

## ORIGINAL ARTICLE

# Diabetes and Risk of Surgical Site Infection: A Systematic Review and Meta-analysis

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**OBJECTIVE.** To determine the independent association between diabetes and surgical site infection (SSI) across multiple surgical procedures.

**DESIGN.** Systematic review and meta-analysis.

**METHODS.** Studies indexed in PubMed published between December 1985 and through July 2015 were identified through the search terms “risk factors” or “glucose” and “surgical site infection.” A total of 3,631 abstracts were identified through the initial search terms. Full texts were reviewed for 522 articles. Of these, 94 articles met the criteria for inclusion. Standardized data collection forms were used to extract study-specific estimates for diabetes, blood glucose levels, and body mass index (BMI). A random-effects meta-analysis was used to generate pooled estimates, and meta-regression was used to evaluate specific hypothesized sources of heterogeneity.

**RESULTS.** The primary outcome was SSI, as defined by the Centers for Disease Control and Prevention surveillance criteria. The overall effect size for the association between diabetes and SSI was odds ratio (OR) = 1.53 (95% predictive interval [PI], 1.11–2.12;  $I^2$ , 57.2%). SSI class, study design, or patient BMI did not significantly impact study results in a meta-regression model. The association was higher for cardiac surgery 2.03 (95% PI, 1.13–4.05) compared with surgeries of other types ( $P = .001$ ).

**CONCLUSIONS.** These results support the consideration of diabetes as an independent risk factor for SSIs for multiple surgical procedure types. Continued efforts are needed to improve surgical outcomes for diabetic patients.

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Diabetes prevalence is increasing in the United States,<sup>1</sup> and the appropriate management of patients with diabetes has become increasingly important for the prevention of hospital-acquired infections. Much has been published in recent years about the impact of diabetes on increased rates of surgical site infection (SSI) and the potentially related impact of hyperglycemia on SSI. Surgical site infections are estimated to have an annual financial impact of more than \$3 billion dollars nationally and are the largest contributor to the overall cost of healthcare-associated infections.<sup>2</sup> Efforts to reduce the rates of SSIs are becoming more urgent since the introduction of Centers for Medicare and Medicaid Services penalties for hospital readmission rates. An understanding of patient risk factors for SSI is key to these efforts because hospitals with a more vulnerable case mix are more likely to incur readmission penalties.<sup>3</sup> Furthermore, the substantial prevalence of hospital-associated infections due to antibiotic resistant pathogens<sup>4</sup> highlights the importance of prevention in individuals at

high risk of infection. To gain a greater understanding of the impact of pre-existing diabetes on the incidence of SSI, we performed a meta-analysis of risk factors for SSIs among patients undergoing surgery in US hospitals. We hypothesize that pre-existing diabetes is a significant contributor to the development of SSI, independently of hyperglycemia at the time of surgery. Secondly, we hypothesize that hyperglycemia is itself an independent contributor to increased risk of SSI in surgical patients.

## METHODS

A systematic literature search and meta-analysis was performed following MOOSE guidelines<sup>5</sup> (Online Supplementary Material).

## Data Sources and Searches

A systematic literature search was performed by 4 study investigators (M.S., C.K., H.N., R.E.) with questions referred to an

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PREVIOUS PRESENTATION. We presented these findings in part at the 2014 American Diabetes Association annual meeting in San Francisco, California (June 13–17, 2014), and the 2014 Society for Epidemiology Research conference in Seattle, Washington (June 24–27, 2014).

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adjudication team consisting of the study principal investigator (E.T.M.), 1 investigator with expertise in diabetes epidemiology (L.J.), and 1 investigator with expertise in infectious diseases and infection prevention (K.S.K.). The search was performed in PubMed and EMBASE using combinations of the search terms “risk factors,” “diabetes,” “glucose,” and “surgical site infections” from December 1985 to July 2015 (see Online Supplementary Material: Search Strategy). The starting date of the search, December 1985, was selected to correspond with the wide implementation of the Centers for Disease Control and Prevention (CDC) SSI surveillance guidelines. The search was inclusive of all study designs unless interventional control of glucose during the study prevented an assessment of the association between diabetes and SSI.

### Study Selection

All abstracts were reviewed for eligibility, and the full-article texts of potentially relevant studies were reviewed in depth. Reference lists for all reviewed articles were hand-searched to identify additional eligible articles. Eligibility criteria for study inclusion were the following: (1) original US data; (2) adult participants; (3) utilized the CDC definition for SSIs; and (4) included measurable risk estimates of the association between diabetes and risk of SSI with 95% confidence intervals or provided adequate information to calculate risk estimates and their 95% confidence intervals. Review articles, meta-analyses, or non-English studies were excluded (Online Supplementary Material: List of Excluded Studies).

Eligible studies included adult patients undergoing surgical procedures of any type, using NHSN operative procedure categories to define surgical procedures. All comparative study designs (including observational, randomized controlled, retrospective, or prospective studies) were considered for inclusion provided they presented an assessment for the association between diabetes and SSI or the absolute patient numbers needed for the calculation of the measure. Each eligible study was required to include both diabetic and non-diabetic patients in the study population. Multiple publications on the same subject population were reviewed together and were restricted such that each patient population was included only once; this is notable particularly for multiple publications from large surveillance databases (eg, National Surgical Quality Improvement Program; see Online Supplementary Material: Excluded Studies). SSI was defined using criteria specified by the CDC for the purposes of surveillance and reporting.

### Data Extraction

Measures for the association between pre-existing diabetes and SSI were collected from studies that ascertained the presence of diabetes prior to the time of surgery either through the patient’s medical record or hemoglobin A1c testing (HbA1c). Assessments of HbA1c levels were noted; however, not enough studies were identified to merit a separate meta-analysis based

on this measure. Measures of the association between peri- or post-operative blood glucose levels were collected from studies that assessed thresholds of glucose levels. Studies that presented only comparisons of mean or median blood glucose levels were excluded from the analysis of peri- or post-operative hyperglycemia due to our inability to define the absolute number of patients with hyperglycemia in the infected and uninfected groups.

Data were abstracted onto standardized forms that included study characteristics, study population, type of SSI (superficial, deep incisional, or organ/space), crude and adjusted estimates, and confidence intervals. For each study, we recorded how diabetes was determined and whether blood glucose was measured prior to, during, or after surgery. Studies were assigned to the following categories based on the type of surgery: obstetrical and gynecological, colorectal, arthroplasty, breast, cardiac, spinal, or other. The abstraction team received training by the principal investigator, including the abstraction of multiple practice cases, before performing data abstraction. A subset of studies included was re-reviewed by 2 study investigators to ensure consistency.

### Data Synthesis and Analysis

The most-adjusted estimate (ie, the adjusted odds ratio for the multivariate regression with the most variables) was used to generate summary estimates.<sup>6</sup> Summary estimates and predictive intervals were calculated using a DerSimonian and Laird random-effects model for each estimate type. Confidence intervals were used for smaller analyses of diabetes and glucose combined models. The use of random-effects models was based on  $I^2$  values exceeding 30% in each overall fixed-effects analysis.<sup>7</sup> Funnel plots were generated to assess publication bias (data not shown) (Stata 11, StataCorp, College Station, TX). Sensitivity analysis was performed through the generation of stratified estimates and the use of multiple meta-regression analyses to assess the presence of meta-confounding by study characteristics including surgery type, study type, inclusion of body mass index (BMI) in the adjusted estimate, and diabetes prevalence in the study population. We determined a priori that the primary confounder of concern was BMI.

## RESULTS

The combined search strategies identified 3,631 abstracts. All of these abstracts were reviewed, and the full texts of 522 articles were reviewed in depth; 3,109 studies were excluded during abstract review (Figure 1), and 428 studies were excluded during full-text review (Online Supplementary Material: List of Excluded Studies).

### Meta-analysis for Diabetes and SSI

A total of 90 studies provided estimates for the association between diabetes and SSI, including 2 studies that provided

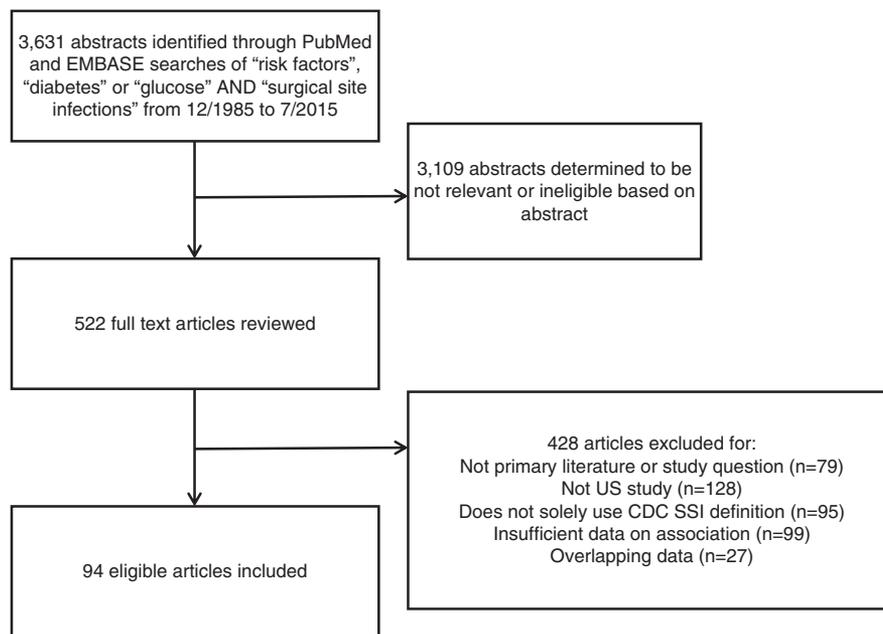


FIGURE 1. Flow diagram of search and selection processes.

multiple estimates (Appendix Table 1). Included studies comprised a total of 866,427 procedures and 32,067 SSIs meeting CDC surveillance criteria. All studies were observational with the exception of 3 randomized controlled trials. We identified 14 studies (16%) that used prospectively collected data. Diabetes prevalence among included study populations ranged from 2% to 39% (median 17%). History of diabetes was ascertained by medical record review in all but 2 studies.<sup>8,9</sup> No included studies differentiated between Type 1 and Type 2 diabetes.

The overall effect size for the association between diabetes and SSI was an odds ratio (OR) of 1.53 (95% predictive interval [PI], 1.11–2.12;  $I^2$ , 57.2%) (Figure 2). Of the included studies, 38 (42%) provided estimates that were adjusted for potential confounding factors. When stratifying the meta-analysis by the availability of crude versus adjusted measures, the effect size was similar (OR, 1.68; 95% PI, 1.03–2.72;  $I^2$ , 63.6%) for all available crude measures (71 studies); OR was 1.77 (95% PI, 1.13–2.78);  $I^2$ , 71.1%) for all adjusted measures (38 studies). Funnel plots demonstrated greater evidence of potential publication bias for adjusted estimates (data not shown).

#### Evaluation of Sources of Heterogeneity for Diabetes Estimate

Study design did not have a significant impact on the overall pooled estimate ( $P = .13$  for retrospective vs prospective data collection;  $P = .41$  for case-control vs cohort or interventional design). Prevalence of diabetes among study participants was also not a significant source of heterogeneity ( $P = .80$ ). Among studies presenting estimates restricted to specific SSI classes,

the combined OR was 1.95 (95% PI, 0.65–5.87) for deep SSIs (7 estimates from 6 studies) and the OR was 1.38 (95% PI, 0.66–2.88) for superficial SSIs (6 estimates from 5 studies).

Among studies reporting on a single surgical category, the most common category was cardiac (15 studies) followed by spinal (14 studies) (Table 1). Estimates by surgery type for the association between diabetes and SSI ranged from 1.16 for colorectal surgeries (95% PI, 0.93–1.44) to 2.03 for cardiac surgeries (95% PI, 1.13–4.05) (Table 1). Meta-regression for impact of surgery type on the association between diabetes and SSI indicated that the combined SSI effect was higher for cardiac surgery than for all other surgery categories ( $P = .001$ ). BMI was hypothesized a priori to be an important confounder in the association between diabetes and SSI. Study estimates were stratified according to whether the presented measure controlled for the effect of BMI. The estimate pooled from the 20 studies that controlled for BMI was higher than that pooled from those that did not; however, this factor was not significant when evaluated by meta-regression ( $P = .79$ ).

#### Meta-analysis for Blood Glucose and SSI

In total, 16 studies were available to assess the association between hyperglycemia and SSI, with 10 papers ( $n = 27,844$  procedures) including pre- or intraoperative assessments of blood glucose levels and 11 papers ( $n = 32,625$  procedures) including postoperative assessments of blood glucose levels. We observed a wide range in the threshold for defining hyperglycemia. Of 10 studies assessing pre-operative blood glucose, 6 used a threshold of 200 mg/dL, and the remaining 3 studies used thresholds of 125 mg/dL (2 studies), 180 mg/dL

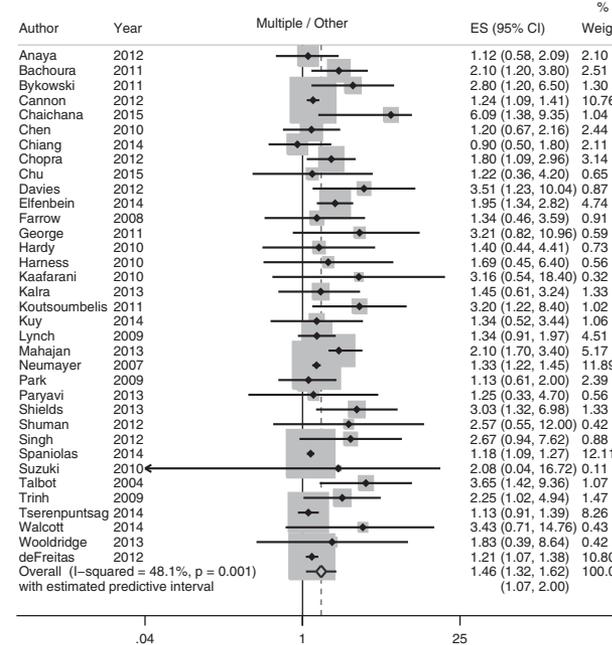
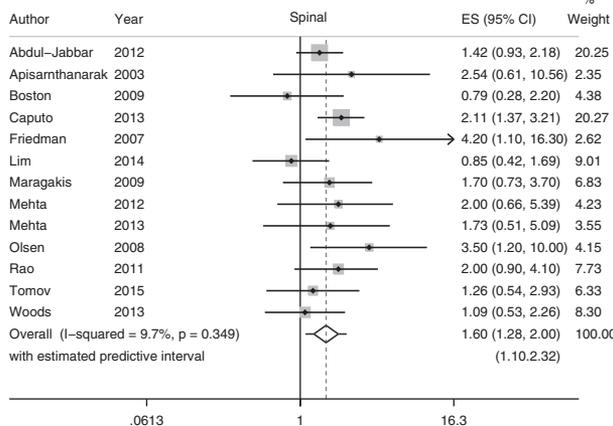
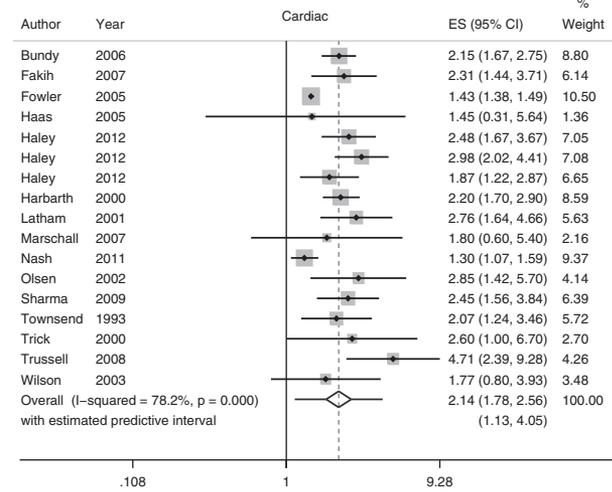
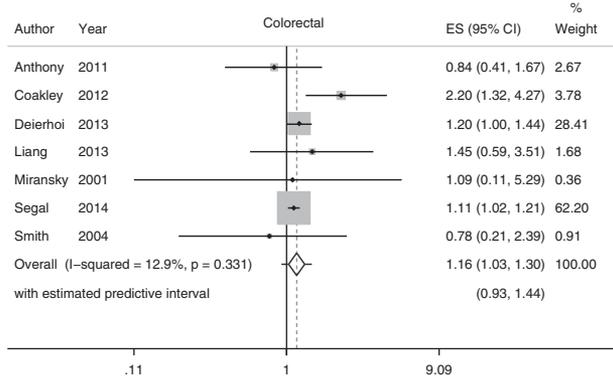
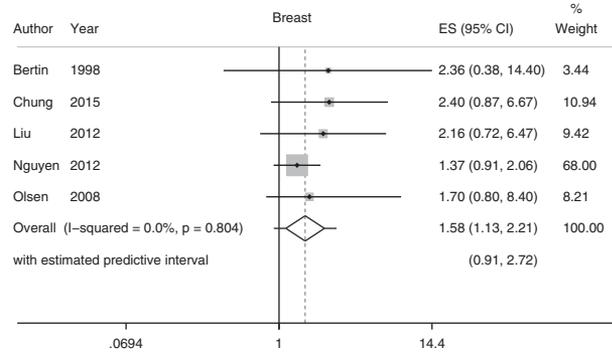
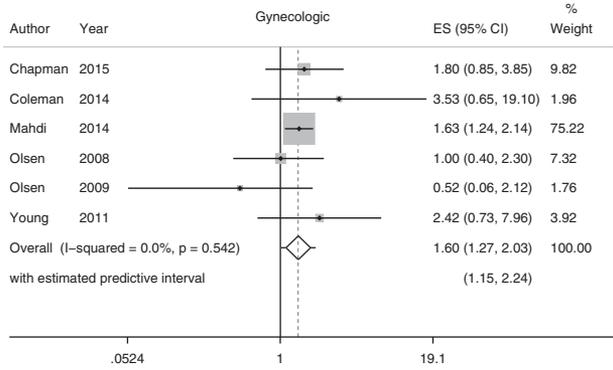


FIGURE 2. Meta-analysis of diabetes and surgical site infection, by surgery type.

(1 study), and 100 mg/dL (1 study). Of the 11 studies assessing post-operative blood glucose, 5 used thresholds of 200 mg/dL, with the remaining studies using lower thresholds ranging from 125 mg/dL to 180 mg/dL. One paper presented a composite exposure of pre- or postoperative hyperglycemia, and this estimate was included in both pooled calculations.<sup>10</sup> The overall estimate for the association between elevated blood glucose and SSI in the pre- or intraoperative period was OR = 1.88 (95% Predictive Interval [PI], 0.66–5.34) (Figure 3). The overall estimate for the association between elevated blood glucose in the post-operative period and SSI was 1.45 (95% PI, 0.77–3.04) (Figure 4).

Only 3 studies presented multivariate models adjusting for blood glucose levels and diabetes in the same model.<sup>8,10,11</sup>

TABLE 1. Pooled Estimates of the Association between Diabetes and Surgical Site Infection by Surgery Type

Surgery Type	No. of Studies	Pooled Estimate	95% Prediction Interval	I <sup>2</sup> , %
Gynecological	6	1.61	1.15–2.24	4.0
Colorectal	7	1.16	0.93–1.44	9.5
Arthroplasty	6	1.26	1.01–1.66	11.7
Breast	5	1.58	0.91–2.72	2.7
Cardiac	15	2.03	1.13–4.05	22.4
Spinal	14	1.66	1.10–2.32	8.1
Other/Multiple surgery types combined	37	1.46	1.07–2.00	41.5

These studies used thresholds of  $\geq 200$  mg/dL<sup>8</sup> and  $\geq 126$  mg/dL<sup>11</sup> to define elevated preoperative glucose levels or combined pre- and postoperative thresholds into a single definition.<sup>10</sup> Pooled estimates of the association between diabetes and SSI, controlling for glucose level was OR = 2.55 (95% confidence interval [CI], 1.70–3.82). Pooled estimates of the association between elevated glucose level and SSI, controlling for a history of diabetes was OR = 2.22 (95% CI, 1.36–3.60).

DISCUSSION

Consistency of Included Studies

We limited our analysis to studies performed at U.S. hospitals after 1985 in an effort to narrow our review to surgeries evaluated with the standard SSI surveillance methods and definitions required by the CDC. We observed some variation in the definitions for hyperglycemia among included studies. Approximately half of the studies used thresholds that met or were more conservative than those proposed by the Society of Thoracic Surgeons<sup>12</sup> and the American Diabetes Association.<sup>13</sup> The remaining studies used a slightly higher threshold of 200 mg/dL to define hyperglycemia, and it is possible that this variation may have introduced heterogeneity into our combined estimates for hyperglycemia.

Almost all included studies used medical record review to assess a patient’s reported history of diabetes. This data may be prone to error and may not reliably identify all patients with diabetes or assess the degree to which an individual patient’s

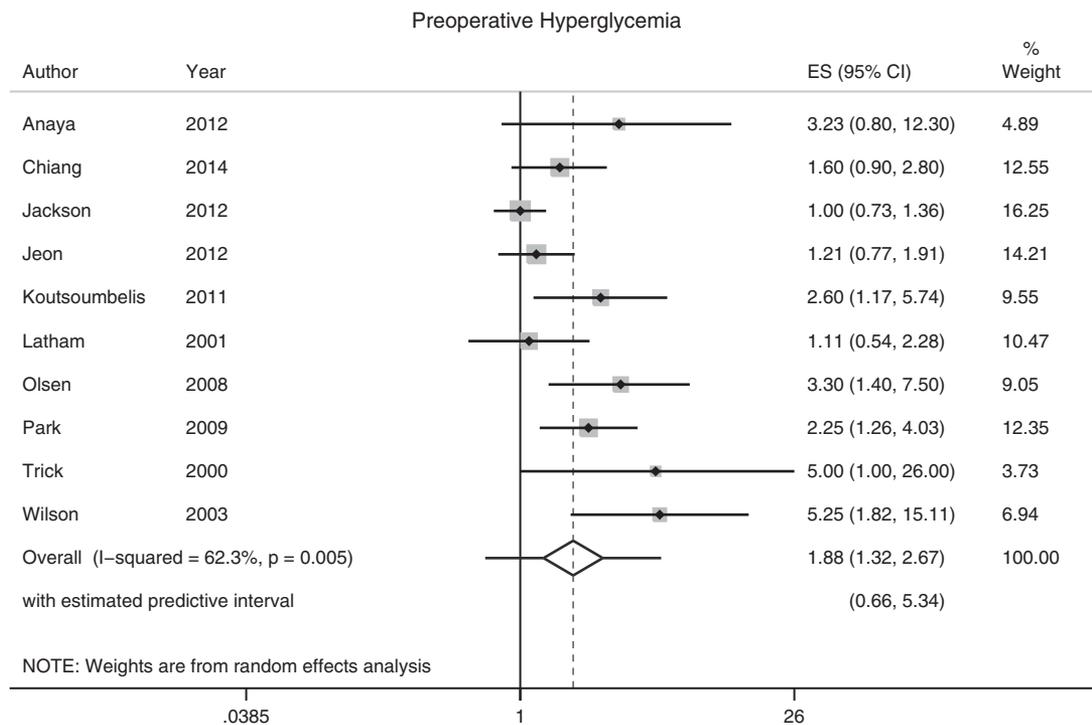


FIGURE 3. Meta-analysis of pre-operative hyperglycemia and surgical site infection.

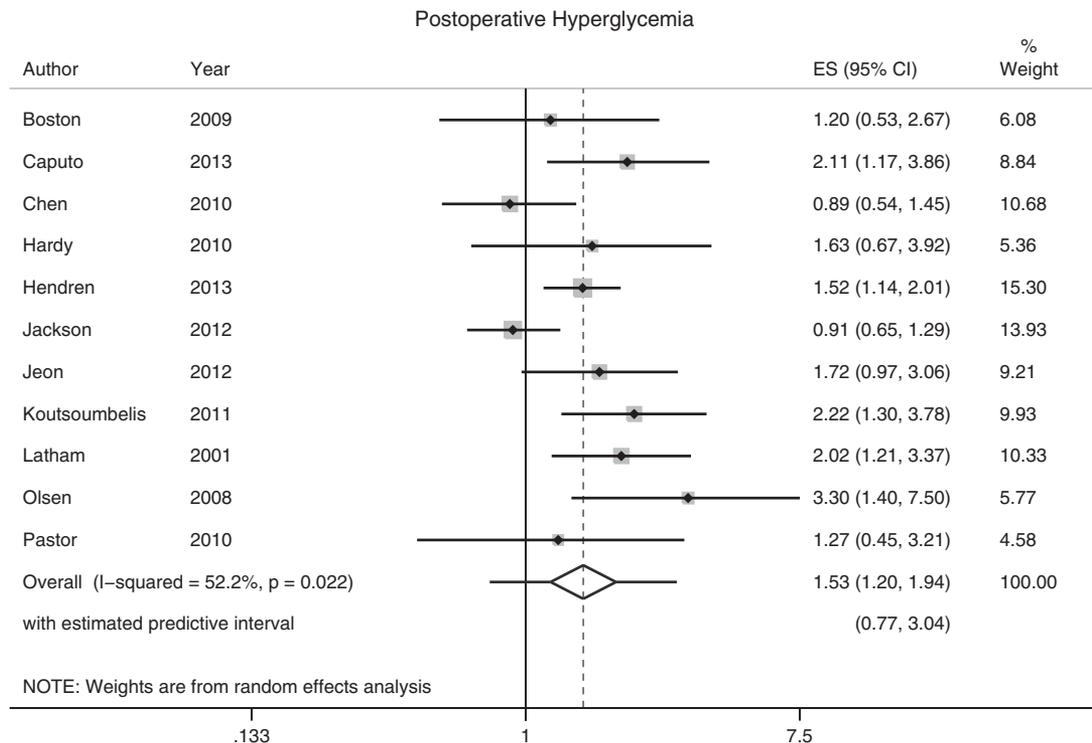


FIGURE 4. Meta-analysis of post-operative hyperglycemia and surgical site infection.

diabetic condition is adequately controlled. Likewise, the assessment of diabetes for use with the revised surgical risk index from the Centers of Disease Control does not recommend the use of HbA1c or other markers of severity of diabetes to gather risk information.<sup>14</sup>

#### Generalizability of Study Estimate

Our requirement that all studies be based in the United States excluded available data from other countries; however, it allowed us to strictly assess SSIs using CDC definitions from hospitals participating in standardized surveillance procedures. While specific quality ratings were not performed for each study, we explored several potential sources of heterogeneity in our pooled estimates through the use of meta-regression. Our stratum-specific estimates show a very consistent association between diabetes and SSIs across categories, including study characteristics, and after controlling for BMI. We were unable to assess variation due to SSI surveillance practices in different hospitals. While studies using active follow-up protocols would be expected to have increased SSI rates, we do not expect that this effect would be differential by diabetes status. Our pooled estimates are based on the use of the most adjusted estimate available in each study.<sup>6</sup> To assess the impact of this rule, summary estimates were generated separately for all available crude effects and all available adjusted effects, and the findings in these models were similar to the most-adjusted models.

The funnel plot for the adjusted estimates indicates the possible presence of publication bias for these estimates in this body of literature (data not shown). This bias is likely due to the tendency of authors to publish only those variables that are significant in multivariate analyses. Given our findings of an association between diabetes and SSI in almost every category of surgery type, it is likely that non-significant findings for diabetes in smaller studies may be due to insufficient sample size in individual studies, rather than a lack of underlying impact. For that reason, it may be prudent to include diabetes as an a priori hypothesized risk factor in future studies with the inclusion of diabetes in adjusted models for risk of SSIs.

#### Interpretation of Findings

Our finding of increased SSI among patients with diabetes was consistent across surgery types, with the exception of obstetrical and gynecological surgery which was based on 2 studies conducted at the same hospital. The surgery-specific findings were statistically significant for arthroplasty, breast, cardiac, and spinal surgeries; the actual pooled estimate was highest among patients undergoing cardiac surgery. These findings contrast with the analysis of National Healthcare Safety Network data that served as the basis for the revised procedure-specific SSI risk-adjustment calculations. This analysis found diabetes to only be associated with SSI for spinal fusion or refusion.<sup>14</sup> In patients with diabetes receiving

colorectal resection, glucose levels were consistently higher in patients with an SSI compared with uninfected patients, even when mean glucose levels were below 200 mg/dL in those with or without SSI.<sup>15</sup> Similar findings have been reported in patients undergoing laminectomy.<sup>16</sup> Elevated blood glucose has been found to be associated with increased rates of infection in orthopaedic spine surgery,<sup>17</sup> cardiac surgery,<sup>11,18,19</sup> and colorectal and bariatric surgery<sup>20</sup>; however, this association has not been consistently found.<sup>21,22</sup>

The notion that diabetes is a significant contributor to SSI risk through mechanisms other than hyperglycemia at the time of surgery is supported by the few studies that included both glucose levels and history of diabetes in the multivariate models. In the pooled estimate from these studies, the magnitude of the effect of diabetes was stronger than that of our primary analysis that included all eligible studies. The results of an interventional study by Trussel et al<sup>23</sup> corroborates this finding. Diabetes remained a significant risk factor for SSI with an odds ratio of 4.71 despite the implementation of a patient care pathway targeting glucose control during the time of surgery and resulting in successfully reducing the overall rates of infection. However, we identified few studies suitable for analysis of potential independent effects of diabetes and hyperglycemia on SSI.

## CONCLUSIONS

In our study, we found a significant association between diabetes and SSI that was consistent across multiple types of surgeries and after controlling for BMI. While we also confirmed an association between both pre- and post-operative hyperglycemia and SSI, history of diabetes remained a significant risk factor in meta-analyses of studies that controlled for hyperglycemia.

Furthermore, we found diabetes to be a significant contributor to the risk of SSIs, potentially beyond its role in causing hyperglycemia during or after surgery. The reasons for this finding are unclear. It is possible that diabetes is a marker for other conditions that may put a patient at risk of infection, including vascular changes and white blood cell dysfunction. In addition, the occurrence of perioperative hyperglycemia and subsequent immune suppression is affected by the complex contributions of factors in addition to the diabetic history of the patient, including physiologic stressors and exogenous glucose administration.<sup>24</sup> Although we were able to assess the confounding effect of body mass index and found no effect on our conclusions, our ability to fully assess potential confounders in the current meta-analysis is limited by the variables assessed in the original studies. However, the most adjusted estimate from each study was used in the final analysis, which should benefit from control of other confounding variables at the individual study level. Our findings point to several directions for future research. Few studies have assessed whether a more detailed assessment of diabetes severity would improve the management of SSI risk in these patients. Secondly, few studies

address the cause of the infection, and thus we are unable to rule out whether the increased risk of SSI among diabetics is related to differences in bacterial etiology.

Overall, these results support the consideration of diabetes as an independent risk factor for SSIs for multiple procedure types and continued efforts are needed to improve surgical outcomes for diabetic patients.

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*Potential conflicts of interest.* All authors report no conflicts of interest relevant to this article.

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## SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit <http://dx.doi.org/10.1017/ice.2015.249>

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APPENDIX TABLE 1. Articles Included in 3 Meta-analyses of Diabetes and Pre- and Postoperative Hyperglycemia

Author	Study Year	No. of Procedures	No. of SSIs	Surgery Type	Diabetes	Postoperative Glucose
Abdul-Jabbar et al <sup>25</sup>	2012	6,628	193	Spinal	X	
Anaya et al <sup>26</sup>	2012	503	122	Any elective	X	X
Anthony et al <sup>27</sup>	2011	197	69	Elective transabdominal colorectal	X	
Apisarnthanarak et al <sup>28</sup>	2003	60	13	Spinal	X	
Bachoura et al <sup>29</sup>	2011	1,783	75	Orthopaedic trauma	X	
Bertin et al <sup>30</sup>	1998	55	18	Breast	X	
Boston et al <sup>31</sup>	2009	234	55	Spinal	X	X
Bundy et al <sup>32</sup>	2006	3,878	322	CABG	X	
Bykowski et al <sup>33</sup>	2011	8,850	31	Elective hand	X	
Cannon et al <sup>34</sup>	2012	9,940	1,497	Elective colorectal resection	X	
Caputo et al <sup>17</sup>	2013	3,138	115	Orthopaedic spine	X	X
Chaichana et al <sup>35</sup>	2015	401	21	Tumor resection	X	
Chapman et al <sup>36</sup>	2015	338	89	Gynecologic oncology	X	
Chen et al <sup>37</sup>	2009	195	27	Elective posterior instrumented lumbar arthrodesis	X	
Chen et al <sup>38</sup>	2010	253	86	Any	X	X
Chiang et al <sup>39</sup>	2014	416	104	Craniotomy or craniectomy	X	X
Chopra et al <sup>40</sup>	2012	751	91	Roux-en-Y gastric bypass surgery (RYGBS)	X	
Chu et al <sup>41</sup>	2015	528	36	Stoma reversal	X	
Chung et al <sup>42</sup>	2015	2,899	143	Free flap breast reconstruction	X	
Coakley et al <sup>43</sup>	2012	59	16	Colectomy for fulminant ulcerative colitis (UC)	X	
Coleman et al <sup>44</sup>	2014	77	17	Hysterectomy	X	
Davies et al <sup>45</sup>	2012	268	49	Ventral hernia repair	X	
deFreitas et al <sup>46</sup>	2012	40,669	1301	Elective vascular procedures	X	
Deierhoi et al <sup>47</sup>	2013	5,750	709	Colorectal	X	
Elfenbein et al <sup>48</sup>	2014	49,326	179	Thyroidectomy	X	
Everhart et al <sup>49</sup>	2012	1,875	29	Total joint arthroplasty	X	
Fakih et al <sup>50</sup>	2007	3,578	144	Coronary artery bypass graft (CABG)	X	
Farrow et al <sup>51</sup>	2008	152	30	Umbilical hernia repairs	X	
Fowler et al <sup>52</sup>	2005	370,133	11,636	Cardiac	X	
Friedman et al <sup>16</sup>	2007	123	41	Laminectomy	X	
George et al <sup>53</sup>	2011	556	14	Laparoscopic urological procedures	X	
Haas et al <sup>54</sup>	2005	12	14	Cardiac	X	
Haley et al <sup>55</sup>	2012	13,894	303	CABG	X	
Harbarth et al <sup>56</sup>	2000	2,641	231	CABG	X	
Hardy et al <sup>21</sup>	2010	114	57	Craniotomy	X	X
Harness et al <sup>57</sup>	2010	2,336	11	Carpal tunnel release	X	
Hellinger et al <sup>58</sup>	2011	1,036	166	Liver transplantation	X	
Hendren et al <sup>59</sup>	2013	4,331	380	Colectomy		X
Jackson et al <sup>60</sup>	2012	7,576 <sup>a</sup> 5,773 <sup>b</sup>	N/A	Colectomy		X
Jeon et al <sup>22</sup>	2012	13,800	260	Any		X
Kaafarani et al <sup>61</sup>	2010	145	21	Ventral hernia repair	X	
Kalra et al <sup>62</sup>	2013	9,006	27	Multiple	X	
Koutsoumbelis et al <sup>63</sup>	2011	3,218	84	Posterior lumbar	X	X
Kuy et al <sup>64</sup>	2014	106	33	Lower extremity revascularization	X	

APPENDIX TABLE 1. *Continued*

Author	Study Year	No. of Procedures	No. of SSIs	Surgery Type	Diabetes	Postoperative Glucose
Latham et al <sup>8</sup>	2001	1,000	74	Cardiothoracic	X	X X
Liang et al <sup>9</sup>	2013	128	46	Stoma reversal	X	
Lim et al <sup>65</sup>	2014	3,353	86	Single level lumbar fusion	X	
Liu et al <sup>66</sup>	2012	256	44	Microsurgical breast reconstruction	X	
Lovecchio et al <sup>67</sup>	2014	43,299	468	Arthroplasty	X	
Lynch et al <sup>68</sup>	2009	869	162	Renal transplant	X	
Mahajan et al <sup>69</sup>	2013	615	47	Intra-abdominal	X	
Mahdi et al <sup>70</sup>	2014	6854	369	Gynecologic cancer	X	
Maragakis et al <sup>71</sup>	2009	208	104	Spinal	X	
Marschall et al <sup>72</sup>	2007	76	19	Pacemaker and implantable cardioverter-defibrillator	X	
Mehta et al <sup>73</sup>	2012	298	24	Lumbar spine fusion	X	
Mehta et al <sup>74</sup>	2013	213	22	Cervical spine fusion	X	
Miransky et al <sup>75</sup>	2001	209	15	Colorectal	X	
Namba et al <sup>76</sup>	2012	30,491	155	Total hip replacement	X	
Namba et al <sup>77</sup>	2013	56,216	404	Total knee arthroplasty	X	
Nash et al <sup>78</sup>	2011	11,879	491	Cardiac	X	
Neumayer et al <sup>79</sup>	2007	163,624	7,035	Multiple	X	
Nguyen et al <sup>80</sup>	2012	9,315	330	Mastectomy with or without immediate reconstruction	X	
Olsen et al <sup>81</sup>	2002	1,980	83	CABG	X	
Olsen et al <sup>82</sup>	2008	325	57	Major breast	X	
Olsen et al <sup>83</sup>	2008	1,605	81	Low transverse cesarean section	X	
Olsen et al <sup>10</sup>	2008	273	46	Spinal	X	X X
Olsen et al <sup>84</sup>	2009	807	85	Hysterectomy	X	
Park et al <sup>85</sup>	2009	680	76	Hepatic transplant	X	X
Paryavi et al <sup>86</sup>	2013	235	33	Lower extremity fracture	X	
Pastor et al <sup>87</sup>	2010	491	95	Elective colorectal resection		X
Ponce et al <sup>88</sup>	2014	18,830	264	Arthroplasty	X	
Rao et al <sup>89</sup>	2011	1,587	57	Spinal fusion	X	
Saleh et al <sup>90</sup>	2002	97	33	Total knee and hip arthroplasty	X	
Segal et al <sup>91</sup>	2014	51,644	7,721	Colon resection	X	
Senekjian and Nirula <sup>92</sup>	2013	61,830	802	Appendectomy	X	
Sharma et al <sup>93</sup>	2009	3,578	86	CABG	X	
Shields et al <sup>94</sup>	2013	586	31	Lung transplantation	X	
Shuman et al <sup>95</sup>	2012	84	14	Head and neck	X	
Singh et al <sup>96</sup>	2012	902	78	Varicose vein surgery	X	
Smith et al <sup>97</sup>	2004	176	45	Elective colorectal resection	X	
Spaniolas et al <sup>98</sup>	2014	503	23	Ventral hernia repair	X	
Suzuki et al <sup>99</sup>	2010	326	17	Acetabular fracture fixation	X	
Talbot et al <sup>100</sup>	2004	153	39	Median sternotomy for CABG, valve repair, and/or replacement	X	
Tomov et al <sup>101</sup>	2015	311	16	Orthopedic spinal	X	
Townsend et al <sup>102</sup>	1993	2,759	241	Non-emergent median sternotomy for cardiac operation	X	
Trick et al <sup>103</sup>	2000	120	30	CABG	X	X
Trinh et al <sup>104</sup>	2009	202	101	Any	X	
Trussell et al <sup>23</sup>	2008	808 <sup>a</sup> , 647 <sup>b</sup>	28/10	CABG	X	
Tserenpuntsa et al <sup>105</sup>	2014	2,656	698	Colon	X	
Walcott et al <sup>106</sup>	2014	399	17	Cranial neurosurgery	X	
Wilson and Sexton <sup>11</sup>	2003	258	129	Open heart surgery	X	X
Woods et al <sup>107</sup>	2013	1,799	56	Lumbar surgery	X	
Wooldridge et al <sup>108</sup>	2013	106	11	High-grade soft tissue sarcoma	X	
Young et al <sup>109</sup>	2011	216	18	Elective total abdominal hysterectomy	X	