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Adverse Impact of Diabetes on Spine Fusion and Patient-Reported Outcomes

A Systematic Review and Meta-analysis

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Study Design. Systematic review and meta-analysis.

Purpose. This meta-analysis aimed to provide a comprehensive evaluation of the impact of diabetes on spinal surgery outcomes.

Background. Diabetes mellitus is believed to be associated with an increased risk of adverse events during spinal surgery. With the increasing prevalence of diabetes and the increasing number of degenerative spinal procedures, understanding postsurgical expectations and optimal care is essential.

Materials and Methods. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic search was conducted across PubMed, EMBASE, Scopus, and the Cochrane Library, selecting studies comparing diabetes and those without diabetes who underwent spine fusion surgeries. Eighteen studies with 118,617 patients were included. The outcomes of interest were the risk of the incidence of spinal pseudoarthrosis and PROMs, including Visual Analog Scale (VAS), Oswestry Disability Index (ODI), EQ-5D, and SF-12/36 score. Odds ratios (OR) were calculated for dichotomous variables, mean differences (MD) for continuous variables, and standard mean differences (SMD) for continuous variables not sharing the same scale or units. Random effects were used if there was evidence of statistical heterogeneity.

Results. Eighteen studies, comprising 118,617 patients, were included in the final analysis. Diabetes patients had a higher incidence of pseudoarthrosis at the lumbar spine (OR: 1.13, 95% CI: 1.02 to 1.25, $P < 0.05$). Patients with diabetes also reported increased VAS back/neck pain scores (SMD: 0.21, 95% CI: 0.14 to 0.28, $P < 0.001$) and worse ODI outcomes (MD: 3.96, 95% CI: 3.10 to 4.82, $P < 0.001$), EQ-5D (MD: −0.06, 95% CI: −0.08 to −0.03, $P < 0.001$) and SF-12/36 scores (SMD: −2.70, 95% CI: −4.99 to −0.41, $P < 0.05$).

Conclusion. Patients with diabetes who underwent spinal surgery had a higher incidence of pseudoarthrosis and worse functional outcomes compared with nondiabetic patients. These findings

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As this research is a meta-analysis, it does not involve any direct human or animal subjects and, therefore, does not require ethical approval from an Institutional Review Board (IRB).

All data relevant to the study are included in the article or uploaded as online supplemental information. Data may be available upon reasonable request.

The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

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underscore the need for targeted clinical management and preventive strategies for patients with diabetes undergoing these procedures.

Level of Evidence. Level III.

Key Words: clinical management, diabetes, incidence, meta-analysis, nonunion, patient-reported outcomes, pseudoarthrosis, spine fusion, surgery, systematic review

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Diabetes mellitus is a growing global pandemic, with its prevalence in spinal surgery ranging from 15% to 25%[1–3] and an expected 35% increase by 2045.[4] It imposes significant economic burdens on health care systems, particularly in the United States, where costs exceed those in other countries, even after GDP adjustment.[5–7]

Diabetes has been linked to higher medical and surgical complications, particularly infections in orthopedic surgeries, such as joint replacements[8,9] and spinal procedures,[10] although its impact on fusion rates and functional outcomes remains debated.

Studies on radiologic outcomes in diabetic spinal surgery patients present varied findings: Emami *et al*[11] observed no differences in pseudarthrosis, while Liow *et al*[12] and Moazzeni *et al*[13] reported reduced fusion rates. Khan *et al*[14] found no change in PROMs, but Lynch *et al*[15] noted better short-term results in nondiabetics, and Armaghani *et al*[16] reported worse functional outcomes for diabetics.

This discrepancy underscores the complexity of this relationship and requires further research. One potential hypothesis for poorer diabetes outcomes in terms of nonunion or clinical results is the microvascular compromise commonly observed in patients with diabetes. Hyperglycemia may cause endothelial dysfunction, thickening of the basement membrane, and narrowing of the blood vessels, which impair blood flow and nutrient delivery to the fusion site. Such compromised vascularity may hinder bone formation and remodeling, ultimately increasing the risk of nonunion and delaying healing.[17] In addition, diabetes can adversely affect bone metabolism by disrupting the balance between bone formation and resorption, thereby further impairing bone healing.[18] These factors collectively contribute to poorer clinical outcomes, which are characterized by increased pain and reduced quality of life.

Diabetes prevention programs are cost-effective, and optimizing glucose control may improve patient outcomes.[19] This meta-analysis aimed to assess the impact of diabetes on nonunion and functional outcomes after spinal fusion surgery.

MATERIALS AND METHODS

Eligibility Criteria

This meta-analysis followed a written protocol that included review questions, search strategy, inclusion/exclusion criteria, and bias assessment (PROSPERO: CRD42023482203). The present study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20] The research question was formulated using the PICOS strategy: "P" adult patients undergoing fusion spine surgery, "I" the intervention group consisted of patients with diabetes (including type I and II diabetes), "C" the comparison group comprised patients without diabetes, "O" the main outcomes were the incidence of pseudarthrosis or nonunion and patient-reported outcome measures (PROMs), "S" the included studies were comparative studies such as cohort or case-control studies.

The following exclusion criteria were applied: studies involving patients under 18 years old, studies at high risk of bias, duplicated or incomplete data reporting, studies that did not evaluate at least one radiologic or clinical outcome measure of interest, and studies not focusing specifically on patients undergoing spinal fusion procedures.

Information Sources

To identify relevant studies, a systematic literature search was conducted using 4 electronic databases: PubMed, EMBASE, Scopus, and Cochrane Collaboration Library. No date or language restrictions were imposed to ensure that all relevant studies were included. The reference lists of the included studies were screened to identify additional relevant studies not included in the initial search.

Search Methods for Identification of Studies

To identify relevant studies, a comprehensive search was conducted using specific terms from all the relevant trial registers and databases. The search terms used were diabetes ("Spinal Fusion" OR "fusion rate" OR "spine failure") AND (diabetes) (Supplementary File 1, Supplemental Digital Content 1, http://links.lww.com/BRS/C717). The search was conducted by 2 independent reviewers who screened the studies for eligibility. Any disagreements were resolved through discussion, and a consensus was reached regarding which studies were included.

Data Extraction and Data Items

Two reviewers independently extracted data from the included studies. Any discrepancies between the reviewers were resolved through discussion. If an agreement could not be reached, a third independent reviewer was consulted. Baseline characteristics of each study were recorded. The main outcomes of interest were the incidence of nonunion and patient-reported outcome measures. PROMs that could be compared included the Visual Analog Scale (VAS) for back and neck pain, the VAS for leg/arm pain, the Oswestry Disability Index (ODI), and for quality-of-life measures, the EuroQol-5D (EQ-5D) and Short Form surveys (SF-12/36, Physical Component Summary (PCS) and Mental Component Summary (MCS) scales) at the final follow-up.

TABLE 1. Assessment of the Quality of Studies Through Methodological Index for Non-Randomized Studies (MINORS)

References	Clearly stated aim	Consecutive patients	Prospective collection data	Endpoints	Assessment endpoint	Follow-up period	Loss < 5%	Study size	Adequate control group	Contemporary group	Baseline control	Statistical analyses	MINORS
Armaghani *et al*[16]	2	2	2	2	2	2	0	2	1	2	0	2	**19**
Arnold *et al*[25]	1	2	1	2	2	2	2	2	2	2	2	2	**22**
Bergin *et al*[1]	2	2	0	2	2	2	0	2	2	2	2	2	**20**
Cho *et al*[26]	1	0	0	2	2	2	0	1	2	1	2	2	**15**
Emami et al[11]	2	2	1	2	2	1	2	1	2	2	2	2	**21**
Freedman *et al*[27]	2	2	1	2	2	2	0	2	1	2	1	2	**19**
Glassman *et al*[28]	2	0	0	2	1	1	2	1	1	1	1	2	**14**
Hills *et al*[29]	2	2	0	2	2	1	0	2	2	2	2	2	**19**
Hofler *et al*[30]	2	2	1	2	2	0	0	2	1	2	0	2	**16**
Khan *et al*[14]	2	2	0	2	2	2	0	2	1	2	0	2	**17**
Liow *et al*[12]	2	2	0	2	2	2	2	1	2	2	2	2	**21**
Lynch *et al*[15]	2	2	1	2	2	1	0	2	1	2	0	2	**17**
Moazzeni *et al*[13]	2	2	2	2	2	1	2	1	1	2	1	2	**20**
Nagata *et al*[31]	2	2	2	2	2	1	0	2	1	2	0	2	**18**
Ren *et al*[2]	2	2	0	2	1	1	1	1	2	2	2	2	**18**
Takahashi *et al*[32]	2	2	0	2	2	2	2	1	2	2	2	2	**21**
Wakao *et al*[33]	2	2	0	2	2	1	0	2	2	2	2	2	**19**
Zhou *et al*[3]	2	2	0	2	2	1	0	2	2	2	1	2	**18**

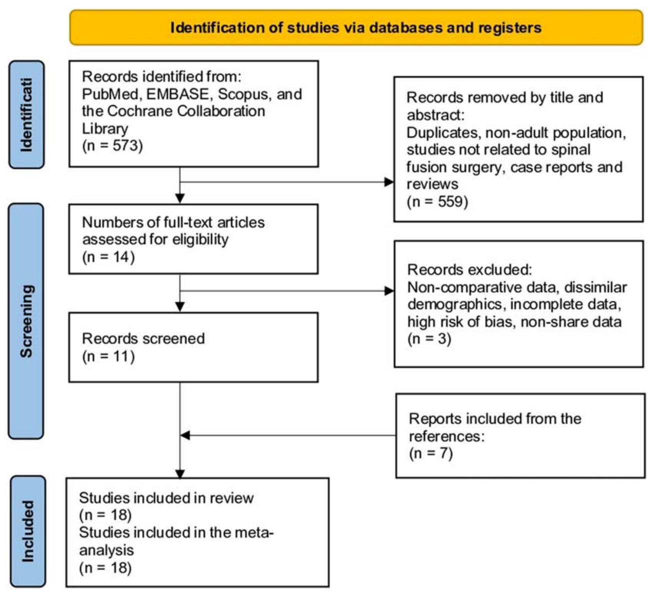

Figure 1. Study selection flow diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

The MCID and cutoff points for each PROM were also considered. The MCID for each PROM was as follows: VAS 2.6,[21,22] ODI 8.1,[21,22] EQ-5D 0.028;[23] SF-36, 4 points.[24] The cutoff points could only be calculated for the VAS and ODI for size effects. The VAS was used to assess pain, where a score of 0 indicated no pain, and a score of 10 indicated the worst imaginable pain. A score of 7 or higher indicates intense pain, 4 to 6 indicates moderate pain, and 3 or lower indicates mild pain. The ODI establishes common cutoff points to assess the level of disability based on everyday activities the patient can perform without significant limitations. The cutoff points were as follows: minimal disability (0% to 20%), moderate disability (21% to 40%), severe disability (41% to 60%), very severe disability (61% to 80%), and total disability (81% to 100%).

Assessment of Risk of Bias in Included Studies

Two authors independently assessed the quality of the included studies using the Methodological Index for Non-Randomized Studies (MINORS) criteria (Table 1).[34] The maximum score was 24 for comparative studies. Scores ranging from 0 to 6 were considered very low quality, 7 to 10 were considered low quality, 11 to 15 were considered fair quality, and scores of 16 or higher were considered high quality.[34]

Assessment of Results

The meta-analysis was conducted using Review Manager version 5.4 (RevMan), a software package provided by the Cochrane Collaboration. Odds ratios (OR) with 95% CIs were calculated for the dichotomous variables. For continuous variables, mean differences (MD) with 95% CI were calculated. For continuous variables not sharing the same scale or units, however, standard mean differences (SMD) with 95% CI were calculated. When individual studies provided risk factors as odds ratios, a generic inverse variance method was used. Heterogeneity was assessed using both the χ^2 test and the I^2 statistic. I^2 values ranging from 0% to 100% were considered indicative of low, moderate, and high heterogeneity, at 25%, 50%, and 75%, respectively. A fixed-effect model was used when there was no statistical evidence of heterogeneity, whereas a random-effect model was used when significant heterogeneity was observed. The meta-analysis included unadjusted estimates (crude associations) and adjusted estimates, accounting for confounders according to Cochrane Handbook guidelines.[35]

Publication Bias

Publication bias was assessed using Review Manager version 5.4.1 through the creation of funnel plots, and visual inspection was conducted to evaluate the symmetry of these plots.

Additional Analyses

Subgroup analyses were conducted by considering the location of the spinal procedure, specifically whether it was performed at the cervical or lumbar level. The lumbar location included thoracolumbar, lumbar, and lumbosacral procedures.

To examine the robustness of the meta-analysis findings, sensitivity analysis was performed using RevMan. The sensitivity analysis involved excluding studies with the highest weight or that exhibited significant differences from the rest of the studies in the comparisons of all outcomes during the main analysis.

The Grade of Recommendation, Assessment, Development, and Evaluation (GRADE) system was used to assess the quality of the evidence and grade the strength of the recommendations using GRADEpro (McMaster University, developed by Evidence Prime). This system assesses the study design, risk of bias, inconsistency, indirectness, imprecision, and summary of findings.[36]

RESULTS

Study Selection

A systematic search was conducted across multiple electronic databases, resulting in 573 citations. Following the evaluation of the titles and abstracts, 559 studies were excluded because they did not meet the predefined inclusion criteria. The full texts of the remaining 14 citations were thoroughly examined, and 3 studies were excluded because they did not meet the inclusion criteria. In addition, the reference lists of the remaining 11 articles were reviewed, leading to the inclusion of 7 additional studies. A total of 18 studies were included in the meta-analysis, as illustrated in Figure 1.[1–3,11–16,25–33]

Study Characteristics

Table 2 presents the baseline characteristics of the included studies. The 18 studies comprised 118,617 patients

TABLE 2. Baseline Characteristics of the 18 Included Studies

References	Period	Follow-up (y)	Region	Type of Study	Location	n Patients (DM/Control)	n Female (DM/Control)	Age (DM/Control)	Surgical technique	Etiologies	Nonunion assessment
Armaghani *et al*[16]	2010 to 2014	2.0	USA	Prospective cohort	Spine	1005 (434/571)	496 (198/298)	61/56	MD, Laminectomy, ACDF, LF, PCF	NS	NA
Arnold *et al*[25]	2005 to 2007	2.0	USA	Retrospective cohort	Cervical	278 (42/236)	113 (18/95)	60/56	Anterior or posterior decompressive/ reconstructive approach	Symptomatic CSM	NS
Bergin *et al*[1]	2014 to 2020	2.0	USA	Retrospective cohort	Cervical	278 (49/229)	NS	NS	Single-level ACDF + allograft cellular bone matrix	NS	CT or x-ray
Cho *et al*[26]	NS	2.0	USA	Retrospective cohort	Spine deformity	46 (23/23)	NS	61/59	PSF, ALIF, TLIF	ASD	NA
Emami *et al*[11]	2012 to 2015	3.1	USA	Retrospective cohort	Lumbar	204 (17/187)	NS	NS	1 or 2-level MIS TLIF	NS	X-ray
Freedman *et al*[27]	2000 to 2005	4.0	USA	Retrospective cohort	Lumbar	2406 (199/2207)	1160 (99/1061)	64/53	Noninstrumented fusion, instrumented fusion, multilevel fusion, or decompression only	Degenerative spondylolisthesis, intervertebral disk herniation, and spinal stenosis	NS
Glassman *et al*[28]	NS	1.0	USA	Retrospective cohort	Lumbar	137 (94/43)	83 (57/26)	32/28	PLIF	NS	NA
Hills *et al*[29]	2010 to 2016	1.0	USA	Retrospective cohort	Spine	2721 (1241/1480)	NS	NS	NS	NS	Surgical exploration
Hofler *et al*[30]	2009 to 2011	NS	USA	Retrospective cohort	Spine	107650 (15759/ 91891)	NS	NS	Spinal fusions	NS	NS
Khan *et al*[14]	2011 to 2018	1.9	USA	Retrospective cohort	Lumbar	850 (78/772)	453 (45/408)	66/58	Elective open posterior lumbar spinal fusion	Radiculopathy and neurogenic claudication	X-ray
Liow *et al*[12]	2002 to 2012	2.0	Singapore	Retrospective cohort	Cervical	58 (29/29)	21 (9/12)	59/59	Single-level ACDF	Cervical myelopathy	NA
Lynch *et al*[15]	2011 to 2020	1.0	USA	Prospective cohort	Cervical	363 (43/320)	152 (20/132)	57/50	Primary, single, or multilevel ACDF	Degenerative spinal pathology	CT
Moazzeni *et al*[13]	2014 to 2015	1.0	Iran	Prospective cohort	Lumbar	96 (48/48)	60 (28/32)	59/56	Lumbar fusion	Canal stenosis, disc herniation with instability, and degenerative spondylolisthesis	CT
Nagata *et al*[31]	2017 to 2018	1.0	Japan	Prospective cohort	Lumbar	993 (152/841)	430 (52/378)	71/66	PLIF, TLIF, PLLIF	Degenerative spine disease	NA
Ren *et al*[2]	2014 to 2017	0.5	China	Retrospective cohort	Cervical	295 (72/223)	NS	NS	ACDF	Cervical spondylotic disease	X-Ray
Takahashi *et al*[32]	2006 to 2009	2.9	Japan	Retrospective cohort	Lumbar	165 (41/124)	87 (20/67)	71/69	NS	Lumbar disc berniation or spinal stenosis	NS
Wakao *et al*[33]	2012 to 2019	1.0	Japan	Retrospective cohort	Lumbar	551 (57/494)	NS	NS	NS	Osteoporotic vertebral fracture	X-ray
Zhou *et al*[3]	2016 to 2020	0.5	China	Retrospective cohort	Cervical	750 (141/609)	NS	NS	ACDF	Cervical spondylotic disease	CT

ACDF indicates anterior cervical discectomy and fusion; ALIF, anterior lumbar interbody fusion; ASD, adult spinal deformity; LF, lumbar fusion; MD, microdiscectomy; MIS, minimally invasive surgery; NA, not applicable; NS, not specified; PCF, posterior cervical fusion; PLIF, posterior lumbar interbody fusion; PSF, posterior spine fusion; TLIF, transforaminal lumbar interbody fusion.

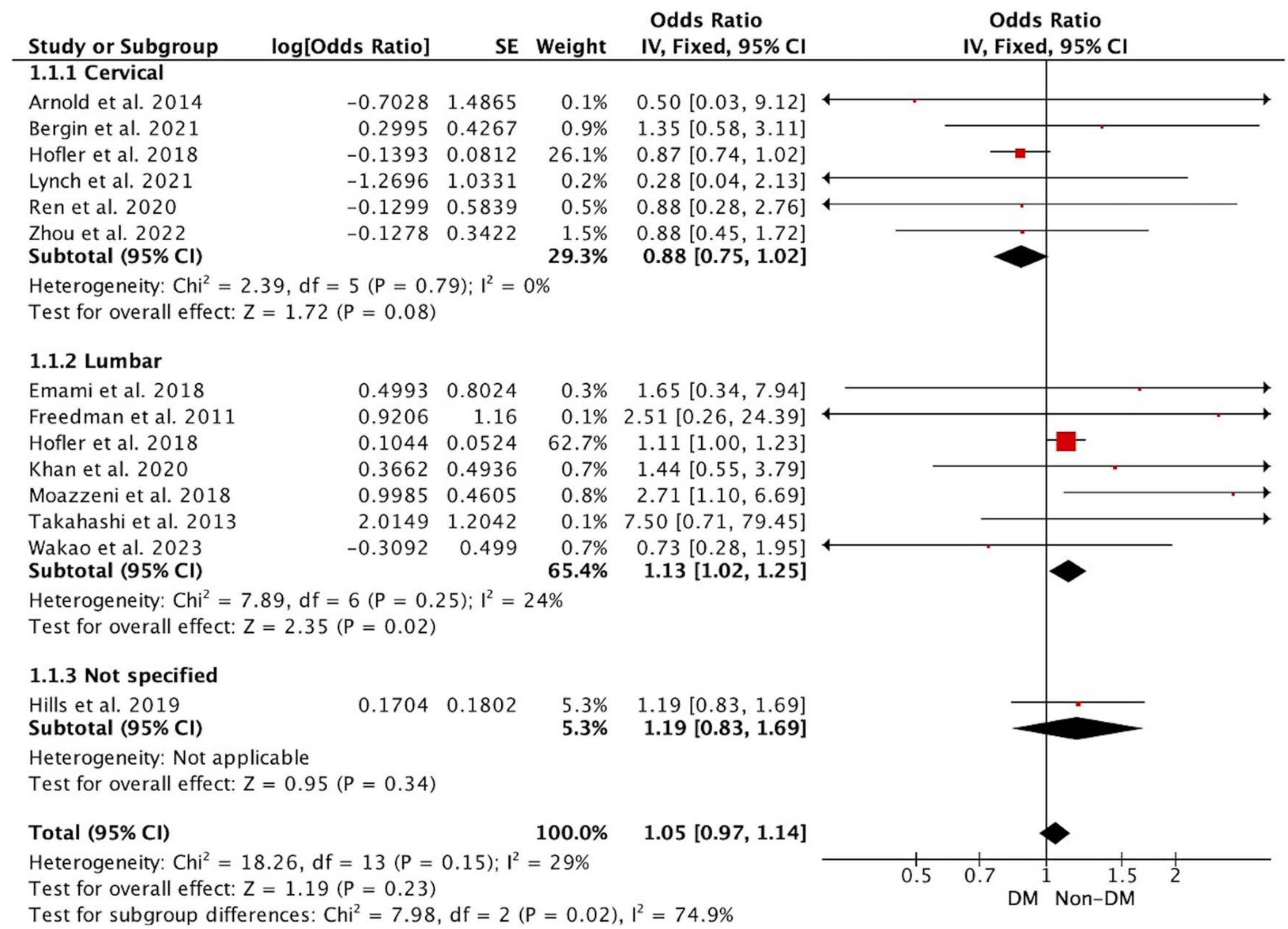

Figure 2. Forest plot showing the effect of diabetes on nonunion. The figure shows that at the cervical level there were no significant differences (OR: 0.88, 95% CI: 0.75–1.02), however, at the lumbar level, the patients with diabetes presented a greater risk of nonunion (OR: 1.13, 95% CI: 1.02–1.25).

(18,478 patients with diabetes and 100,139 patients without diabetes). The reported percentage of women in the diabetes and nondiabetes groups was 47.1% and 48.3%, respectively. The mean age ranged from 32 to 71 years in the diabetes group, and from 28 to 69 years in the nondiabetes group. The follow-up duration varied from 6 months to 4 years across the studies. Most studies (11/18, 61.1%) were conducted in the USA. All studies were cohort studies, of which 14 were retrospective and 4 were prospective. The location, surgical technique, etiology, and diagnostic assessment of nonunion are presented in Table 2. The evaluation of nonunion using each diagnostic test is presented in Supplemental Table 1 (Supplemental Digital Content 2, http://links.lww.com/BRS/C718).

Nonunion/Pseudoarthrosis

In univariate analysis, no significant differences were found between diabetic and nondiabetic patients regarding the incidence of nonunion at the cervical level (OR: 0.88, 95% CI: 0.75 to 1.02; studies = 6). However, diabetic patients had a higher incidence of nonunion at the lumbar level (OR: 1.13, 95% CI: 1.02 to 1.25; studies = 7; Figure 2). Three included studies performed multivariate analyses considering baseline patient and operative characteristics; however, no significant differences were found in the multivariate analysis (OR: 1.07, 95% CI: 0.96 to 1.19; studies = 3; Supplemental Fig. 1, Supplemental Digital Content 3, http://links.lww.com/BRS/C719). Subgroup analyses were not conducted because of the limited number of articles.

The sensitivity analysis did not change the direction of the results when removing the study with the highest weight, both at the cervical level (OR: 0.93, 95% CI: 0.59 to 1.47; studies = 6) and at the lumbar level (OR: 1.64, 95% CI: 1.00 to 2.68; studies = 7). Sensitivity analysis was not performed for the multivariate analysis because of the limited number of available articles.

Statistical Evaluation of PROMs

The VAS for back/neck pain indicated that diabetic patients had higher levels of pain than nondiabetic patients

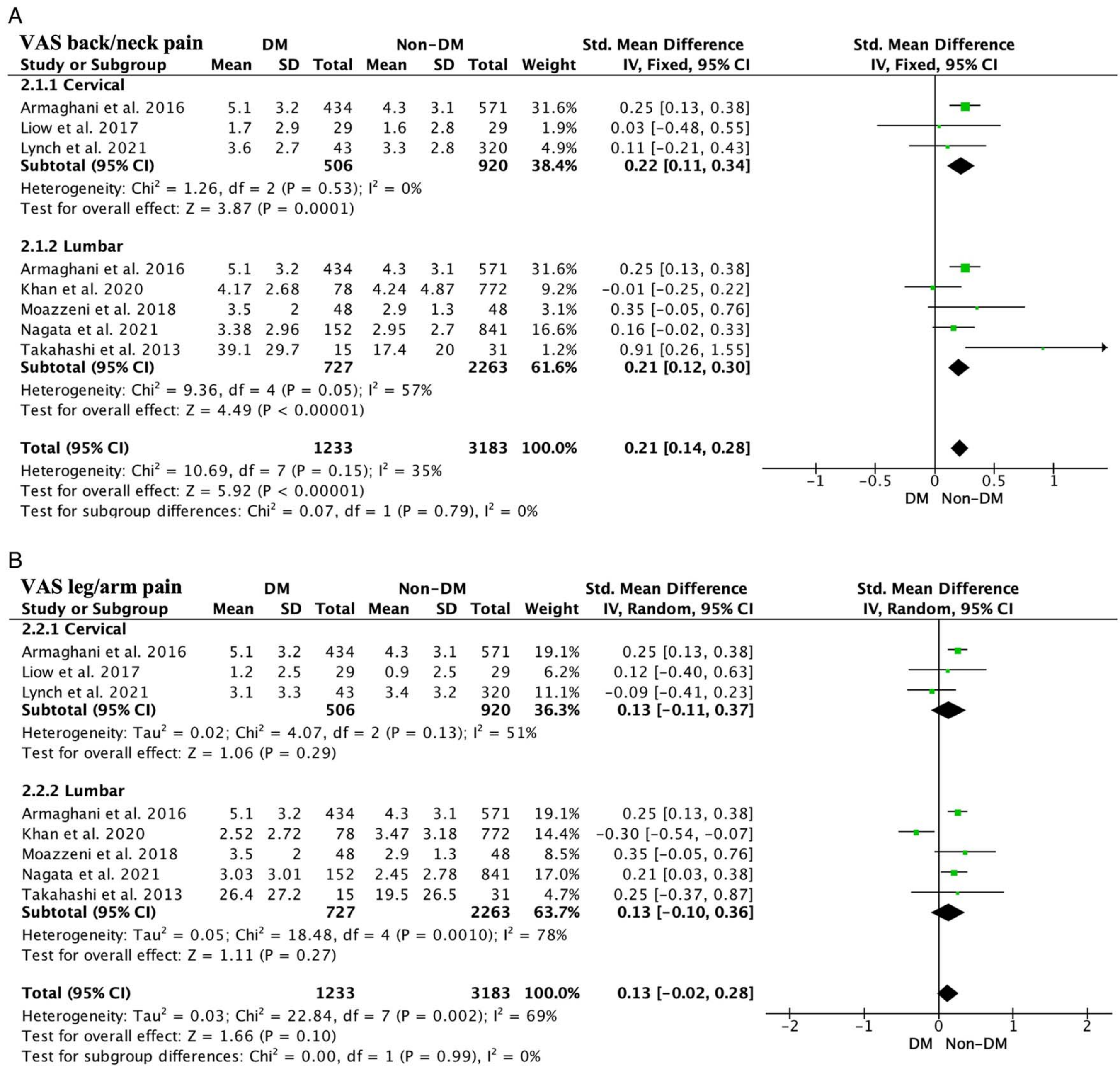

Figure 3. Forest plot showing the effect of diabetes on pain assessed by VAS for back/neck pain (A) and VAS for leg/arm pain (B). A, Diabetic patients presented with significantly greater pain than nondiabetic patients at the lumbar or cervical level. B, There were no differences in leg or arm pain between the two groups.

(SMD: 0.21, 95% CI: 0.14 to 0.28; participants = 4416; studies = 8; I^2 = 35%; Figure 3A). Subgroup analysis revealed that patients with diabetes had worse outcomes at both the cervical level (SMD: 0.22, 95% CI: 0.11 to 0.34; participants = 1426; studies = 3; I^2 = 0%) and lumbar level (SMD: 0.21, 95% CI: 0.12 to 0.30; participants = 2990; studies = 5; I^2 = 57%). The sensitivity analysis was consistent at the lumbar level (SMD: 0.15, 95% CI: 0.03 to 0.28; participants = 1985; studies = 5; I^2 = 63%), but no significant differences were found at the cervical level (SMD: 0.09, 95% CI: -0.18 to 0.36; participants = 421; studies = 3; I^2 = 0%). Overall, the diabetes group had significantly worse outcomes (SMD: 0.14, 95% CI: 0.03 to 0.26; participants = 2406; studies = 8; I^2 = 41%).

The VAS scores for leg/arm pain did not show any differences between the two groups (SMD: 0.13, 95% CI: -0.02 to 0.28; participants = 4416; studies = 8; I^2 = 69%; Figure 3B). Similarly, no differences were observed between the cervical (SMD: 0.13, 95% CI: −0.11 to 0.37; participants = 1426; studies = 3; I^2 = 51%) and lumbar

Study or Subgroup	DM Mean	DM SD	DM Total	Non-DM Mean	Non-DM SD	Non-DM Total	Weight	Mean Difference IV, Fixed, 95% CI
2.5.1 Cervical								
Armaghani et al. 2016	32.1	20	434	25.5	18.6	571	12.6%	6.60 [4.18, 9.02]
Arnold et al. 2014	33.1	4.8	42	30.8	1.4	326	34.6%	2.30 [0.84, 3.76]
Liow et al. 2017	20.5	20.9	29	21.1	20.3	29	0.7%	−0.60 [−11.20, 10.00]
Lynch et al. 2021	27.3	20.1	43	22.9	21	320	1.8%	4.40 [−2.03, 10.83]
Subtotal (95% CI)			**548**			**1246**	**49.6%**	**3.43 [2.21, 4.65]**
Heterogeneity: $Chi^2 = 9.52$, df = 3 (P = 0.02); $I^2 = 68\%$								
Test for overall effect: Z = 5.51 (P < 0.00001)								
2.5.2 Lumbar								
Armaghani et al. 2016	32.1	20	434	25.5	18.6	571	12.6%	6.60 [4.18, 9.02]
Cho et al. 2012	29.4	17.4247	23	29.5	18.3483	23	0.7%	−0.10 [−10.44, 10.24]
Freedman et al. 2011	−34.3	4.3	24	−37.4	0.8	768	24.9%	3.10 [1.38, 4.82]
Khan et al. 2020	34.33	19.99	78	30.42	20.63	772	3.4%	3.91 [−0.76, 8.58]
Moazzeni et al. 2018	40.7	15.4	48	31.5	12.5	48	2.3%	9.20 [3.59, 14.81]
Nagata et al. 2021	24.6	19.6	152	19.8	17.6	841	6.6%	4.80 [1.46, 8.14]
Subtotal (95% CI)			**759**			**3023**	**50.4%**	**4.49 [3.28, 5.70]**
Heterogeneity: $Chi^2 = 8.98$, df = 5 (P = 0.11); $I^2 = 44\%$								
Test for overall effect: Z = 7.28 (P < 0.00001)								
Total (95% CI)			**1307**			**4269**	**100.0%**	**3.96 [3.10, 4.82]**
Heterogeneity: $Chi^2 = 19.97$, df = 9 (P = 0.02); $I^2 = 55\%$								
Test for overall effect: Z = 9.05 (P < 0.00001)								
Test for subgroup differences: $Chi^2 = 1.47$, df = 1 (P = 0.23), $I^2 = 31.9\%$								

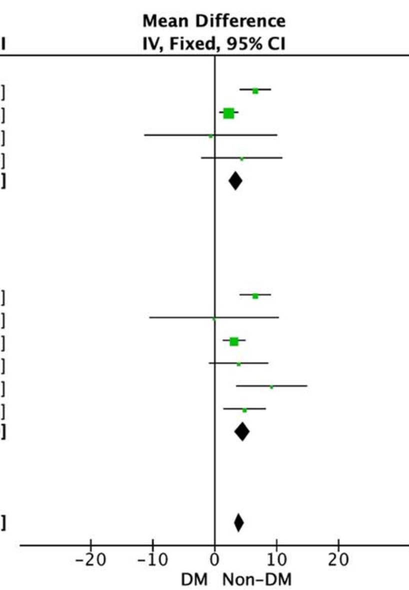

Figure 4. Forest plot showing the effect of diabetes on ODI. Patients with diabetes presented significantly worse results.

regions (SMD: 0.13, 95% CI: -0.10 to 0.36; participants = 2990; studies = 5; I^2 = 78%). Sensitivity analysis showed that when excluding 2 studies (one at the cervical level and one at the lumbar level) having completely opposite results as compared with the rest of the studies, patients with diabetes still demonstrated worse outcomes (SMD: 0.25, 95% CI: 0.17 to 0.32; participants = 3203; studies = 8; I^2 = 0%). This association persisted at both the cervical level (SMD: 0.25, 95% CI: 0.12 to 0.37; participants = 1063; studies = 3; I^2 = 0%) and lumbar level (SMD: 0.24, 95% CI: 0.15 to 0.34; participants = 2140; studies = 5; I^2 = 0%).

The ODI showed worse results in diabetic patients (MD: 3.96, 95% CI: 3.10 to 4.82; participants = 5576; studies = 10; I^2 = 55%; Figure 4). Subgroup analyses were conducted for both the cervical level (MD: 3.43, 95% CI: 2.21 to 4.65; participants = 1794; studies = 4; I^2 = 68%) and lumbar level (MD: 4.49, 95% CI: 3.28 to 5.70; participants = 3782; studies = 6; I^2 = 44%), which showed that diabetic patients had worse results than the nondiabetic group. The sensitivity analysis demonstrated consistency, and the associations remained in the overall assessment (MD: 5.91, 95% CI: 4.56 to 7.25; participants = 4416; studies = 10; I^2 = 0%), cervical level (MD: 6.02, 95% CI: 3.81 to 8.24; participants = 1426; studies = 4; I^2 = 0%), and lumbar level (MD: 5.84, 95% CI: 4.14 to 7.53; participants = 2990; studies = 6; I^2 = 1%).

The EQ-5D was assessed in 2 studies and showed significantly worse results in patients with diabetes (MD: −0.06, 95% CI: −0.08 to −0.03; participants = 1998; I^2 = 46%; Figure 5A). As only 2 studies were compared, no subgroup or sensitivity analyses were performed.

Finally, the SF-12/36 PCS revealed worse results in diabetic patients than in nondiabetic patients (SMD: −2.70, 95% CI: −4.99 to −0.41; participants = 2496; studies = 5; I^2 = 100%; Figure 5B). Subgroup analyses demonstrated significantly worse results for patients with diabetes at the cervical level (SMD: −0.23, 95% CI: −0.44, −0.02; participants = 699; studies = 5; I^2 = 0%), while no differences were found for studies at the lumbar level (SMD: −6.56, 95% CI: −18.82 to 5.70; participants = 1797; studies = 5; I^2 = 100%). The sensitivity analysis showed consistent results, maintaining that patients with diabetes exhibited worse outcomes than the control group (SMD: −3.30, 95% CI: −6.51, −0.09; participants = 2133; studies = 5; I^2 = 100%). Regarding SF-12/36 MCS, no differences were found between the groups (MD: 0.10, 95% CI: −0.43 to 0.62; participants = 1128; studies = 3; I^2 = 27%; Figure 5C). No sensitivity or subgroup analysis was conducted because only 3 studies were included.

Clinical Evaluation of PROMs

The MCID and comparison of the ranges for different clinical variables are shown in Table 3. The MCID was not reached for the VAS back/neck, VAS arm/leg, ODI, and EQ-5D scales, except for one study on VAS back/neck and ODI. In 3 studies, the SF-36 PCS exceeded the MCID, while in one study, the SF-36 MCS did so.

In contrast, in 3 out of 5 studies using VAS back pain, there were differences in pain threshold, with nondiabetic patients experiencing mild or low-intensity pain (<3 points on the VAS/NRS scale), and diabetic patients experiencing moderate pain. The same pattern was observed in 2 out of the 5 studies on the VAS leg pain.

Regarding the ODI, in 2 studies, the mean ODI score for diabetic patients indicated severe disability compared with nondiabetic patients who showed moder-

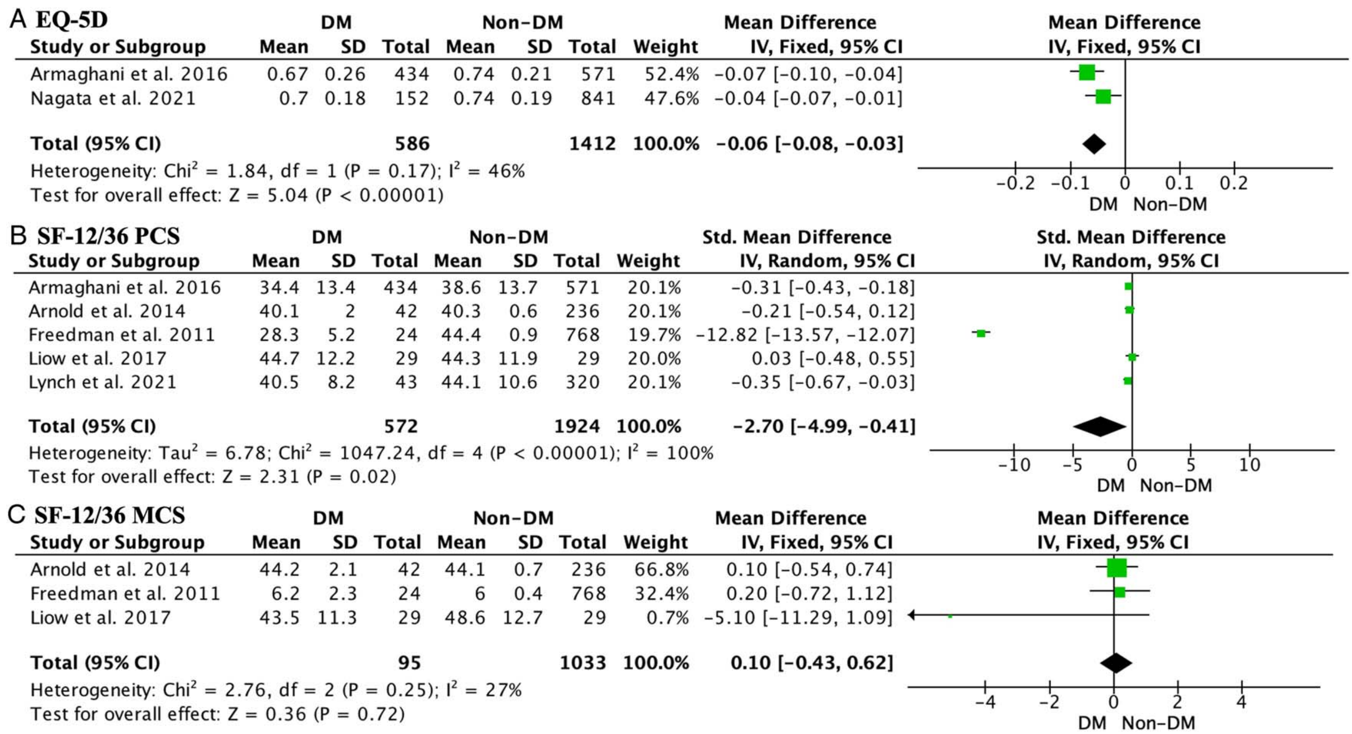

Figure 5. Forest plot showing quality of life scores with EQ-5D (A), SF-12/36 PCS (B), and SF-12/36 MCS (C).

ate disability. In the remaining studies, although the ODI scores were higher, indicating greater disability in patients with diabetes, all scores remained within the range of 20 to 40 points.

Publication Bias

No publication bias was detected for the main variables analyzed, except for VAS leg/arm pain, which showed heterogeneity and possible publication bias (Figure 6).

Grade of Recommendation, Assessment, Development, and Evaluation

The GRADE summary of the results for nonunion, VAS, and ODI are shown in Table 4. There was moderate certainty that patients with diabetes had a higher incidence of nonunion, pain, and disability. The main factors leading to lower certainty were clinical heterogeneity between studies in terms of surgical procedure, location, and etiology.

DISCUSSION

This systematic review and meta-analysis found that patients with diabetes had a higher incidence of lumbar nonunion. Diabetics also experienced more pain and disability, as assessed by the VAS, ODI, EQ-5D, and SF-12/36, although clinical interpretation remains controversial.

It was found significant differences in lumbar nonunion rates between diabetic and nondiabetic patients. When individual studies such as those by Emami *et al*,[11] Khan *et al*,[14] and Freedman *et al*[27] were examined, they tend to show that patients with diabetes have a higher incidence of nonunion, though the differences are not statistically significant. However, when data are pooled in a meta-analysis, significant differences emerge, indicating a higher risk of nonunion in the diabetic group. This could be attributed to the greater statistical power of the meta-analysis, which allows for a more robust analysis of trends. A possible hypothesis for the increased incidence of nonunion in diabetic patients could be related to microvascular changes that impair blood flow to the fusion site. However, it is important to note that there are no specific studies demonstrating this physiological finding in the lumbar area.[37] These alterations affect osteocyte and osteoblast functions, compromising bone repair and healing.[38] Consequently, patients with diabetes have higher lumbar nonunion rates, potentially requiring more revisions, as seen in the study by Arnold *et al*,[25] showing a 60% reoperation rate. No differences were observed at the cervical level, possibly because of the structural resistance of the cervical spine, lower biomechanical stress, and better vascularization compared with the lumbar spine, which may be further impaired in diabetes.[39]

The graft type may affect fusion surgery outcomes in patients with diabetes. Liow and colleagues and Bergin and colleagues used allografts, with Bergin also incorporating mesenchymal stem cells, yet found no significant differences favoring nondiabetics.[1,14] Moazzeni

TABLE 3. Clinical Assessment of Patient-Reported Outcomes Measures

References	VAS back/neck MCID	VAS back/neck pain DM	VAS back/neck non-DM	VAS leg/arm MCID	VAS leg/Arm pain DM	VAS leg/arm non-DM	ODI MCID	ODI DM	ODI non-DM	EQ-5D MCID	SF-12/36 PCS MCID	SF-12/36 MCS MCID
Cervical												
Armaghani *et al*[16]	No	Moderate	Moderate	No	Moderate	Moderate	No	Moderate	Moderate	No	Yes	NA
Arnold *et al*[25]	NA	NA	NA	NA	NA	NA	No	Moderate	Moderate	NA	No	No
Liow *et al*[12]	No	Mild	Mild	No	Mild	Mild	No	Moderate	Moderate	NA	No	Yes
Lynch *et al*[15]	No	Moderate	Moderate	No	Moderate	Moderate	No	Moderate	Moderate	NA	No	NA
Lumbar												
Armaghani *et al*[16]	No	Moderate	Moderate	No	Moderate	Moderate	No	Moderate	Moderate	NA	Yes	NA
Cho *et al*[26]	NA	NA	NA	NA	NA	NA	No	Moderate	Moderate	NA	NA	NA
Freedman *et al*[27]	NA	NA	NA	NA	NA	NA	No	Moderate	Moderate	NA	Yes	No
Khan *et al*[14]	No	Mild	Moderate	No	Mild	Moderate	No	Moderate	Moderate	NA	NA	NA
Moazzeni *et al*[13]	No	Moderate	Mild	No	Moderate	Mild	Yes	Severe	Moderate	NA	NA	NA
Nagata *et al*[31]	No	Moderate	Mild	No	Moderate	Mild	No	Moderate	Moderate	No	NA	NA
Takahashi *et al*[32]	Yes	Mild	Mild	No	Mild	Mild	NA	Moderate	Moderate	NA	NA	NA

DM indicates diabetes mellitus; MCID, minimally clinical important difference; NA, not applicable; ODI, Oswestry Disability Index; VAS, Visual Analog Scale.

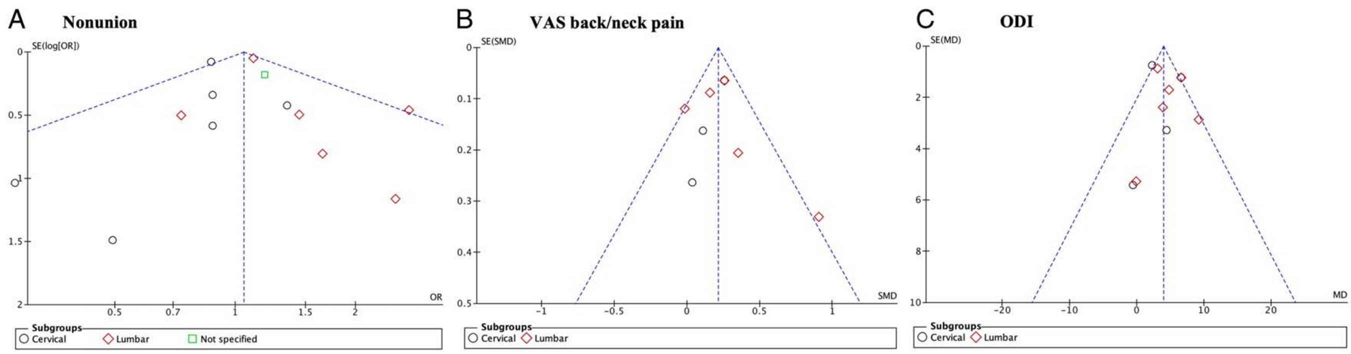

Figure 6. A–C, Funnel plot analysis for publication bias. No publication bias was observed in this study.

et al[13] noted larger disparities using local bone grafts, while Emami *et al*[11] saw no significant differences with autologous grafts. Vascular impairment in diabetics may worsen outcomes with nonlocal grafts.

Diabetic patients showed worse outcomes in PROMs, likely due to microvascular impairment causing chronic pain that was not fully resolved by surgery, similar to smoking studies.[27] Possible reasons why patients with diabetes have more pain may be due to both microvascular compromise[40] and pseudarthrosis.[41] Although the included studies did not specify whether these parameters result from diabetic neuropathy, it is recognized that peripheral nerve dysfunction can lead to spontaneous pain and increased pain sensitivity. These symptoms may originate from microvascular damage and impaired nerve conduction.[42] Microvascular complications in diabetes can further impair nerve function by reducing blood flow and oxygen supply to the nerves, leading to ischemia and subsequent nerve damage as well as contributing to nonunions.[43] Both scenarios, along with the increased rate of nonunion, could heighten pain levels and potentially lead to disability. In addition, preoperative microvascular compromise in diabetic patients may result in chronic and severe pain that surgery may not fully alleviate. It has also been noted that diabetic patients exhibit slower nerve conduction,[44] which could extend recovery periods compared with nondiabetic patients.

Longer follow-up is needed to better assess long-term pain and functional recovery, as patients with diabetes may take longer to recover due to nerve impairment and surgical stress.[45] Diabetes is a risk factor for complications in spinal surgery owing to factors such as age, BMI, prolonged operative times, and increased opioid consumption.[13–16,29,44] It is also associated with metabolic syndrome and comorbidities such as hypertension and cardiovascular disease, which further complicate outcomes.[46] Patients with diabetes and chronic kidney disease (CKD) have a lower quality of life,[47] worse surgical outcomes, and higher incidence of pseudoarthrosis.[48]

Postsurgical spine alignment and aggressive surgeries can influence outcomes.[14,27] Most studies did not differentiate between type I and II diabetes, or between controlled and uncontrolled cases. Future studies should explore surgical approaches, particularly minimally invasive techniques, considering the impact of diabetes on vascularization and healing.

Most studies did not reach the MCID for the VAS, ODI, or EQ-5D. However, 3 out of 5 studies surpassed the MCID in the SF-36 PCS, and one out of 3 in the SF-36 MCS. Diabetic patients showed moderate differences in lumbar and leg pain VAS scores compared with mild differences in nondiabetic patients. Silverstein *et al*[47] found nondiabetics surpassed the MCID more often after lumbar decompression.

These results may offer insightful recommendations for spine surgeons, such as selecting bone substitutes that demonstrate high fusion rates or better outcomes in high-risk patients.[49] In addition, there is a call for more aggressive postoperative pain management and intensive rehabilitation early on to enhance functionality in patients with diabetes. It is also crucial to manage the expectations of diabetic patients undergoing spinal surgery effectively and to ensure clear communication before surgery to better understand the additional risks associated with the disease. Ultimately, these practices are essential for proper risk stratification and management of economic resources, especially since diabetes has been shown to incur higher hospital costs compared with patients without diabetes undergoing the same surgeries.[50]

Limitations

This study had several limitations. All the studies included in this meta-analysis were cohort studies; 14 were retrospective and 4 were prospective. Therefore, it is helpful to consider the nature of these studies and their inherent limitations when attempting to establish causality regarding the definitive effect of diabetes on the included outcomes. Also, there was variability in the duration of follow-up among the included studies, ranging from 1 to 4 years. This diversity, together with the small number of studies on some variables, precluded a formal subgroup analysis based on follow-up

TABLE 4. GRADE Assessment of the Quality of the Evidence and the Strength of the Recommendations

Certainty Assessment							No. Patients		Effect			
No. studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention	Comparison	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Pseudo/nonfusion univariate												
12	Observational studies	Not serious	Not serious	Serious*	Not serious	Not detected	-/0	-/0	**OR: 1.05** (0.97 to 1.14)	**1 fewer per 1000** (from 1 fewer to 1 fewer)	⊕⊕⊕ Moderate	Critical
VAS/NRS back/neck FFU												
6	Observational studies	Not serious	Not serious	Serious*	Not serious	Not detected	1218	3152	—	MD **0.59 higher** (0.38 higher to 0.8 higher)	⊕⊕⊕ Moderate	Critical
ODI												
8	Observational studies	Not serious	Not serious	Serious*	Not serious	Not detected	1284	4246	—	MD **3.99 higher** (3.13 higher to 4.85 higher)	⊕⊕⊕ Moderate	Critical

*Differences in surgical procedure, location, and etiology.
MD indicates mean difference; OR, odds ratio.

times. However, upon visual inspection, no clear trend was observed, suggesting there is no relationship between the outcomes and follow-up duration. The “Physical Functioning” and “Physical Component” scores from SF-12/36 were combined using standardized mean difference (SMD), and the type of diabetes was not specified in some studies, which may have influenced results. The small number of studies has limited the ability to correlate spinal fusion with functional outcomes. Another limitation of the study was that the included articles only reported overall incidence rates of pseudarthrosis without detailing temporal aspects or possible contributing factors, such as instrumentation failure. It is crucial to acknowledge the heterogeneity present in our meta-analysis, particularly in terms of the pooling data from various institutions, which encompasses different patient demographics and employs diverse surgical interventions. Furthermore, patients with diabetes often have additional significant comorbidities that could influence the final outcomes. This complexity introduces additional contributing factors beyond diabetes. In addition, the methodologies for assessing spinal fusion varied across the included studies, which must be considered when interpreting the outcomes of the fusion procedures. Although our meta-analysis aimed to control for confounding factors, the possibility of iatrogenic errors, instrumentation failure, and the influence of revision surgeries on outcomes cannot be entirely ruled out. This is because the vast majority of individual studies did not provide adjusted data. In the case of nonunion, only 3 studies offered multivariable analyses considering different confounding factors, and there were no significant differences. In the case of PROMs, it was not possible to establish multivariable analysis in any case. MCID estimations based on mean differences could benefit from more detailed patient-level data. Furthermore, the lack of information on graft type limited the interpretation of the results.

However, the strengths of this study include its large sample size, which provides more representative results. In addition, most of the studies were conducted in the USA, potentially enhancing the validity of the results for this population. Furthermore, the use of quality-of-life data adjusted for confounders offers reliable insights into the impact of diabetes on patients undergoing spinal surgery.

CONCLUSIONS

This systematic review and meta-analysis provide evidence that patients with diabetes, as compared with those without, have a higher risk of developing lumbar pseudarthrosis following spinal fusion surgery. Analyses of patient-reported outcomes showed that patients with diabetes experience higher postoperative pain and functional disability. Diabetes is a relevant risk factor to consider in the perioperative management and follow-up of patients undergoing spinal fusion surgery.

➢ Key Points

- ❑ Diabetes significantly increases the risk of pseudarthrosis following lumbar spinal fusion surgery.
- ❑ Postoperative pain and disability are worse in patients with spinal fusion and diabetes. Our findings underscore the importance of optimized pain management and rehabilitation strategies in the diabetic population.
- ❑ Diabetes status is an important patient characteristic to evaluate and account for risk stratification, surgical planning, and follow-up care for spinal fusion. The recognition of diabetes as a risk factor can help improve outcomes in vulnerable patients.

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