abdominal surgery. Furthermore, we investigate if there is a threshold HbA1c level predictive of increased postoperative complications. The findings from this meta-analysis could have implications on policies in various countries as different HbA1c cut-off thresholds are currently being used in clinical practice.

Materials and Methods

This meta-analysis has been reported in line with PRISMA Guidelines[10] and registered on PROSPERO (CRD42020167347)[11]. The full methods have been previously described[12].

Search Strategy

These electronic databases were searched using a search strategy (**Supplementary Digital Content 1**), from the earliest record to 1st April 2020: PubMed, Embase, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, China Knowledge Resource Integrated Database (CNKI).

Study Selection

Study selection was performed by two independent reviewers (JKLW, YK). Discrepancies were resolved by HRA. The eligibility criteria included randomized controlled trials (RCTs) and observational studies investigating the association between HbA1c and postoperative complications by reporting outcomes in at least two HbA1c groups in adult patients undergoing elective major abdominal surgery. Studies in patients undergoing bariatric, total pancreatectomy, pediatric, emergency and transplant surgery were excluded[12].

Data Collection

Data extraction was performed by two independent reviewers (JKLW, YK) and stored on proformas. Data items extracted include study characteristics (author, year, country, study design, type of surgery), patient demographics (age, gender, sample size), intervention and comparator data (HbA1c cut-off), and outcome data (postoperative complications including major, overall, gastrointestinal, infectious, cardiopulmonary and renal complications) which were guided by the American College

of Surgeons National Surgical Quality Improvement Program (NSQIP)[13]. The exhaustive list of data extracted has been previously published[12]. Raw outcomes for each HbA1c group were extracted and estimates of effect using methods recommended by Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1.0.17) were calculated.

Risk of Bias and Quality of Evidence Assessment

The risk of bias for non-randomized observational studies included was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS)[14] and converted to The Agency for Healthcare Research and Quality (AHRQ) standards (**Supplementary Digital Content 2**). The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was used to grade the quality of evidence as recommended by COCHRANE[15].

Data Synthesis and Statistical Analysis

The primary and secondary aims of this meta-analysis was to investigate the association between preoperative HbA1c with major and overall postoperative complications respectively, where major complications were defined as complications fulfilling the Clavien-Dindo (CD) classification Grade 3, 4 and 5, and overall complications defined as complications fulfilling CD Grade 1-5[16]. Table 1 details the definitions of the CD classification Grades 1 to 5. The corresponding primary and secondary outcomes were the Odds Ratios (OR) of postoperative complication events between low and elevated HbA1c groups.

The postoperative complications extracted from the primary studies were initially graded according to CD classification, and then grouped for intent of either the primary outcome (major postoperative complications) or secondary outcome (overall postoperative complications) analyses. Examples of

postoperative complications from the primary studies that fulfilled the definition of our primary outcome of 'Major Postoperative Complications' include "reoperation"[17], "anastomotic leak"[18]–[23], "30-day mortality"[23] and "major complications fulfilling CD3-5"[24]–[26]. Secondary outcomes were categorised into overall complications, anastomotic leak, postoperative ileus, overall infections, wound infection, pneumonia, sepsis, cardiopulmonary complications, and renal failure[13], and quantitatively analysed. Qualitative analyses were conducted for outcomes reported by two or fewer studies.

Statistical analyses were performed using Stata (2019). Funnel plots, Begg's rank correlation test and Egger's regression asymmetry test were used to assess publication bias[27]. The Duval and Tweedie nonparametric 'trim and fill' method of accounting for publication bias was performed to formalise the use of funnel plots and adjust the meta-analysis by incorporating theoretical missing trials[27]. Q-statistic was used to investigate heterogeneity between studies. As a limitation of Cochran's Q-test is the fact that it might be underpowered when studies in a meta-analysis have small sample sizes or have low event rates, it is recommended by Cochrane to adopt a higher standard to conclude that there is indeed no significant heterogeneity between studies. Hence, a higher p-value of 0.1 was used (rather than the conventional 0.05)[28]. I^2 statistical test[29] was carried out to describe the proportion of total variation caused by heterogeneity[30]. I^2 of less than 30% was considered as mild heterogeneity, more than 50% as notable heterogeneity, and anything in between as moderate heterogeneity. Caution in interpretation must be taken as low I^2 values suggest that inconsistency may not necessarily be important as the importance of the I^2 value depends on magnitude and direction of effects, strength of evidence for heterogeneity including the p-value from the chi-squared test, or the confidence interval for I^2 [36]. The random effects model (DerSimonian–Laird) was used to derive pool estimates to account for inter-study heterogeneity. A meta-regression

was performed to evaluate the effect of different HbA1c cut off values on the following outcomes: major postoperative complications, overall postoperative complications, anastomotic leak, overall infection and wound infection.

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Results

Search Results

The search yielded 2539 records. One record was identified through manual searching of bibliographies. Fifteen and twelve records met criteria for a qualitative analysis and quantitative analysis respectively (**Figure 1**). Three records were not included in the quantitative analysis. The study by Lee *et al* was not included because it was the only study that used the outcome measures “Progression-free survival”, “Cancer specific survival”, and “Overall survival” and hence could not be combined with other studies. The study by Goh *et al* was not included because it used a HbA1c cut-off value of 8.0%, which is higher than the cut-off values used by other studies and would have confounded the quantitative analysis. The study by Zhang *et al* was not included because the number of patients in each HbA1c group was not reported by the study.

Study Characteristics

Study characteristics are summarised in **Table 2**. All studies were conducted between 2008 and 2019. Eleven studies were conducted in Asia, two in the USA[24],[31] and two in Europe. [18],[26] There were no RCTs that met our inclusion criteria. Twelve were performed retrospectively whilst three employed a prospective design[18],[24],[26] where patients were followed up from two months[26] to four years[24]. Most studies included gastrointestinal (GI) tract surgeries[17],[18],[32],[33],[20]–[26],[31], one included esophagectomies only[19], one included GI tract and hepato-pancreato-biliary (HPB) surgery[26], one was exclusively biliary[34], one included genitourinary surgery[24], and one was exclusively genitourinary surgery[35]. The HbA1c cut-off used to dichotomise case and control groups were variable. The most common cut-off points were HbA1c 6.5%[19],[24],[26],[31],[32] and 7.0%[17],[20],[23],[34] with five and four studies respectively. Most studies used a HbA1c measurement within at least 3 months before surgery, except for one study which used HbA1c

measurements within 6 months before surgery[35]. A few studies did not state the timeframe window between HbA1c measurement and surgery[17],[20]–[23],[32],[34]. A total of 25036 patients were included in the quantitative analysis.

The most studied outcome measures were infection[17],[18],[20],[22],[23],[31],[34] and anastomotic leak[18]–[23],[34]. Some studies investigated the individual effects of different types of infection such as pneumonia, urinary tract infection (UTI), wound infection, and sepsis[17],[18],[23],[31], whilst some only investigated the collective effect of all infections[20],[22],[34]. A few studies only investigated total postoperative complications according to CD classifications[24]–[26].

Risk of Bias and Quality of Evidence Assessment

Risk of bias (ROB) assessment found that all studies scored at least 7/9 on the NOS which equates to “good quality” after converting this to AHRQ standards. Only one was graded as “poor quality”. Most studies lost points in the “Selection” and “Outcome” parameters (**Supplementary Digital Content 3**). Quality of evidence assessment using GRADE found that two outcome parameters were “Moderate” in quality and the remaining four were “Low” in quality. (**Table 3**)

Major Postoperative Complications

Nine studies were included in this analysis[17]–[24],[26]. Both Begg’s rank correlation test ($P=0.175$) and Egger’s regression asymmetry test ($P=0.565$) did not find significant publication bias in our meta-analysis, consistent with funnel plots (**Supplementary Digital Content 4**). Q-statistic and I^2 -statistic did not show the presence of heterogeneity among different studies included ($P=0.711$, $I^2=0\%$). Pooled results showed that patients with an elevated HbA1c tended to have a higher risk of developing major complications after surgery (OR 2.16, 95% CI 1.54–3.01, $P<0.001$) (**Figure 2**).

Overall Postoperative Complications

Overall Postoperative Complications

Among the 12 studies reporting overall complications[17],[18],[32],[33],[19]–[24],[26],[31], Wang *et al.* reported anastomotic leak and postoperative infections data separately[22]. We included this study in our primary analysis and conducted a sensitivity analysis with the study excluded to ensure no double-counting of patients with complications, as we were unable to obtain the original patient-level data from the authors.

For the primary analysis using Wang *et al.*'s data on postoperative infections[22], Egger's test for small-study effects found significant publication bias ($P=0.001$), consistent with funnel plots (**Supplementary Digital Content 5**). Q-statistic and I^2 -statistics showed heterogeneity among studies ($P<0.001$, $I^2=75.6\%$). Pooled results showed that patients with an elevated HbA1c tended to have a higher risk of developing overall complications ($\geq CD1$) after surgery (OR 2.12, 95% CI 1.48–3.04, $P<0.001$) (**Figure 3**). The Duval and Tweedie nonparametric 'trim and fill' method adopted to adjust for publication bias, and meta-analysis with the 'trim and fill' method did not result in different conclusions. Sensitivity analysis did not result in different conclusions (OR 2.00, 95% CI 1.41–2.85). The funnel and forest plots of these are shown in **Supplementary Digital Content 6**.

Gastrointestinal complications

Anastomotic leak

Six studies were included in this analysis[18]–[23]. Egger's test for small-study effects ($P=0.401$) and Begg's rank correlation test ($P=0.452$) did not find significant publication bias (**Supplementary Digital Content 7**). Q-statistic and I^2 -statistic did not show significant heterogeneity between studies

($P=0.600$, $I^2=0\%$). Pooled results showed that patients with elevated HbA1c levels tended to have a higher risk of developing anastomotic leaks (OR 2.80, 95% CI 1.63-4.83, $P<0.001$) (**Figure 4**).

Postoperative ileus

Only two studies investigated the impact of HbA1c level on postoperative ileus[18],[23]. Gustafsson *et al* found that the rate of events was 9.7% in the HbA1c>6% group and 1.1% in the HbA1c<6% group. Although the rate of events in the elevated HbA1c group was higher, the significance of this was not reported[18]. When a HbA1c cut-off of 7% was used, Huang *et al* found no difference between the HbA1c groups ($p=0.284$)[23].

Infectious complications

Overall infections

Six studies were included in this analysis[17],[18],[20],[22],[23],[31]. Egger's test for small-study effects found significant publication bias ($P=0.038$) (**Supplementary Digital Content 8**). Although the Q-statistic did not show significant heterogeneity among studies ($P=0.113$), the I^2 -statistic found moderate heterogeneity ($I^2=43.8\%$). Pooled results showed that patients with an elevated HbA1c tended to have a higher risk of developing infections (OR 1.69, 95% CI 1.05-2.71) (**Figure 5**). However, meta-analysis with the 'trim and fill' method showed that this effect became insignificant (OR 1.18, 95% CI 0.77-1.82, $P=0.031$).

Wound infection

Three studies were included in this analysis[18],[23],[31]. Egger's test for small-study effects ($P=0.947$) and Begg's rank correlation test ($P=1.000$) did not find significant publication bias. However, the funnel plot suggested otherwise (**Supplementary Digital Content 9**). Both Q-statistic

and I^2 -statistic did not find significant heterogeneity among studies ($P=0.757$, $I^2=0\%$). Pooled results showed that patients with an elevated HbA1c tended to have a higher risk of developing wound infections (OR 1.21, 95% CI 1.08-1.36, $P=0.001$) (**Figure 6**). Meta-analysis with the ‘trim and fill’ method did not change this conclusion.

Pneumonia

Four studies were included in this analysis[17],[18],[23],[31]. Egger's test for small-study effects ($P=0.385$) and Begg's rank correlation test ($P=1.000$) did not find significant publication bias in our meta-analysis. However, funnel plots suggested otherwise. Q-statistic and I^2 -statistics did not show the presence of significant heterogeneity between studies ($P=0.424$, $I^2=0\%$). Pooled results showed that patients with an elevated HbA1c tended to have a lower risk of developing pneumonia after surgery (OR 0.77, 95% CI 0.61-0.97). However, this effect became insignificant (OR 0.74, 95% CI 0.44-1.25, $P=0.026$) when the ‘trim and fill’ method was used to adjust for publication bias (**Supplementary Digital Content 10**).

Sepsis

Only two studies reported outcomes of postoperative sepsis[18],[31]. Gustafsson *et al* found an event rate of 0% in the HbA1c >6% group and 1.1% in the HbA1c <6% group. However, significance was not reported[18]. Jones *et al* used three HbA1c cut-off values of HbA1c <5.7%, 5.7-6.4% and $\geq 6.5\%$. There was no difference in event rates for the three groups ($p=0.80$). The adjusted OR, using the “HbA1c<5.7%” group as the reference group, found no difference between all groups in both studies.

Cardiopulmonary complications

Only two studies reported on cardiopulmonary complications[18],[20]. Although the complication rates for respiratory failure, pleural fluid, cardiac failure and cardiac arrhythmia were reported, no p-values were reported by Gustafsson *et al.* For acute myocardial infarctions, Dai *et al* reported an event rate of 8% in the HbA1c >7% group and 2.2% in the HbA1c <7% group ($p<0.05$)[20].

Renal complications

Only one study reported acute kidney injury (AKI) events postoperatively[33]. Oh *et al.* measured the association between a HbA1c cut-off of 6% and stages of AKI (KDIGO staging) and total AKI. For each stage of AKI, there was no difference between the HbA1c<6% and HbA1c>6% group ($p>0.05$). Similarly, for total AKI, there was no difference between the HbA1c groups (aOR=1.38, 95% CI 0.85-2.26, $p=0.194$).

Meta-regression

There was no statistically significant effect of different HbA1c cut-off values from the range of 5.7% to 7.0% on the development of major postoperative complications, overall postoperative complications, anastomotic leaks, overall infections and wound infections ($p>0.05$ for all). Bubble plots of the meta-regressions are presented in **Supplementary Digital Content 11**.

Discussion

Results from our meta-analysis showed that elevated HbA1c (above the range of 6-7%) was associated with a higher risk of anastomotic leaks, wound infections, major postoperative complications (CD 3-5) and overall postoperative complications (CD 1-5), but not with overall infections and pneumonia.

The most important finding from this meta-analysis is the fact that elevated HbA1c levels are associated with a higher risk of anastomotic leaks. This is an important observation as anastomotic leaks are one of the most feared and serious complications in gastrointestinal surgery, resulting in a mortality rate of as high as 16.4% and long hospital and ICU admissions[37]. A further interesting finding is the fact that wound infection was the only type of infection associated with an elevated HbA1c. Taken together, these results indicate that elevated HbA1c may mark the impairment of wound healing physiology. Impaired glucose tolerance causes both macrovascular and microvascular complications which may result in inadequate angiogenesis and decreased perfusion to wound site[38], as well as poorer immune function[39]. This corroborates with previous findings from various levels of evidence in different types of surgery[3],[40],[41]. If a target HbA1c level were preoperatively set for patients undergoing elective surgery, the risk of anastomotic leaks and wound infections could be markedly reduced.

Our meta-analysis found that lower HbA1c levels are not only associated with a lower risk of major postoperative complications (CD3-5), but also overall postoperative complications (CD1-5). This has significant implications as it shows that it may be worthwhile postponing elective surgery until an optimal HbA1c level is achieved to reduce the risk of both major and overall postoperative complications which affect patients' quality of life. This could facilitate counselling during

preoperative assessments to motivate patients in making lifestyle modifications and improving medication compliance.

It should be noted that our pooled results did not find a significant association between preoperative HbA1c and risk of overall infections and pneumonia. These findings were not corroborated by a well-cited study by Dronge *et al* who showed that a cut-off HbA1c of 7% was significantly associated with lower postoperative infection risks in the major non-cardiac surgical population (which also included non-abdominal surgeries)[42]. This difference could be explained by the different cut-off HbA1c levels used, as Dronge *et al* used a cut-off of 7% whilst our study accepted a range of 6-7%. This may suggest that a HbA1c of 6% may be too low a level to prognosticate postoperative infections.

The rationales for exclusion of certain populations are explained here. Patients undergoing pancreatic and bariatric surgery were excluded from this meta-analysis as the postoperative glucose metabolism in these patients are different to those undergoing other types of abdominal surgery[43],[44]. As perioperative glucose control has been demonstrated to be an independent predictor of postoperative complications[45], it would be unfair to group pancreatic and bariatric surgery patients with other non-pancreatic and non-bariatric patients undergoing surgery. Patients undergoing emergency surgery were excluded as these patients are different to those undergoing elective surgery, as they are by default subject to higher postoperative complications due to the nature of the surgery (for example, the unprepared bowel, fecal contamination, hemodynamic instability, sepsis). Additionally, preoperative HbA1c optimisation is impossible in patients undergoing emergency surgery due to the lack of the 'preoperative period'. Finally, transplant patients were excluded as the nature of transplant surgery is unique to that of "major abdominal surgery", as defined in our Methods.

The main strength of this study is the fact that this is the first meta-analysis investigating the association between preoperative HbA1c and postoperative complications exclusively in the elective major abdominal surgery population, as the majority of previous meta-analyses were in the cardiac, bariatric and orthopedic populations[3],[5],[46]. Another strength is the inclusion of the Chinese database CNKI that will ensure extensive coverage of literature as the database has grown significantly in the past decade. Furthermore, inclusion of CNKI also ensures ethnic diversity and representation.

There are some limitations in this meta-analysis. Some studies which were considered for inclusion as they met the criteria of abdominal surgery, had to be excluded as they included non-abdominal surgery as well, of which data including only abdominal surgery was unattainable. This was overcome by applying the Duval and Tweedie nonparametric 'trim and fill' method to adjust the meta-analysis by incorporating theoretical missing trials. Some studies had categorised patients according to status of diabetes diagnosis instead of HbA1c status, whilst not everyone who had a diabetes diagnosis had an elevated HbA1c. To adjust for this, we only included patients who had HbA1c results and categorised them according to HbA1c status. Another limitation is the fact that different studies used different HbA1c cut-off points. For this reason, we have provided a conservative conclusion that HbA1c >6-7 is associated with higher postoperative complications. Additionally, it was not possible to perform subgroup analyses accounting for cancer patients and other comorbidities although their importance is crucial, as patient-level data for these factors were unavailable. While this is a possible limitation of this review, when it comes to diabetes optimisation, the HbA1c also merits attempt at optimisation in the pre-operative phase just as there are attempts to optimise pre-operative patients at high-risk of malnutrition (for example, gastrointestinal cancer patients).

The main implication from this paper is its ability to guide future RCTs. Our findings suggest that elevated HbA1c of 6-7% may be associated with higher postoperative complications. Currently, only the US guidelines recommend a target HbA1c of 7%[7], whilst the Great Britain and Australian guidelines recommend a target HbA1c of 8.5% and 9% respectively[6],[8]. Our findings may imply that under current guidelines, patients would have undergone elective surgery pre-optimised and therefore not stand the best chance of being complication-free postoperatively. Caution must however be taken as association should not be mistaken for causation. Conducting an RCT to determine causation of HbA1c and postoperative complications would be the next step to determine if change in current guidelines is warranted. However, we accept that there are challenges in conducting an RCT in this field. Many elective major abdominal surgery operations are undertaken for cancer resection and are therefore urgent cases that do not allow sufficient time for pre-optimisation of HbA1c. Future studies should also investigate the specific cut-off value of HbA1c before which complications increase in different types of surgeries using a Receiver-Operating Characteristic (ROC) analysis design.

Conclusively, the findings from our meta-analysis show that elevated HbA1c is associated with a higher risk in developing anastomotic leaks, wound infections, major and overall postoperative complications, but not overall infections and pneumonia. This implies that patients fare better post-operatively if a target HbA1c level of $\leq 7\%$ was set for patients to achieve before they undergo elective major abdominal surgery. Our findings help to guide future RCTs to determine if current guidelines on recommended cut-off HbA1c levels should be reviewed as the HbA1c thresholds currently used in clinical practice are all above 7%. Further studies using ROC analysis to investigate the exact HbA1c cut-off before postoperative complications increase should also be performed.

Declarations

Ethics approval and consent to participate

No ethics approval and consent to participate were required as only secondary data were used. Parts of this study was written as a graduating requirement from University College London (UCL) Master's degree programme within the UCL Centre for Perioperative Medicine by HRA.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JKLW contributed to the conceptualisation, methodology, formal analysis, investigation, data curation and writing (original draft) of the manuscript. YK contributed to the methodology, formal analysis, investigation, data curation and writing (original draft) of the manuscript. YJO contributed to the methodology, formal analysis, investigation, data curation and writing (original draft) of the manuscript. HL was contributed to the methodology, formal analysis, investigation, writing (original draft) of the manuscript. THW contributed to the methodology and writing (review & editing) of the

manuscript. HRA contributed to the conceptualisation, methodology, writing (original draft, review & editing) of the manuscript, supervision and project administration.

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Table 1. Clavien Dindo Classification Definitions

Grades	Definition[16]
I	Any deviation from normal postoperative course without need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens: drugs as antiemetics, antipyretics, analgesia, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusion and total parenteral nutrition are also included.
III	Requiring surgical, endoscopic or radiological intervention a: not under general anaesthesia b: under general anaesthesia
IV	Life-threatening complication (including CNS complications)* requiring intensive care unit management a: single organ dysfunction (including dialysis) b: multi-organ dysfunction
V	Death

*brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks

Table 2. Study Characteristics

Study	Country	Study design	Type of surgery	Sample size, N	HbA1c cut-off (no. of patients, percentage)	Time window between HbA1c result and surgery	Outcome measures
Lee et al., 2015[35]	South Korea	Retrospective	Nephrectomy (radical and partial) for renal cell carcinoma	N = 3075 <i>316 (75.8%) patients had recorded HbA1c</i>	≥6.8% (n=158, 50%) <6.8% (n=158, 50%) <i>*HbA1c 6.8% used as cut-off point as it was the median value</i>	Within 6 months prior to surgery	• Progression-free survival • Cancer specific survival • Overall survival
Gustafsson et al., 2009[18]	Sweden	Prospective	Elective colorectal resection (including cancer, inflammatory bowel disease, benign pathology)	N = 120	>6.0% (n=31, 25.8%) ≤6.0% (n=89, 74.2%)	1 day before surgery	• Postoperative glucose control • Magnitude of inflammatory response • Postoperative recovery • 30-day overall morbidity
Goh et al., 2017[25]	Singapore	Retrospective	Colorectal surgery	N = 149 <i>130 (87.2%) patients had recorded HbA1c</i>	≥8% (n=31, 23.8%) <8% (n=99, 76.2%)	Within 3 months prior to surgery	• Postoperative complications (CD2 and above)
Goodenough et al., 2015[24]	USA	Prospective	*Abdominal surgery	N = 1017 <i>438 (43.1%) patients had recorded HbA1c</i>	≥6.5% (n=183, 41.8%) <6.5% (n=255, 52.8%)	Within 3 months prior to surgery	• Primary: Major complication CD3 to CD5 within 30 days • Secondary: Any complication including CD1 and CD2
Kamarajah et al., 2018[26]	UK	Prospective	Gastrointestinal and hepatobiliary surgery	N = 381 <i>181 (47.5%) patients had recorded HbA1c</i>	≥6.5% (n=49, 27.1%) <6.5% (n=132, 72.9%)	Within 3 months prior to surgery	• Primary: 30-day complications defined by CD • Secondary: Major complications, 30-day readmission rates, postoperative care setting
Huang et al., 2017[23]	China	Retrospective	Surgical resection for gastrointestinal cancer	N = 209 <i>118 (56.4%) patients had recorded HbA1c</i>	≥7% (n=67, 56.8%) <7% (n=51, 43.2%)	Not stated	• 30-day and 180-day mortality rates • Postoperative complications • Length of hospital stay

Jones et al., 2017[31]	USA	Retrospective	Gastrointestinal surgery	N = 21541	>6.5% (n=8822, 41.0%) 5.7-6.5% (n=8118, 37.7%) <5.7% (n=4601, 21.4%)	Within 3 months prior to surgery	- Any post-operative complication - Infectious complications (wound infection, pneumonia, urinary tract infection, sepsis) - Post-discharge outcomes (readmission within 14d, readmission within 30d)
Villamiel et al., 2019[17]	Philippines	Retrospective	Elective colorectal surgery	N = 157 44 (28%) patients had recorded HbA1c	>7% (n=15, 34.1%) ≤7% (n=29, 65.9%)	Not stated	Primary: Length of hospital stay Secondary: Discharge within 30 postoperative days, postoperative complications, reoperation, pneumonia, wound infection
Okamura et al., 2017[19]	Japan	Retrospective	Esophagectomy for oesophageal cancer	N = 300	≥6.5% (n=27, 9%) 6.0-6.4% (n=50, 16.7%) <6.0% (n=223, 74.3%)	Within 3 months prior to surgery	Anastomotic leak
Oh et al., 2018[33]	South Korea	Retrospective	Elective major laparoscopic abdominal surgery	N = 1885	≥6.0% (n=628, 33.3%) <6.0% (n=1257, 66.7%)	Within 1 month prior to surgery	Acute kidney injury (post-operative day 0-3, stage 1-3)
Chen et al., 2018[21]	China	Retrospective	Colorectal surgery	N = 126	>6.3% (n=67, 53.2%) ≤6.3% (n = 59, 46.8%)	Not stated	Anastomotic leak
Zhou et al., 2019[32]	China	Retrospective	Colorectal and Upper gastrointestinal surgery	N = 118	7-8% (n=27, 22.9%) 6.5-7% (n=27, 22.9%) 5.7-6.5% (n=34, 28.8%) <5.7% (n=30, 25.4%)	Not stated	Postoperative delirium
Dai et al., 2017[20]	China	Retrospective	Colorectal surgery	N = 201	>7% (n=112, 55.7%) <7% (n=89, 44.3%)	Not stated	- Anastomotic leak - Length of stay - Time of operation - Major intra-operative bleeding - Infections - Acute myocardial infarction
Zhang et al., 2008[34]	China	Retrospective	Cholecystectomy	N = 86	>7.0 <7.0 *Number of patients per group not reported	Not stated	- Anastomotic leak - Infection

Wang et al., 2010[22]	China	Retrospective	Gastrointestinal tumour surgery	N = 82	<6.2 (n=47, 79.7%) >6.2 (n=35, 42.7%)	Not stated	• Bloating • Nausea and vomiting • Anastomotic leak • Time to flatus • Length of hospital stay
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*Included four gynecological procedures which constitutes only 0.7% of total number of surgeries

Table 3. GRADE Evidence Profile

Quality assessment							No. of patients		Relative Effect (95% CI)	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Elevated HbA1c	Low HbA1c		
Major postoperative complications										
9	Observational studies	Moderate	-	-	-	-	586	1024	OR 2.16 (1.54-3.01)	⊕⊕⊕⊖ MODERATE
Overall postoperative complications										
12	Observational studies	Moderate	-	-	-	Large effect size	10063	15030	OR 2.12 (1.48-3.04)	⊕⊕⊕⊖ MODERATE
Anastomotic leak										
6	Observational studies	Moderate	-	-	-	-	339	608	OR 2.80 (1.63-4.83)	⊕⊕⊕⊖ LOW
Overall infections										
6	Observational studies	Moderate	-	-	Serious		9082	13024	OR 1.69 (1.05-2.71)	⊕⊕⊕⊖ LOW
Wound infection										
3	Observational studies	Moderate	-	-	Serious		8920	12859	OR 1.21 (1.08-1.36)	⊕⊕⊕⊖ LOW
Pneumonia										
4	Observational studies	Moderate	Serious	-	Serious	-	8935	12888	OR 0.77 (0.61-0.97)	⊕⊕⊕⊖ LOW

CI, confidence interval; OR, odds ratio

Figure legends

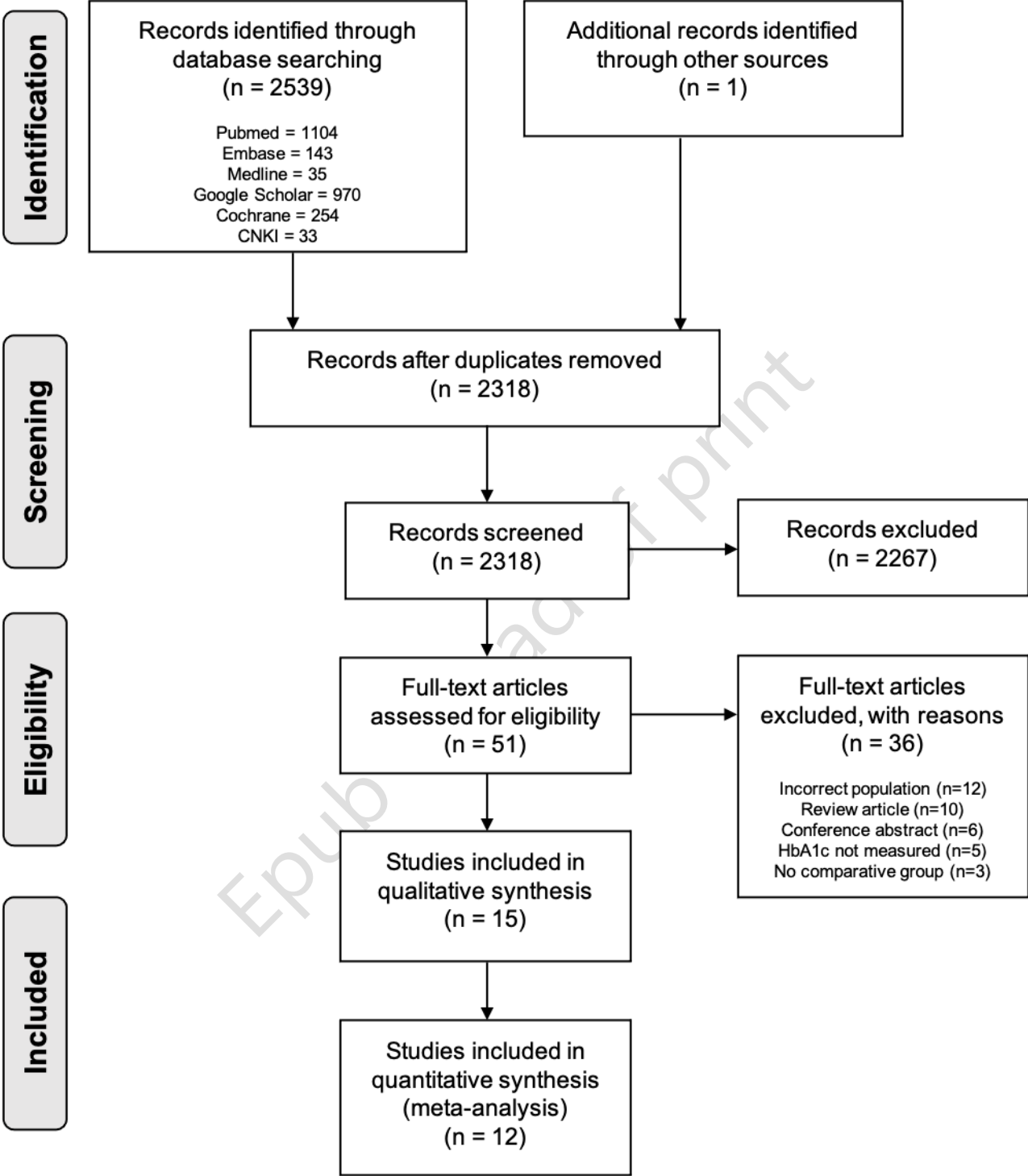


Figure 1: PRISMA Flowchart

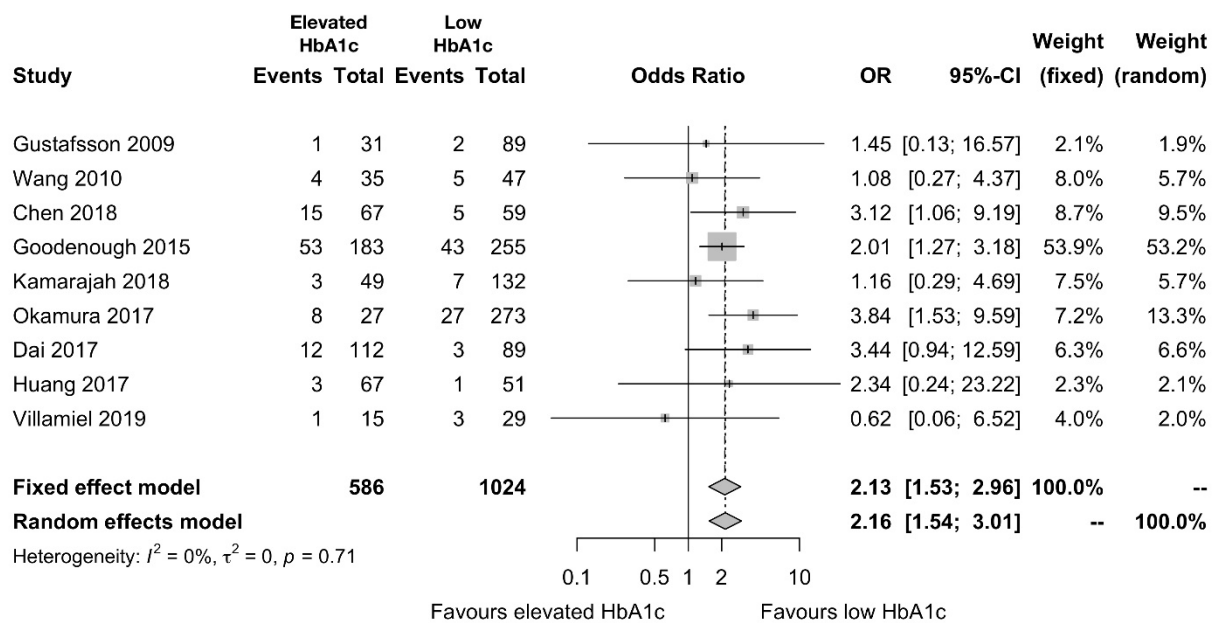


Figure 2: Forest plot of the effect of HbA1c on major postoperative complications ($P < 0.001$)

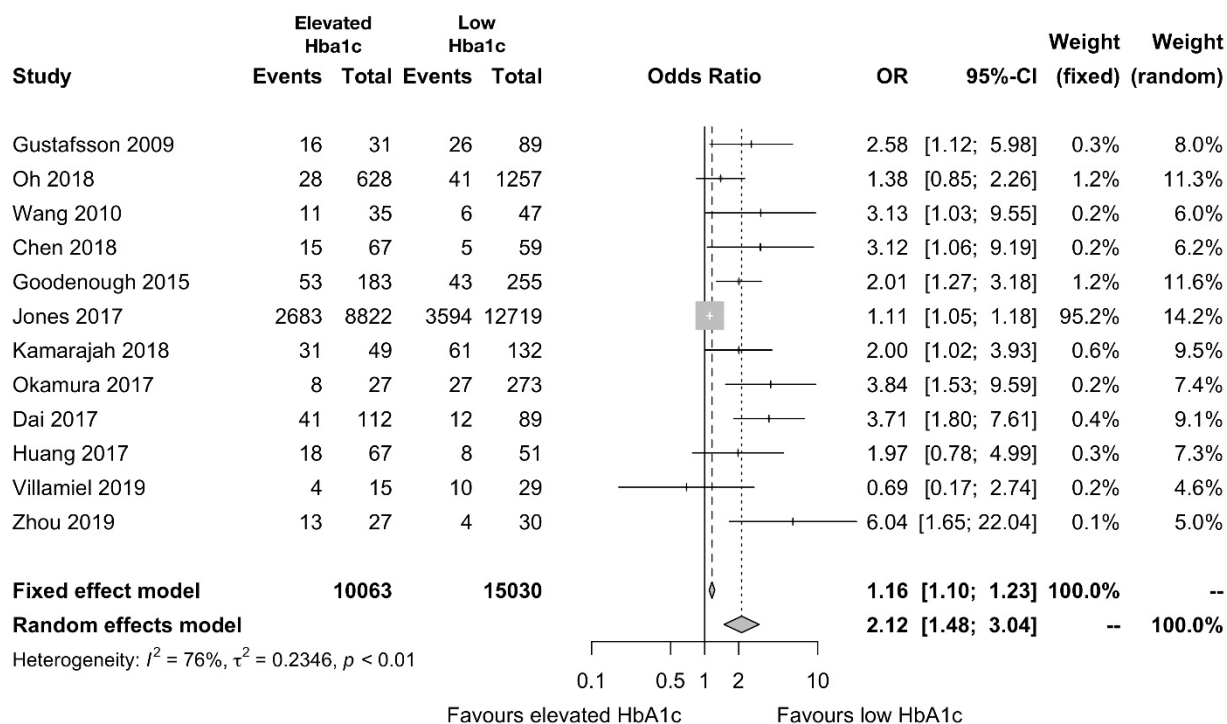


Figure 3: Forest plot of the effect of HbA1c on overall complications ($P < 0.001$)

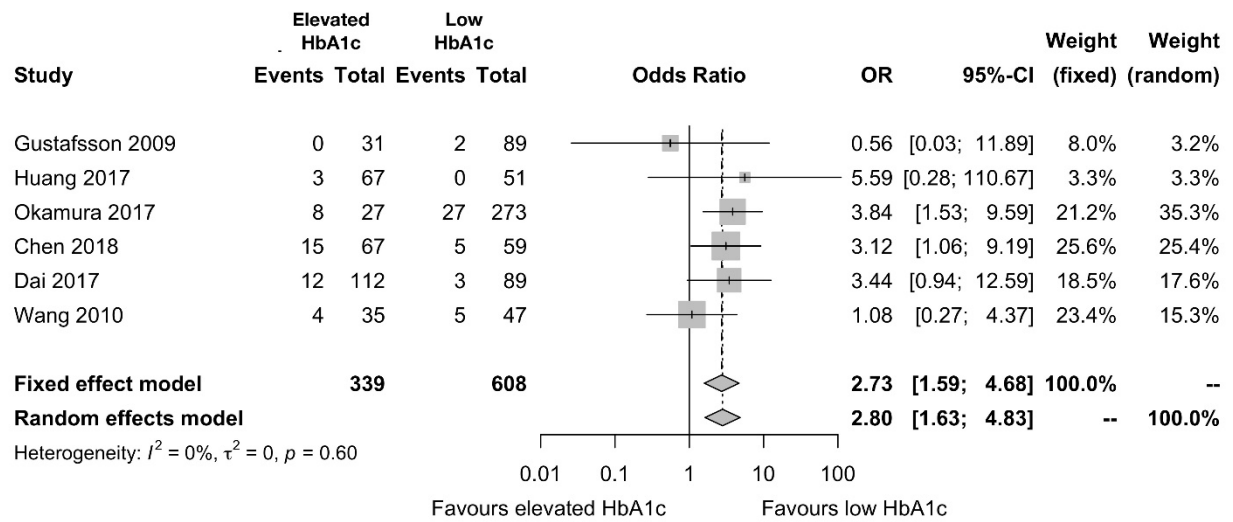


Figure 4: Forest plot of the effect of HbA1c on anastomotic leak (P<0.001)

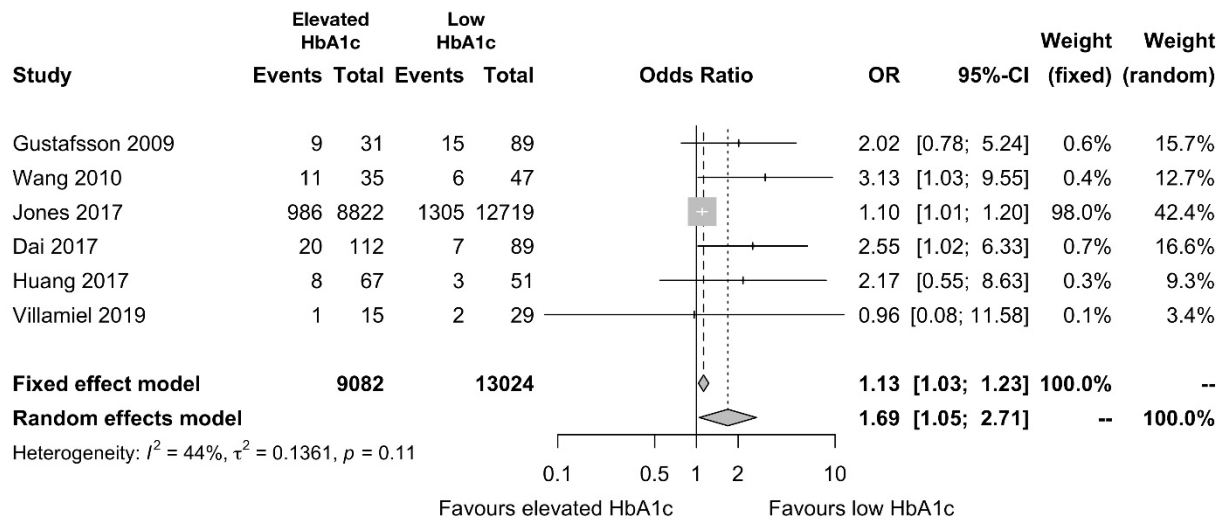


Figure 5: Forest plot of the effect of HbA1c on overall infections (P=0.031)

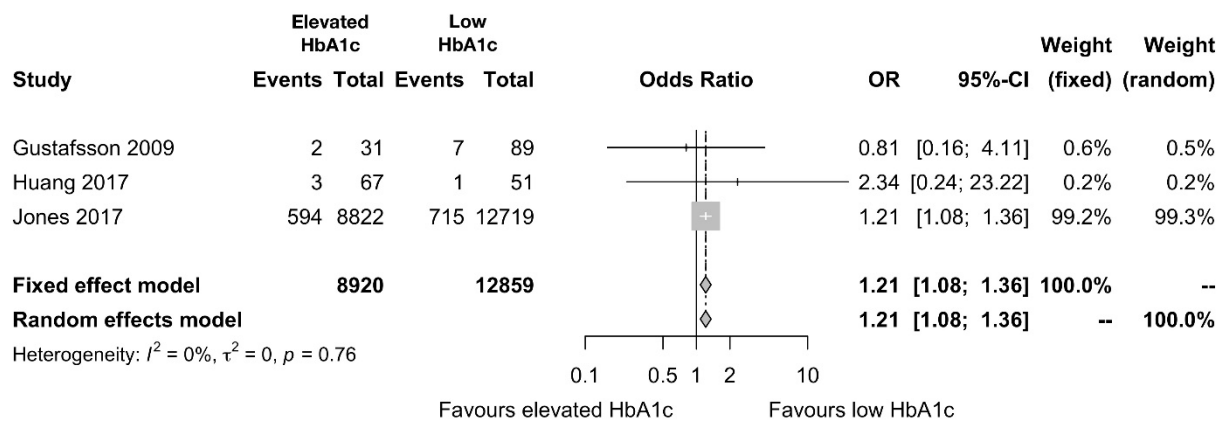


Figure 6: Forest plot of the effect of HbA1c on wound infections (P=0.001)