North American Spine Society Journal (NASSJ) 12 (2022) 100168

Contents lists available at ScienceDirect

North American Spine Society Journal (NASSJ)

journal homepage: www.elsevier.com/locate/xnsj

Systematic Reviews /Meta-analyses

A Systematic Review and Meta-Analysis of Silicon Nitride and Biomaterial Modulus as it Relates to Subsidence Risk in Spinal Fusion Surgery

Jared D. Ament [1,2,3,4,*], Amir Vokshoor [1,2], Randy Yee [3], J. Patrick Johnson [4]

[1] *Neurosurgery & Spine Group, Los Angeles CA*
[2] *Institute for NeuroInnovation, Los Angeles, CA*
[3] *Neuronomics, Los Angeles, CA*
[4] *Cedars Sinai Medical Center, Los Angeles, CA*

ARTICLE INFO

Keywords:
spinal fusion
biomaterials
subsidence

ABSTRACT

Introduction: For decades, researchers and surgeons have sought to determine the optimal biomaterial for spinal fusion implants. Successful fusion is associated with improved quality of life while failures are often associated with costly and complex revisions. One common failure is subsidence. Biomaterials with higher modulus are thought to be related to subsidence risk but this has not been thoroughly investigated. The aim of this systematic review and meta-analysis is to assess silicon nitride and biomaterial modulus as they relate to subsidence risk in spinal fusions.

Methods: A systematic review was conducted using the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. Databases searched included PubMed-Medline, Google Scholar, Embase, EBSCO, and Cochrane Library. Study quality was assessed according to the Newcastle-Ottawa Scale. A network meta-analysis was chosen, allowing for direct and indirect comparisons for multiple treatments using a Bayesian hierarchical framework with Markov chain Monte Carlo methods. Outcomes were reported as odds ratios with 95% confidence intervals. Heterogeneity between studies was evaluated using the I^2 test. A pairwise meta-analysis was also produced to compare the results of network analysis for consistency. Publication bias was assessed using a funnel plot, Egger test, and Begg test. All analyses were conducted using R (Project for Statistical Computing, ver. 4.0.4).

Results: The initial search yielded a total of 821 articles. After removal of duplicates and screening based on inclusion and exclusion criteria, 64 articles were available for review and 13 were selected for meta-analysis. Biomaterial implant types in the final studies included: silicon nitride (Si_3N_4), polyetheretherketone (PEEK), titanium (Ti), and two composites, nano-hydroxyapatite/polyamide 66 (n-HA/PA66) and a carbon fiber reinforced polymer (CFRP). A total of 1,192 patients were included in this analysis – 419 with titanium implants, 460 with PEEK, 96 with Si_3N_4, 332 with n-HA/PA66, and 35 with CFRP. Titanium had the highest rate of subsidence compared to other biomaterials. Pairwise analysis was consistent with these results. Both the Egger test ($p = 0.28$) and Begg test ($p = 0.37$) were found to be non-significant for publication bias.

Conclusions: Spinal fusion implants derived from Si_3N_4, compared to PEEK and titanium, do not appear to be correlated with increased subsidence risk.

Introduction

For decades, researchers and surgeons have sought to determine the most optimal biomaterials for spinal fusion surgery. The rational is both sensible and economic. Improved healing and adequate fusion are associated with improved quality of life, faster return to work, less pain, less opiate use, and fewer repeat surgeries.[1] This is in stark contrast to failed fusions, often due to pseudoarthrosis or subsidence. Failures are associated with costly and often more complicated revisions as well as serious downstream consequences for patients. Many have posited that biomaterials with higher modulus of elasticity are directly related to subsidence and, therefore, failed fusion.[2] However, this belief has not been thoroughly investigated. To best facilitate fusion, it has been posited that biomaterials used within the disc space had to mimic the

FDA device/drug status: Not applicable.

Author disclosures: ***JAD***: Fees: SINTX Inc ((D). Payment for writing or reviewing the manuscript: SINTX Inc (C). ***AV***: Nothing to disclose. ***RY***: Fees: Neuronomics LLC (C). ***JPJ***: Nothing to disclose.

* Corresponding author: Neurosurgery & Spine Group, 7320 Woodlake Ave., Suite 215, West Hills, CA 91307. 800-899-0101
E-mail address: jared.ament@cshs.org (J.D. Ament).

https://doi.org/10.1016/j.xnsj.2022.100168
Received 23 June 2022; Received in revised form 1 September 2022; Accepted 2 September 2022
Available online 9 September 2022

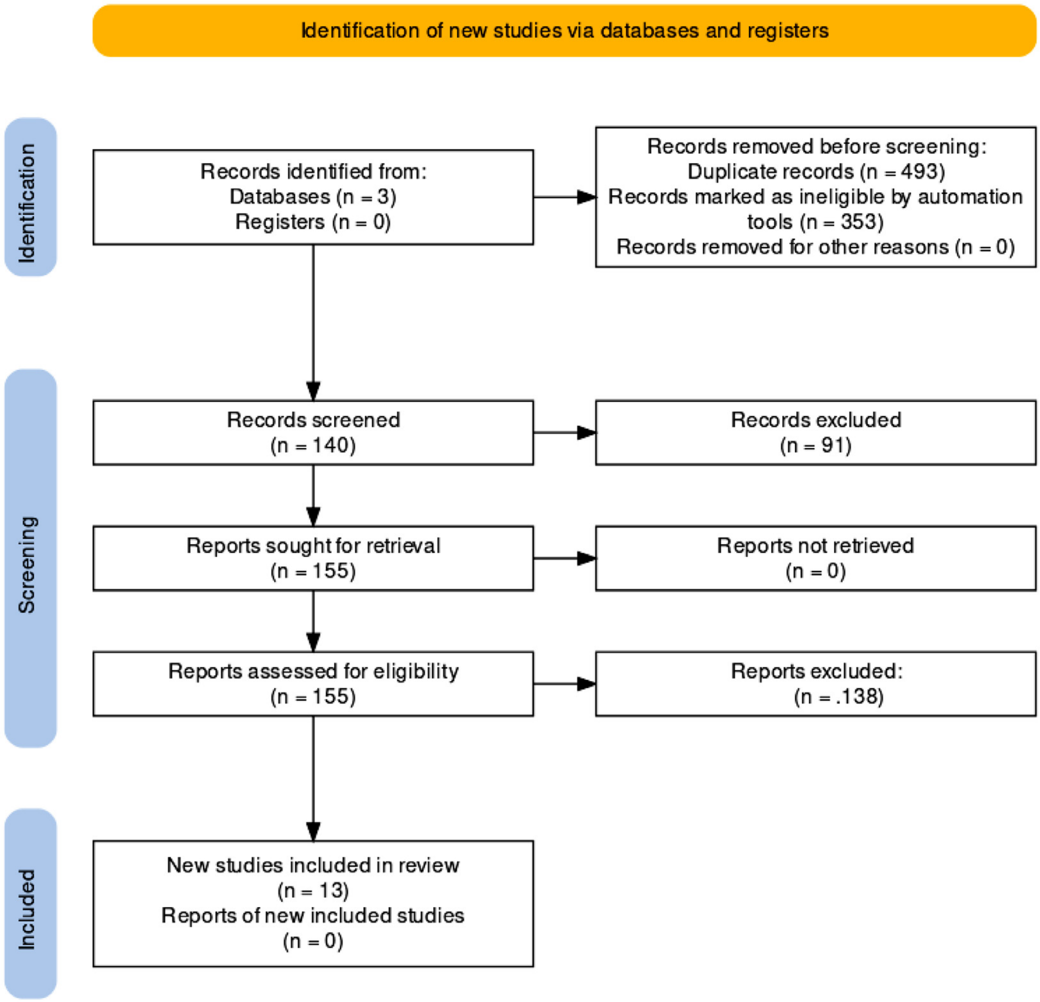

Figure 1. PRISMA Flow Diagram
Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis Campbell Systematic Reviews, 18, e1230. https://doi.org/10.1002/cl2.1230

properties of native bone. Similarly, radiolucent biomaterials were preferred so that future radiographic interpretation was not hindered. This resulted in decades of widespread adoption of polyetheretherketone (PEEK). However, as implant biology and surface interfaces were more closely evaluated at the cellular level, new concerns arose over PEEK's bioreactivity and healing.[3] The properties of both PEEK and titanium for interbody fusions were rigorously compared in the literature with little consensus after over two-hundred-and-fifty papers published on the topic.[4]

Many novel biomaterials have since been introduced, purporting various benefits with respect to fusion rates, healing, anti-bacterial properties, radiographic properties, surface interfaces, and more. Despite innumerable publications comparing some of the options, the ultimate choice in utilization has often been relegated to surgeon comfort or devices and options they used in training. Silicon nitride (Si_3N_4) is one particular biomaterial that the authors felt lacked organized clinical data and conclusions despite a plethora of strong basic science data. It also appeared to be a viable competitor to the increasingly popular advances in titanium technology, such as 3D printed and surface engineered options. The sparse data that does exist suggests that silicon nitride may afford earlier fusions and less infections from inherent bacteriostatic properties.[5–7] However, contradictory data also exists (i.e., SNAP trial[8]) that alludes to the fact that Si_3N_4 may not be superior or even comparable to PEEK, whereas another RCT by McEntire BJ et al.[9], demonstrated non-inferiority to PEEK.

To provide evidence-based practice recommendations, our objective was to conduct a systematic review to better understand the totality and quality of the data available. Secondarily, we sought to analyze subsidence risk as it relates to modulus of elasticity. The purpose of this study was to therefore conduct a meta-analysis based on a structured systematic literature review to assess silicon nitride and biomaterial modulus as they both relate to subsidence risk in spinal fusion surgery.

Materials and Methods

Search Strategy

A systematic review was first conducted using the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines.[10] Databases searched included PubMed-Medline, Google Scholar, Embase, EBSCO, and Cochrane Library. The literature search was conducted by authors JA and RS and was restricted to articles published in English from January 2000 to September 2021. It was performed using specific key words related to prospective or retrospective studies involving patients undergoing spinal fusion surgery using cage implants with an identified biomaterial, with assessment for subsidence.

Table 1
Summary of Studies

Study	Quality of Evidence	Study Design	Country	Surgery	Biomaterial					Surgical Indication	Biomaterial by Levels				
					Ti	PEEK	Si_3N_4	n-HA/PA66	Carbon Fiber		Ti	PEEK	Si_3N_4	n-HA/PA66	Carbon Fiber
Arts et al. 2017	Good	RCT	Netherlands	ACDF	-	PEEK (Medicrea Manta)	Valeo C+CSC (Sintx)	-	-	Cervical Radicular Syndrome	-	C3-4 (1); C4-5 (6); C5-6 (30); C6-7 (10); C7-T1 (1)	C3-4 (1); C5-6 (30); C6-7 (19); C7-T1 (2)	-	-
Cabraja et al. 2012	Good	Retrospective	Germany	ACDF	CeSpace Titan cage with Plasmapore coating (Aesculap)	CeSpace PEEK cage (Aesculap)	-	-	-	Degenerative Disc Disease	C3-4 (1); C4-5 (7); C5-6 (23); C6-7 (13)	C3-4 (6); C4-5 (10); C5-6 (20); C6-7 (6)	-	-	-
Chen et al. 2013	Good	RCT	China	ACDF	SynCage-C (Synthes)	PEEK box cage (Depuy Spine)	-	-	-	Cervical spondylotic myelopathy	C3-6 (14); C4-7 (15)	C3-6 (18); C4-7 (13)	-	-	-
McEntire et al. 2020	Good	RCT	Netherlands	TLIF	-	PEEK cage (Phantom)	ValeoTM OL (Sintx)	-	-	Chronic LBP and disc degeneration of Pfirmann grade III or higher and/or isthmic or degenerative spondylolisthesis grade I or II	-	L3-4 (4); L4-5 (19); L5-S1 (23); L5-6 (1); L6-S1 (1); L3-4 (2); L4-5 (2); L5-S1 (1)	L3-4 (6); L4-5 (11); L5-S1 (24); L5-6 (1); L6-S1 (2); L4-5 (7); L5-S1 (1)	-	-
Nemoto et al. 2014	Good	Retrospective	Japan	TLIF	Capstone (Medtronic)	PEEK (Medtronic)	-	-	-	Chronic low back pain (LBP) and irradiating lower extremity symptoms	L4-5 (7); L5-S1 (16)	L4-5 (10); L5-S1 (15)	-	-	-
Niu et al. 2010	Good	Prospective	Taiwan	ACDF	VIGOR-r cage (Advanced Spine Technology)	Solis PEEK cage (Stryker)	-	-	-	Cervical degenerative disc disease	C3-4 (6); C4-5 (10); C5-6 (17); C6-7 (4)	C3-4 (2); C4-5 (6); C5-6 (15); C6-74 (10)	-	-	-
Wrangel et al. 2017	Fair	Retrospective	Germany	PLIF	NR	NR	-	-	-	Degenerative lumbar instability	L3-4 (5); L4-5 (6); L5-S1 (6)	L2-3 (2); L3-4 (8); L4-5 (11); L5-S1 (7)	-	-	-

(*continued on next page*)

Table 1 (*continued*)

Study	Quality of Evidence	Study Design	Country	Surgery	Biomaterial					Surgical Indication	Biomaterial by Levels				
					Ti	PEEK	Si_3N_4	n-HA/PA66	Carbon Fiber		Ti	PEEK	Si_3N_4	n-HA/PA66	Carbon Fiber
Deng et al. 2016	Fair	Retrospective	China	TLIF	-	Shandong We-go Orthopedic Group Medical Polymer CO	-	Sichuan University and Department of Orthopedics, The First Affiliated Hospital of Chongqing Medical University	-	Degenerative or isthmus spondylolisthesis, degenerative disc disease, lumbar stenosis, lumbar disc herniation or recurrent lumbar disc herniation	-	-	-	L2-3 (2); L3-4 (16); L4-5 (86); L5-S1 (55)	L1-2 (4); L2-3 (1); L3-4 (21); L4-5 (89); L5-S1 (63)
Hu et al. 2019a	Good	Retrospective	China	ACCF	Titanium Mesh Cage	-	-	NR	-	Cervical spondylosis	C4 (7); C5 (25); C6 (20)	-	-	C4 (9); C5 (29); C6 (17)	-
Hu et al. 2019b	Good	Retrospective	China	ACDF	-	NR	-	NR	-	Cervical spondylosis	-	C3-4 (5); C4-5 (10); C5-6 (18); C6-7 (14)	-	C3-4 (4); C4-5 (12); C5-6 (22); C6-7 (13)	-
Yang et al. 2013	Good	RCT	China	ACCF	Titanium Mesh Cage (Medtronic Sofamor Danek)	-	-	Cage (Sichuan National Nano Technology Co.)	-	Cervical degenerative diseases	C3 (3); C4 (8); C5 (15); C6 (6)	-	-	C3 (3); C4 (11); C5 (13); C6 (8)	-
Yoo et al. 2014	Good	Retrospective	South Korea	ACDF	-	Solis PEEK cage (Stryker)	-	-	Carbon fiber composite frame cages (Co-Ligne AG)	Cervical degenerative diseases	-	C3-4 (1); C4-5 (4); C5-6 (16); C6-7 (2)	-	-	C3-4 (3); C4-5 (2); C5-6 (20); C6-7 (10)
Zhang et al. 2014	Fair	Retrospective	China	ACCF	Titanium Mesh Cage (Medtronic Sofamor Danek)	-	-	Cage (Sichuan National Nano Technology Co.)	-	Multilevel cervical spondylotic myelopathy	C4 (6); C5 (16); C6 (3); C4-5 (10); C5-6 (11)	-	-	C4 (7); C5 (36); C6 (9); C4-5 (11); C5-6 (8)	-

*NR = not reported
Ti = titanium
PEEK = polyetheretherketone
Si_3N_4 = silicon nitride
n-HA/PA66 = nano-hydroxyapatite/polyamide66

Table 2
Patient Demographics by Included Study:

Study	Number of Patients (Female/Male)					Age (range or ±SD)					Smoking Status				
	Ti	PEEK	Si_3N_4	n-HA/PA66	Carbon Fiber	Ti	PEEK	Si_3N_4	n-HA/PA66	Carbon Fiber	Ti	PEEK	Si_3N_4	**n-HA/PA66**	**Carbon Fiber**
Arts et al. 2017	-	48 (23/25)	52 (23/29)	-	-	-	49.4 [28-67]	53.3 [34-74]	-	-	-	39.6% (19/48)	46.2% (24/52)	-	-
Cabraja et al. 2012	44 (18/26)	42 (14/28)	-	-	-	51.1 ± 8.9	57.6 ± 11.1	-	-	-	61.4% (27/44)	52.4% (22/42)	-	-	-
Chen et al. 2013	29 (12/14)	31 (15/16)	-	-	-	45.7 ± 7.2	47.2 ± 6.8	-	-	-	24.1% (7/29)	25.8% (8/31)	-	-	-
McEntire et al. 2020	-	48 (33/15)	44 (28/16)	-	-	-	53.0 ± 9.5	55.2 ± 11.7	-	-	-	35.4% (17/48)	27.3% (12/44)	-	-
Nemoto et al. 2014	23 (1/22)	25 (2/23)	-	-	-	40.7 ± 10.2	42.9 ± 10.4	-	-	-	NR	NR	-	-	-
Niu et al. 2010	28 (13/15)	25 (13/12)	-	-	-	49.5 ± 11.5	52.2 ± 10.5	-	-	-	NR	NR	-	-	-
Wrangel et al. 2017	15 (5/10)	25 (18/7)	-	-	-	63 ± 12	69 ± 10	-	-	-	NR	NR	-	-	-
Deng et al. 2016	-	142 (82/60)	-	124 (63/61)	-	-	53.65 ± 14.43	-	53.28 ± 12.51	-	-	NR	-	NR	-
Hu et al. 2019a		52 (24/28)	-	55 (29/26)	-	54.9 ± 9.5	-	-	-	56.5 ± 10.4	NR	-	-	NR	-
Hu et al. 2019b	-	51 (23/28)	-	47 (22/25)	-	-	51.3 ± 9.5	-	52.5 ± 10.4	-	-	15.7% (8/51)	-	21.3% (10/47)	-
Yang et al. 2013	32 (12/20)	-	-	35 (13/22)	-	46.8 ± 7.2	-	-	47.6±7.1	-	31.3% (10/32)	-	-	40.0% (14/35)	-
Yoo et al. 2014	-	23 (13/10)	-	-	35 (13/22)	-	53.9	-	-	51.8	-	34.8% (8/23)	-	-	40.0% (14/35)
Zhang et al. 2014	46 (22/24)	-	-	71 (30/41)	-	1 level 55.04 ± 11.09; 2 level 57.81 ± 11.50	-	-	1 level 56.56 ± 12.13; 2 level 57.00 ± 10.95	-	NR	-	-	NR	-

*NR = not reported
Ti = titanium
PEEK = polyetheretherketone
Si_3N_4 = silicon nitride
n-HA/PA66 = nano-hydroxyapatite/polyamide66

Table 3
Summary of Subsidence Definition, Follow-up, Modality Used for Assessment, Events:

Study	Definition	Mean Follow-up	Modality	Results (Events)				
				Ti	PEEK	Si_3N_4	n-HA/PA66	Carbon Fiber
Arts et al. 2017	[≥2 mm] *multiple measurements reported	24 months (last)	CT and Medical Metrics, Inc. (MMI, Houston, TX, USA) software	-	52.2% (24/46)	50.0% (23/46)	-	-
Cabraja et al. 2012	≥2 mm	28.4 months	NR	20.5% (9/44)	14.3% (6/42)	-	-	-
Chen et al. 2013	≥3 mm	99.7 months	NR	34.5 % (17/87)	5.4% (5/93)	-	-	-
McEntire et al. 2020	≥2 mm	24 months (last)	X-Ray and CT	-	0.0% (0/53)	0.0% (0/52)	-	-
Nemoto et al. 2014	≥2 mm	24 months (last)	CT	34.8% (8/23)	28.0% (7/25)	-	-	-
Niu et al. 2010	≥3 mm	Ti 31.9 ± 3.4; PEEK 30.4 ± 3.3	NR	16.2% (6/37)	0% (0/34)	-	-	-
Wrangel et al. 2017	NR	Ti 62 ± 13; Peek 39 ± 12	CT	0.0% (0/15)	0.0% (0/25)	-	-	-
Deng et al. 2016	>3 mm	PEEK 14.61 ± 4.08; n-HA/PA66 14.69 ± 4.13	CT	-	9.0% (16/178)	-	7.6% (12/159)	-
Hu et al. 2019a	≥3 mm; radiographic > 2 mm	Ti 102.4 ± 4.6; n-HA/PA66 103.6 ± 6.3	X-Ray and CT	40.4% (22/52)	-	-	18.2% (10/55)	-
Hu et al. 2019b	radiographic >2 mm	PEEK 95.4 ± 8.4; n-HA/PA66 98.6 ± 11.3	CT	-	9.8% (5/51)	-	10.6% (5/47)	-
Yang et al. 2013	>3 mm	48 months (last)	CT	21.9% (7/32)	-	-	5.7% (2/35)	-
Yoo et al. 2014	>3 mm	24 months	MRI	-	26.1% (6/23)	-	-	34.3% (12/35)
Zhang et al. 2014	>3 mm	45.28 ± 12.83 months	CT	30.4% (14/46)	-	-	4.2% (3/71)	-

* NR = not reported

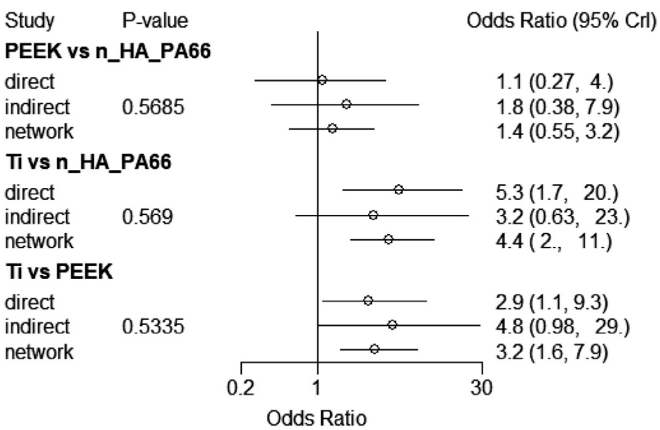

Figure 2. Node-split Analysis

The selection process included identifying and excluding duplicate entries, followed by reviews of titles and abstract for relevance, and finally full-text review. Manuscripts selected for review and final inclusion were based on MINORS criteria for quality.[11]

Study elements (metadata, abstract, full text, PICO elements) were managed using the Zotero reference management software.

Inclusion and Exclusion Criteria

Studies were selected if subsidence rates were reported and feasible for data extraction; and if the study evaluated at least two different types of biomaterials. Studies were excluded if the focus was on novel device design only (i.e., 3D printed cages) or involved solely metallic-polymer composite biomaterial devices (i.e., Ti/PEEK or Ti-coated PEEK).

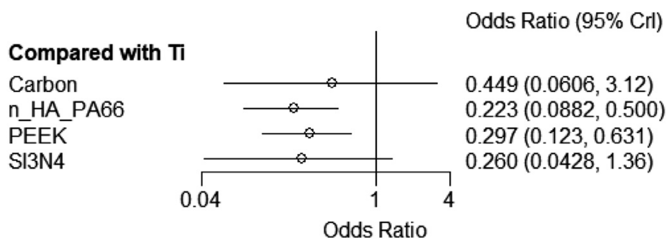

Figure 3. Meta-Analysis Forest Plot

Quality Assessment

Quality was assessed according to the Newcastle-Ottawa Scale,[12] which scores studies under three main categories: selection, comparability, and outcome. The maximum score was nine, and studies meeting seven or more of the items were considered of good quality in this analysis.

Data Synthesis and Statistical Methods

Once the structured literature review was deemed adequate and representative, a formal meta-analysis was conducted. Outcomes of interest were reported as odds ratios with 95% confidence intervals. A network meta-analysis was chosen since it allowed for direct and indirect comparisons for multiple treatments using a Bayesian hierarchical framework and Markov chain Monte Carlo methods. Heterogeneity between studies was evaluated using the I^2 test. The I^2 statistic determined suitability for fixed effect (I^2 <50%) or random effect (I^2 >50%) method. A pairwise meta-analysis was also produced to compare the results of the network analysis for consistency and tendency. Publication bias was assessed using a funnel plot, Egger test, and Begg test. All analyses were conducted using R (ver. 4.0.4; R Project for Statistical Computing, Vi-

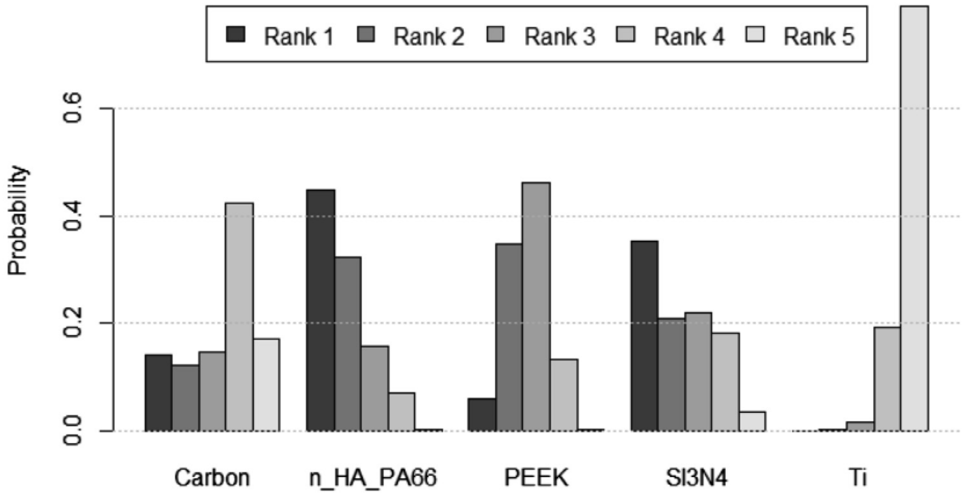

Figure 4. Treatment Ranking

Table 4
Ranking Probabilities (Extended Model):

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Carbon	0.14	0.12	0.15	0.42	0.17
nHA/PA66	0.45	0.32	0.16	0.07	0.00
PEEK	0.06	0.35	0.46	0.13	0.00
Si_3N_4	0.35	0.21	0.22	0.18	0.04
Titanium	0.00	0.00	0.02	0.19	0.79

enna, Austria; the packages used include: tidyverse, metafor, gemtc, and igraph).

Results

Study Network

The initial search yielded a total of 821 articles (Figure 1). After removal of duplicates and preliminary title and abstract screening, the collection was reduced to 140 articles. A second round of screening based on inclusion and exclusion criteria on full paper readings resulted in 64 articles for review and 17 for consideration (Table 1)[13–31].

Quality Assessment

A total of 65% of the included studies (11/17) scored above six ("good'); 18% (3/17) of the studies scored six or five ("fair") and 24% (4/17) of studies scored lower than five ("poor"). These 4 "poor" studies were excluded from the final meta-analysis.

Baseline Characteristics

The biomaterial assessed from the final selected studies included: silicon nitride (Si_3N_4), polyetheretherketone (PEEK), titanium (Ti), nanohydroxyapatite/polyamide 66 (n-HA/PA66), and a carbon fiber reinforced polymer composite (*i.e.*, polyether-ketone-ether-ketone-ketone composite (CFRP). A total of 1,192 patients were included in this analysis – 419 with titanium implants, 460 with PEEK, 96 with Si_3N_4, 332 with n-HA/PA66, and 35 with CFRP (Table 2). The definition of subsidence, by individual study, is summarized in Table 3.

Network Meta-Analysis

The models were tuned according to tests for convergence, node-split, and Gelman diagnostics. The final parameters used were chains = 4; burn-in = 5,000; iterations = 14,000, thinning interval = 5. A fixed effect model (I^2 <50%) was found to be suitable for our study selection. The multivariate potential scale reduction factor (PSRF) value for the model was 1.00 - 1.01 indicating acceptable model convergence; node-splitting results were all p > 0.05 indicating acceptable network consistency (Figure 2).

In our analysis, titanium had the highest rate of subsidence compared to other biomaterials. Notably, PEEK, Si_3N_4, and N-HA/PA66 all had significantly lower rates. CRFP also had a lower subsidence rate than titanium, though the difference was not statistically significant. Compared to titanium the estimate for subsidence in ascending order were nHA/PA66 (OR=0.236, 95% CI 0.137 to 0.394), followed by Si_3N_4 (OR=0.287, 95% CI 0.106 to 0.770), then PEEK (OR=0.314, 95% CI 0.182 to 0.521), and lastly, CFRP (OR = 0.477, 95% CI 0.134 to 1.83).

For the network analyses comparing subsidence risks in titanium, PEEK, and Si_3N_4 – PEEK and Si_3N_4 were on par, and titanium ranked last (Figure 3). Subsidence risk rankings were also expressed as a bar chart (Figure 4). In the extended network analysis, treatment performance was summarized as Surface Under the Cumulative Ranking (SUCRA) scores, which illustrates the probability of a treatment being most effective. The SUCRA values were nHA/PA66 0.84, Si_3N_4 0.67, CFRP 0.38, PEEK 0.58, and titanium 0.03.

Forest plot results for subgroups of pair-wise studies are presented in Figure 5a-e. Arts et al., 2017, compared Si_3N_4 versus PEEK. Point estimate favors Si_3N_4 (OR=0.92, 95% CI 0.41 to 2.08), but this did not attain statistical significance. In a pair-wise comparison involving titanium, there is favorability towards alternative biomaterials: PEEK (OR = 0.45, 95% CI 0.25 to 0.78) and nHA/PA66 (OR = 0.22, 95% CI 0.11 to 0.42).

Publication Bias

Both the Egger test (p = 0.28) and the Begg test (p = 0.37) were found to be non-significant for publication bias. This is illustrated by the funnel plot with points symmetrically distributed around the effect mean (Figure 6).

Discussion

This analysis focuses on biomaterial type and its relation to subsidence in spinal fusion. Other studies have discussed the relative importance of biomaterial modulus of elasticity compared to other factors, such as cage height, bone quality, cage shape, cage footprint. For example, Igarashi et al. 2017 did not find a significant difference in subsidence rates between PEEK and titanium cages when restricting cage heights to less than 5mm.[32] They did, however, conclude that increasing general cage height was associated with increased subsidence risk.

Cabraja et al. 2012, compared PEEK and titanium and determined that biomaterial modulus did not appear to be a major factor in cage subsidence and instead surmised that patient bone quality may be more critical.[33] A notable and potential bias in their paper was a tendency for surgeons to select PEEK implants for older patients. Similarly, Campbell et al. 2020 identified that an increase in age directly correlated with an increase in subsidence risk.[34] Kim et al. 2012 studied curved and wedged shaped PEEK cages and suggested that implant shape was an important risk factor.[35] Similarly, Le et al. 2012 found that wider cages significantly mitigated the risk of subsidence while length was not significant.[36] Suh et al. 2017 identified substrate density and cage footprint as being greater contributors to subsidence than biomaterial when comparing titanium, PEEK, and silicon nitride.[37]. Recently, Fiani et al., 2021, found that Si_3N_4 and other biomaterials can act as suitable fusion expanders given their favorable properties.[38]

Significant limitations must be considered while assessing the generalizability of the results. The literature is inconsistent in its definitions of subsidence and the lack of randomized control trials remains pervasive. Also, despite acceptable levels of statistical heterogeneity, many of the studies evaluated in this analysis introduce potentially significant disparate clinical variables, such as implants of varying footprints/sizes, the inclusion of cervical and lumbar patients, and biomaterials with

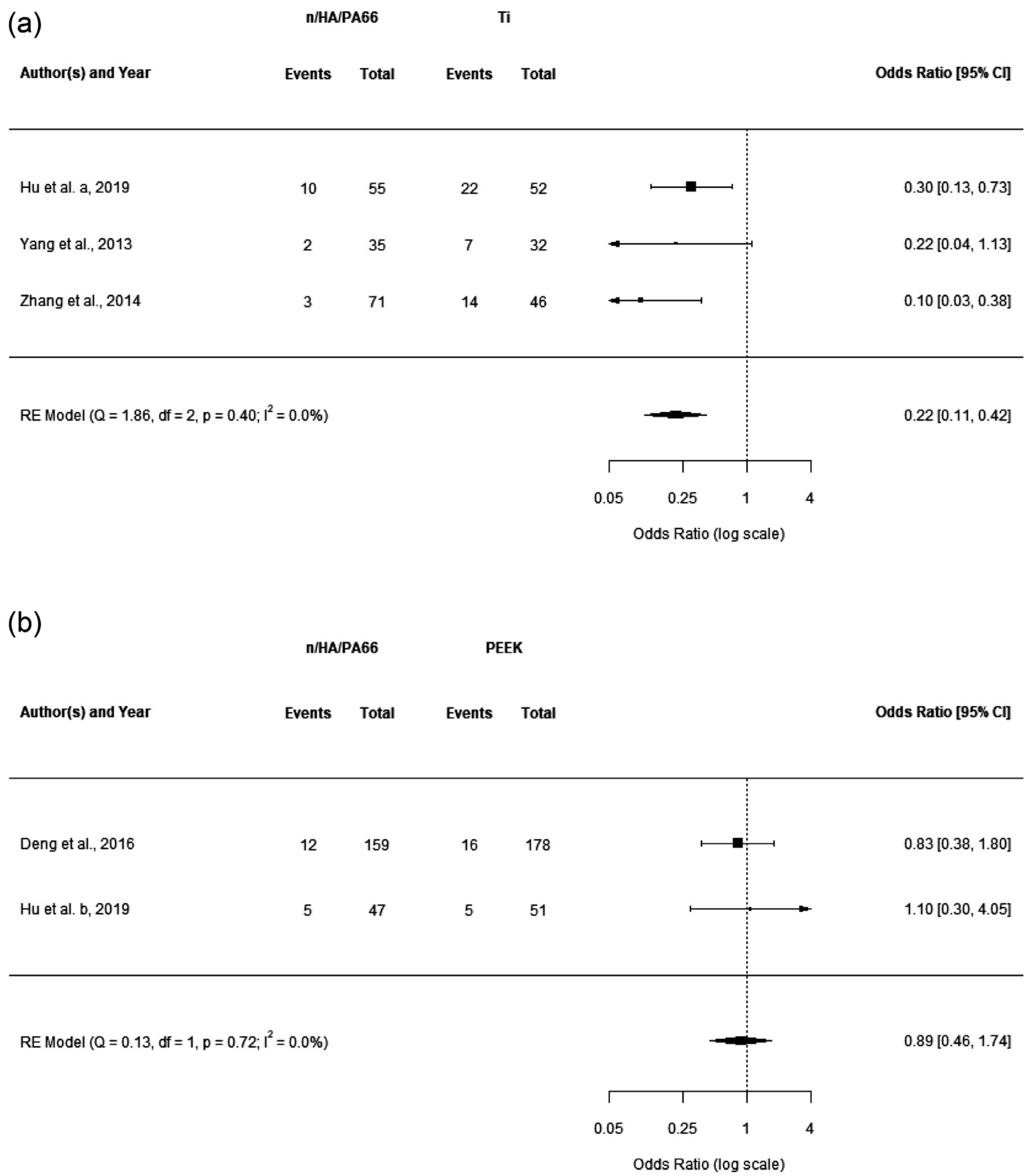

Figure 5. a. Forest Plot: n-HA/PA66 vs Ti
b. Forest Plot: n-HA/PA66 vs PEEK
c. Forest Plot: PEEK vs Ti
d. Forest Plot: Si_3N_4 vs PEEK
e. Forest Plot: CFRP vs PEEK

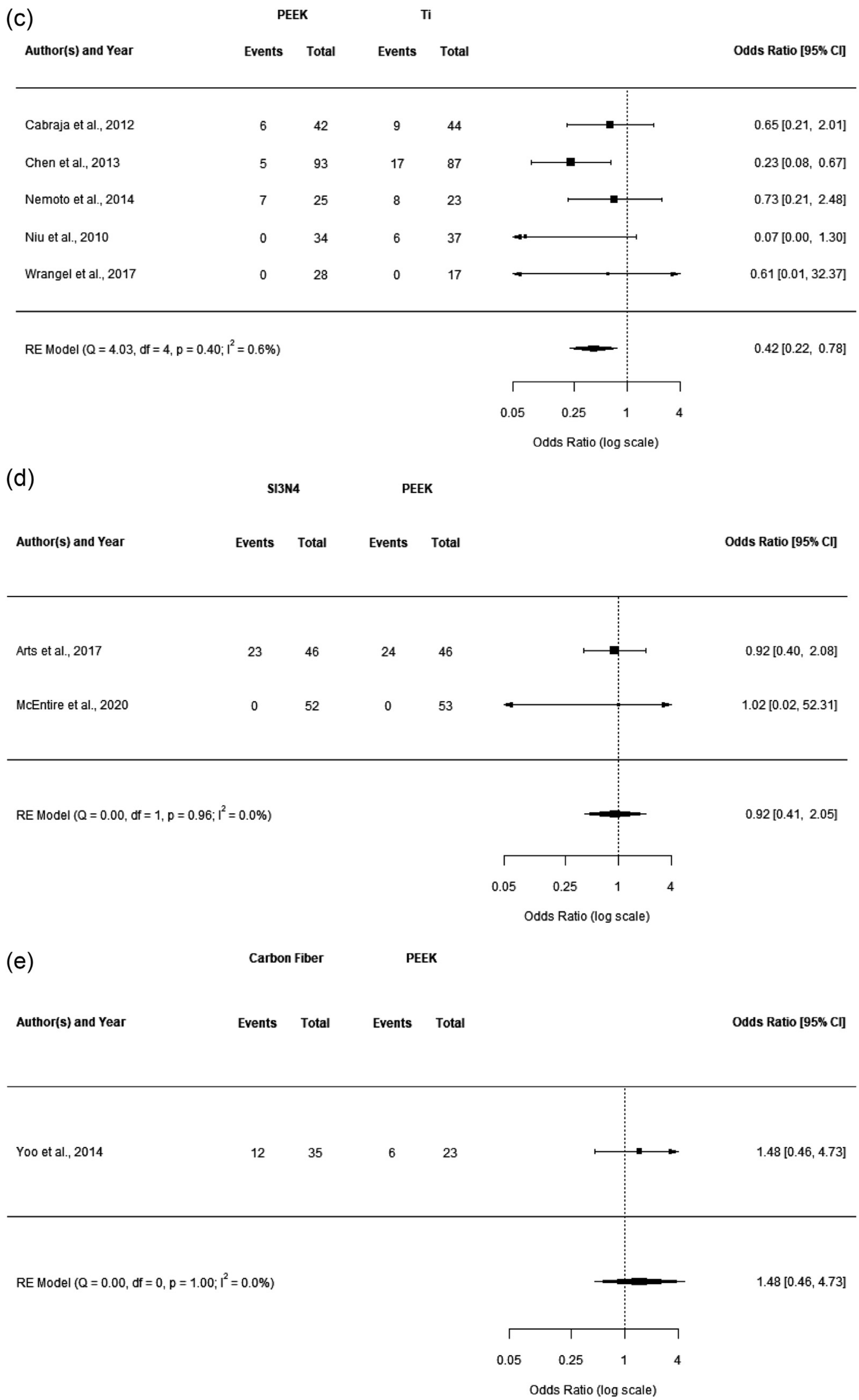

Figure 5. Continued

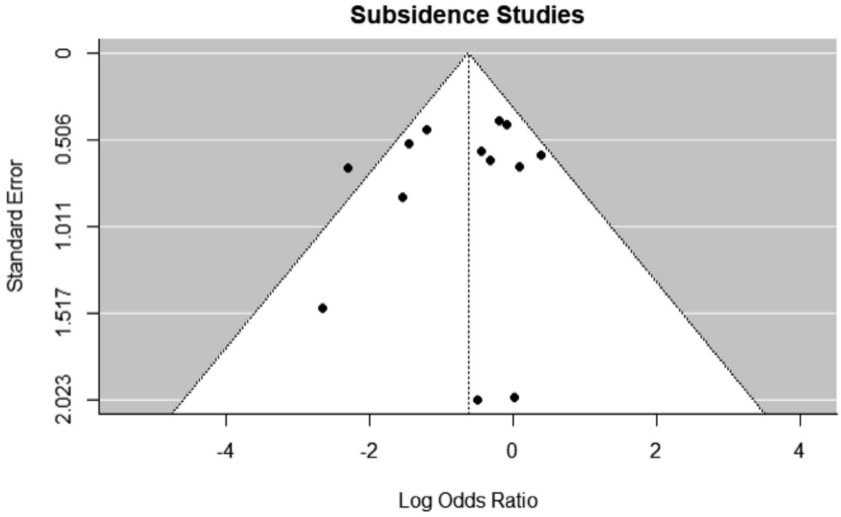

Figure 6. Funnel Plot

mesh/porous designs. Despite this, the authors contend that some level of clinical heterogeneity was necessary to attain sufficient power for the analysis. It is also unclear how this would bias our results although it may affect the generalizability of our conclusion. We continue to believe that this meta-analysis represents the most complete clinical assessment of Si_3N_4 and its associated subsidence risk compared to other readily implanted biomaterial for spinal fusion. Given the additional benefits of Si_3N_4, it seems reasonable to consider their more widespread adoption in spinal fusion surgery.

Conclusion

Taken in context of the limitations of this analysis, the subsidence risk of Si_3N_4 appears most similar to PEEK, while both appear to fare better than titanium. The true risk of subsidence may therefore not be related to modulus of elasticity alone and is likely multifaceted and nuanced, requiring further investigation.

Author Contributions

(I) Conception and design: JA, RS
(II) Administrative support: JA, AV, RS, JPJ
(III) Provision of study materials or patients: JA
(IV) Collection and assembly of data: JA, RS
(V) Data analysis and interpretation: JA, AV, RS, JPJ
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding Disclosure

SINTX LLC provided research funding support for the project but had no role in the analysis or the production

Footnote

The authors have completed the PRISMA reporting checklist.

Conflict of Interest

All authors have completed the ICMJE uniform disclosure form. JA is the president/CEO of a research think-tank organization (Neuronomics) that received funding from SINTX to conduct this research. SINTX was not involved in the data acquisition, data analysis, or creation of this manuscript. RS is an employee of Neuronomics. The other authors have no conflicts of interest to declare.”

Acknowledgements

This work was supported by SINTX

References

[1] Thaci B, Yee R, Kim K, Vokshoor A, Johnson JP, Ament J. Cost-effectiveness of peptide enhanced bone graft i-factor versus use of local autologous bone in anterior cervical discectomy and fusion surgery. Clinicoecon Outcomes Res 2021;13:681–91 PMID: 34335035; PMCID: PMC8318088. doi:10.2147/CEOR.S318589.
[2] Heary RF, Parvathreddy N, Sampath S, Agarwal N. Elastic modulus in the selection of interbody implants. J Spine Surg 2017;3(2):163–7 PMID: 28744496; PMCID: PMC5506312. doi:10.21037/jss.2017.05.01.
[3] Loenen ACY, Peters MJM, Bevers RTJ, Schaffrath C, van Haver E, Cuijpers VMJI, Rademakers T, van Rietbergen B, Willems PC, Arts JJ. Early bone ingrowth and segmental stability of a trussed titanium cage versus a polyether ether ketone cage in an ovine lumbar interbody fusion model. Spine J 2022;22(1):174–82 Epub 2021 Jul 15. PMID: 34274502. doi:10.1016/j.spinee.2021.07.011.
[4] Literature query comparing titanium and PEEK interbody fusions. https://www-ncbi-nlm-nih-gov.mlprox.csmc.edu/pmc/?term=Titanium+vs.+polyetheretherketone+(PEEK)+interbody+fusion. Accessed May 10, 2022.
[5] Gray MT, Davis KP, McEntire BJ, Bal BS, Smith MW. Transforaminal lumbar interbody fusion with a silicon nitride cage demonstrates early radiographic fusion. J Spine Surg 2022;8(1):29–43 PMID: 35441113; PMCID:PMC8990392. doi:10.21037/jss-21-115.
[6] Fiani B, Jarrah R, Shields J, Sekhon M. Enhanced biomaterials: systematic review of alternatives to supplement spine fusion including silicon nitride, bioactive glass, amino peptide bone graft, and tantalum. Neurosurg Focus 2021;50(6):E10 PMID: 34062502. doi:10.3171/2021.3.FOCUS201044.
[7] Calvert GC, VanBuren Huffmon G 3rd, Rambo WM Jr, Smith MW, McEntire BJ, Bal BS. Clinical outcomes for lumbar fusion using silicon nitride versus other biomaterials. J Spine Surg 2020;6(1):33–48 PMID: 32309644;PMCID: PMC7154368. doi:10.21037/jss.2019.12.11.
[8] Kersten RFMR, Öner FC, Arts MP, Mitroiu M, Roes KCB, de Gast A, van Gaalen SM. The SNAP trial: 2-year results of a double-blind multicenter randomized controlled trial of a silicon nitride versus a PEEK cage in patients after lumbar fusion surgery. Global Spine J 2021:2192568220985472 Epub ahead of print. PMID: 33406905. doi:10.1177/2192568220985472.
[9] McEntire BJ, Maislin G, Bal BS. Two-year results of a double-blind multicenter randomized controlled non-inferiority trial of polyetheretherketone (PEEK) versus silicon nitride spinal fusion cages in patients with symptomatic degenerative lumbar disc disorders. J Spine Surg 2020;6:523–40. doi:10.21037/jss-20-588.
[10] Page Matthew J, McKenzie Joanne E, Bossuyt Patrick M, Boutron Isabelle, Hoffmann Tammy C, Mulrow Cynthia D, Shamseer Larissa, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372(March):n71. doi:10.1136/bmj.n71.

[11] Slim Karem, Nini Emile, Forestier Damien, Kwiatkowski Fabrice, Panis Yves, Chipponi Jacques. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73(9):712–16. doi:10.1046/j.1445-2197.2003.02748.x.
[12] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013, http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
[13] Arts Mark P, Wolfs Jasper FC, Corbin Terry P. Porous silicon nitride spacers versus PEEK cages for anterior cervical discectomy and fusion: clinical and radiological results of a single-blinded randomized controlled trial. Eur Spine J 2017;26(9):2372–9. doi:10.1007/s00586-017-5079-6.
[14] Chen Yu, Wang Xinwei, Lu Xuhua, Yang Lili, Yang Haisong, Yuan Wen, Chen Deyu. Comparison of titanium and polyetheretherketone (PEEK) cages in the surgical treatment of multilevel cervical spondylotic myelopathy: a prospective, randomized, control study with over 7-year follow-up. Eur Spine J 2013;22(7):1539–46. doi:10.1007/s00586-013-2772-y.
[15] Chou Yu-Cheng, Chen Der-Cherng, Hsieh Wanhua Annie, Chen Wu-Fu, Yen Pao-Sheng, Harnod Tomor, Chiou Tsung-Lang, et al. Efficacy of anterior cervical fusion: comparison of titanium cages, polyetheretherketone (PEEK) cages and autogenous bone grafts. J Clin Neurosci 2008;15(11):1240–5. doi:10.1016/j.jocn.2007.05.016.
[16] Davis RJ, Kim KD, Hisey MS, et al. Cervical total disc replacement with the Mobi-C cervical artificial disc compared with anterior discectomy and fusion for treatment of 2-level symptomatic degenerative disc disease: a prospective, randomized, controlled multicenter clinical trial: clinical article. J Neurosurg Spine 2013;19(5):532–45.
[17] Deng Qian-xing, Ou Yun-sheng, Zhu Yong, Zhao Zeng-hui, Liu Bo, Huang Qiu, Du Xing, Jiang Dian-ming. Clinical outcomes of two authors of cages used in transforaminal lumbar interbody fusion for the treatment of degenerative lumbar diseases: N-HA/PA66 cages versus PEEK cages. J Mater Sci Mater Med 2016;27(6):102. doi:10.1007/s10856-016-5712-7.
[18] Junaid Muhammad, Rashid Mamoon Ur, Bukhari Syed Sarmad, Ahmed Mamoon. Radiological and clinical outcomes in patients undergoing anterior cervical discectomy and fusion: comparing titanium and PEEK (Polyetheretherketone) cages. Pakistan J Med Sci 2018;34(6). doi:10.12669/pjms.346.15833.
[19] McEntire Bryan J, Maslin Greg, Bal BSonny. Two-year results of a double-blind multicenter randomized controlled non-inferiority trial of polyetheretherketone (PEEK) versus silicon nitride spinal fusion cages in patients with symptomatic degenerative lumbar disc disorders. J Spine Surg 2020;6(3):523–40. doi:10.21037/jss-20-588.
[20] Nemoto Osamu, Asazuma Takashi, Yato Yoshiyuki, Imabayashi Hideaki, Yasuoka Hiroki, Fujikawa Akira. Comparison of fusion rates following transforaminal lumbar interbody fusion using polyetheretherketone cages or titanium cages with transpedicular instrumentation. Eur Spine J 2014;23(10):2150–5. doi:10.1007/s00586-014-3466-9.
[21] Niu Chi-Chien, Liao Jen-Chung, Chen Wen-Jer, Chen Lih-Huei. Outcomes of interbody fusion cages used in 1 and 2-levels anterior cervical discectomy and fusion: titanium cages versus polyetheretherketone (PEEK) cages. Clin Spine Surg 2010;23(5):310–16. doi:10.1097/BSD.0b013e3181af3a84.
[22] Schomacher Markus, Finger Tobias, Koeppen Daniel, Süss Olaf, Vajkoczy Peter, Kroppenstedt Stefan, Cabraja Mario. Application of titanium and polyetheretherketone cages in the treatment of pyogenic spondylodiscitis. Clin Neurol Neurosurg 2014;127(December):65–70. doi:10.1016/j.clineuro.2014.09.027.
[23] Wrangel Christof von, Karakoyun Ali, Buchholz Kaye-Marie, Süss Olaf, Kombos Theodoros, Woitzik Johannes, Vajkoczy Peter, Czabanka Marcus. Fusion rates of intervertebral polyetheretherketone and titanium cages without bone grafting in posterior interbody lumbar fusion surgery for degenerative lumbar instability. J Neurol Surg Part A 2017;78(6):556–60. doi:10.1055/s-0037-1604284.
[24] Deng Qian-xing, Ou Yun-sheng, Zhu Yong, Zhao Zeng-hui, Liu Bo, Huang Qiu, Du Xing, Jiang Dian-ming. Clinical outcomes of two authors of cages used in transforaminal lumbar interbody fusion for the treatment of degenerative lumbar diseases: N-HA/PA66 cages versus PEEK cages. J Mater Sci Mater Med 2016;27(6):102. doi:10.1007/s10856-016-5712-7.
[25] Hu Bowen, Wang Linnan, Song Yueming, Hu Yujie, Lyu Qiunan, Liu Limin, Zhu Ce, Zhou Chunguang, Yang Xi. A comparison of long-term outcomes of nanohydroxyapatite/polyamide-66 cage and titanium mesh cage in anterior cervical corpectomy and fusion: a clinical follow-up study of least 8 years. Clin Neurol Neurosurg 2019;176(January):25–9. doi:10.1016/j.clineuro.2018.11.015.
[26] Hu Bowen, Yang Xi, Hu Yujie, Lyu Qiunan, Liu Limin, Zhu Ce, Zhou Chunguang, Song Yueming. The N-HA/PA66 cage versus the PEEK cage in anterior cervical fusion with single-level discectomy during 7 years of follow-up. World Neurosurg 2019;123(March):e678–84. doi:10.1016/j.wneu.2018.11.251.
[27] Kabir Syed MR, Alabi J, Rezajooi Kia, Casey Adrian TH. Anterior cervical corpectomy: review and comparison of results using titanium mesh cages and carbon fibre reinforced polymer cages. Br J Neurosurg 2010;24(5):542–6. doi:10.3109/02688697.2010.503819.
[28] Yang Xi, Chen Qi, Liu Limin, Song Yueming, Kong Qingquan, Zeng Jiancheng, Xue Youdi, Ren Chunpeng. Comparison of anterior cervical fusion by titanium mesh cage versus nano-hydroxyapatite/polyamide cage following single-level corpectomy. Int Orthop 2013;37(12):2421–7. doi:10.1007/s00264-013-2101-4.
[29] Yoo Minwook, Kim Wook-Ha, Hyun Seung-Jae, Kim Ki-Jeong, Jahng Tae-Ahn, Kim Hyun-Jib. Comparison between two different cervical interbody fusion cages in one level stand-alone ACDF: carbon fiber composite frame cage versus polyetheretherketone cage. Korean J Spine 2014;11(3):127–35. doi:10.14245/kjs.2014.11.3.127.
[30] Zhang Yuan, Quan Zhengxue, Zhao Zenghui, Luo Xiaoji, Tang Ke, Li Jie, Zhou Xu, Jiang Dianming. Evaluation of anterior cervical reconstruction with titanium mesh cages versus nano-hydroxyapatite/polyamide66 cages after 1- or 2-level corpectomy for multilevel cervical spondylotic myelopathy: a retrospective study of 117 patients. PLoS One 2014;9(5):e96265. doi:10.1371/journal.pone.0096265.
[31] Kersten RFMR, Öner FC, Arts MP, Mitroiu M, Roes KCB, de Gast A, van Gaalen SM. The SNAP trial: 2-year results of a double-blind multicenter randomized controlled trial of a silicon nitride versus a PEEK cage in patients after lumbar fusion surgery. Global Spine J 2021 January, 2192568220985472. doi:10.1177/2192568220985472.
[32] Igarashi Hidetoshi, Hoshino Masahiro, Omori Keita, Matsuzaki Hiromi, Nemoto Yasuhiro, Tsuruta Takashi, Yamasaki Koji. Factors influencing interbody cage subsidence following anterior cervical discectomy and fusion. Clin Spine Surg 2019;32(7):297–302 12. doi:10.1097/BSD.0000000000000843.
[33] Cabraja Mario, Oezdemir Soner, Koeppen Daniel, Kroppenstedt Stefan. Anterior cervical discectomy and fusion: comparison of titanium and polyetheretherketone cages. BMC Musculoskeletal Disord 2012;13(September):172. doi:10.1186/1471-2474-13-172.
[34] Campbell Peter G, Cavanaugh David A, Nunley Pierce, Utter Philip A, Kerr Eubulus, Wadhwa Rishi, Stone Marcus. PEEK versus titanium cages in lateral lumbar interbody fusion: a comparative analysis of subsidence. Neurosurg Focus 2020;49(3):E10. doi:10.3171/2020.6.FOCUS20367.
[35] Kim Hwan Soo, Joon Suk Song, Weon Heo, Jae Hoon Cha, Dong Youl Rhee. Comparative study between a curved and a wedge PEEK cage for single-level anterior cervical discectomy and interbody fusion. Korean J Spine 2012;9(3):181–6. doi:10.14245/kjs.2012.9.3.181.
[36] Le Tien V, Baaj Ali A, Dakwar Elias, Burkett Clinton J, Murray Gisela, Smith Donald A, Uribe Juan S. Subsidence of polyetheretherketone intervertebral cages in minimally invasive lateral retroperitoneal transpsoas lumbar interbody fusion. Spine 2012;37(14):1268–73. doi:10.1097/BRS.0b013e3182458b2f.
[37] Suh Paul B, Puttlitz Christian, Lewis Chad, Bal BSonny, McGilvray Kirk. The effect of cervical interbody cage morphology, material composition, and substrate density on cage subsidence. J Am Acad Orthop Surg 2017;25(2):160–8. doi:10.5435/JAAOS-D-16-00390.
[38] Brian Fiani, Jarrah Ryan, Shields Jennifer, Sekhon Manraj. Enhanced biomaterials: systematic review of alternatives to supplement spine fusion including silicon nitride, bioactive glass, amino peptide bone graft, and tantalum. Neurosurg Focus 2021;50(6):E10. doi:10.3171/2021.3.FOCUS201044.