

RESEARCH ARTICLE

PROSTHETIC REHABILITATION OF SHORT DENTAL ARCH: SYSTEMATIC REVIEW.

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Abstract

..... **Objectives:** To compare the available prosthetic treatment options of patients with short dental arch (SDA) in regard to oral related health quality of life and biological complication. Methods: An electronic search was performed using PubMed and Cochrane CENTRAL databases for articles published in English till the end of March 2017. Inclusion criteria were randomized controlled trials (RCTs) which compared shortened dental arches concept to their restoration to complete arch lengths with different prosthodontic interventions. Two reviewers independently screened titles and abstract, made data extraction and appraised the quality of included studies. Findings From a total of 19 relevant studies identified, 8 RCTs fulfilled the inclusion criteria. A narrative explanation of the outcomes is reported for the 3 comparison groups (which were based on the different interventions used for the individual clinical trials). The shortened dental arch as a treatment option is encouraging in terms of oral health life and biological related quality of complication. Application/Improvements: To perform a true comparison, well designed RCTs should be held out.

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Introduction:-

Kayser named partial edentulism of distal extension edentulous space in posterior area as shortened dental arch (SDA). He proposed that patients with at least 4 occlusal units (premolar occlusion) have sufficient adaptive capacity to maintain oral function 1 . 2 reported that the oral function, occlusal stability and periodontal support of SDA patients were well maintained, and there was no marked effect of lacking molar support on signs and symptoms of temporomandibular disorders (TMDs)².

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Research suggests that this seemingly beneficial SDA concept and its variations can be utilized to improve accessibility and affordability to treatment for socially- and economically-deprived middle-aged and elderly communities $^{3-13}$.

Prosthodontic goals includes the replacement of all missing teeth with the intention of restoring the continuity of dental arches ^{14,15}. The rationale for this approach includes: improve impaired oral function with a perceived detrimental impact on chewing ability, occlusal stability and temporomandibular joint (TMJ) function due to the loss

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of the molar teeth ¹⁶. Contrary, several studies and reviews have indicated that twenty occluding teeth provide sufficient oral functional ability and the need to replace all missing posterior teeth has been questioned ^{1,7,11,14,16–20}

When dentists extend or reconstitute reduced, shortened or discontinuous dental arches and replace missing teeth in either anterior or posterior regions to create a complete dental arch (CDA), the following interventions are usually recommended: removable partial denture prosthesis (RPDP) or cantilever fixed denture prosthesis (CFDP), including resin-bonded bridges and implant-retained fixed partial dentures (IFPDs)^{18,21,22}.

Treatment with RPDs is the most common of these options, because it is noninvasive and inexpensive. However, patients who have missing posterior teeth frequently stop wearing RPDs ^{23–25} Furthermore, treatment with RPDs has a high 'biological cost' with high caries incidence and periodontal breakdown of abutment teeth ^{26–28}. Thus, fixed restorations using CFPDs or IFPDs are recommended as alternative options for replacement of distal extension edentulous space especially in patients who have high risk for caries occurrence and periodontal disease ^{29–32}.

RPDPs, FDPs and implant procedures evidently operate on the premise of optimal occlusion encompassing the aesthetics, oral function, oral health and comfort created by the occluding teeth. This practice appears to have evolved empirically, with no scientific or clinical evidence to support its widespread acceptance by clinicians^{14,21,22,33–37}. Restoration for distal extension edentulous space using CFPDs is usually limited up to the second premolar, thus missing molars remain unrestored (premolar occlusion).

The aim of this systematic review was to identify and analyses existing clinical trials which compare the biological effect and quality of life outcomes of prosthodontic interventions used for treating shortened arches versus unrestored shortened arches in partially dentate adult patients.

The following research question addresses the aim and objectives of the study: In adult patients with shortened dental arches, what is the effect of prosthodontics interventions on the harmful effect and OHRQoL compared to having no treatment?

Review method:-

A prior protocol was made for this systematic review and registered at the International prospective register of systematic reviews (PROSPERO2016: CRD42017056090). Accessible from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017056090.

Search Strategy:-

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

An electronic search was carried out utilizing the PubMed and the Cochrane CENTRAL databases for articles published in English till the end of March 2017. The following keywords were used: "short dental arch or SDA or removable partial dentures or PPDs or cantilever fixed partial dentures or CFPDs or implant supported fixed partial dentures or IFPDs or biological complication and oral health quality of life".

A manual search of the reference lists of the included studies and dental journals was conducted: International Journal of Prosthodontics, , Journal of Prosthetic Dentistry, Journal of the American Dental Association, Implant Dentistry, British Dental Journal, Journal of Clinical Periodontology, Journal of Periodontology, Periodontology 2000, , Journal of Prosthodontics, , International Journal of Periodontics and Restorative Dentistry, Journal of Advanced Prosthodontics, Journal of Prosthodontic Research, , International Journal of Oral and Maxillofacial Implants. Contact was made with authors of the published articles through e-mail if any data was missing.

2.2 inclusion criteria

Inclusion criteria were adapted using the following PICOS items: (P) Types of patients: they are unilateral or bilateral distal extension partially edentulous patients in either the maxilla or the mandible or both arches. (I) Type of intervention: RPDs, CFPDs and IFPDs. (C) Type of comparator: patient with short dental arch SDA. (O)Type of outcome: biological complication and oral health related quality of life after a follow-up period of no less than 1 year. (S) Type of study: human randomized clinical trials in English language only. 2.3 exclusion criteria

Exclusion criteria were as follows: any clinical trial other than RCTs, In vitro studies, case reports, technical reports, studies on animals, studies on maxillofacial defects and studies in language other than English language.

2.4 data collection

The search included two stages. During the first stage titles and abstracts were monitored by two independent reviewers. Full texts were obtained if the studies meet the inclusion criteria or if the titles and abstracts are not giving obvious data to make a clear decision. In the second stage, data extraction was done separately by the same reviewers. Disagreements were discussed to reach a decision, and if not resolved a third reviewer was conferred. Data extraction from the included studies were as follows: Authors, time of publication, gender, mean of age in years, follow-up period in years, number of patients in every group and mode of treatment.

2.5 Quality assessment

Assessment of the quality of individual studies was done separately and in duplicate by the same reviewers. The criteria for quality assessment among RCTs were performed by means of Cochrane Collaboration Risk of Bias Tool³⁸. This tool covers sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting (reporting bias), and other potential sources of bias. Each domain was judged as low risk or high risk otherwise, when there is deficient data to make a decision the study is rated, unclear risk.

2.6 summary measures

Meta-analysis of the included studies was done in case of similarity of comparisons and outcomes considering the patients as the statistical unit.

2.7 publication bias

In case of inclusion of 10 or more studies in the present systematic review, a funnel plot is performed. If asymmetry was shown in the plot, there is a possibility of publication bias.

Results:-

3.1 search result

Search results are summarized using PRISMA flow chart (Figure 1). 487 titles were selected from Initial search and an additional one study identified through other sources, after removal of duplicates, 313 Records screened and 294 records excluded. From 19 Full-text publications evaluated for eligibility, a11 Full-text publications were excluded with reasons, thus, an 8 full text randomized clinical trials were selected and considered eligible for inclusion (Table 1). The reasons for study exclusion are given in (Table 2).

3.2 Characteristics of included studies

The selected eight studies were RCTs and were published between1987 to 2017. The observation period ranged from 12 months to 5 years. All of the studies were conducted in a university setting. Characteristics of included studies are listed in (Table 1). The included trials comprise the following comparisons: compare between rehabilitated of free end saddle with RPDs and CFPDs versus SDA concept. The studies were grouped according to types of interventions into the following comparisons:

Comparison 1: FDPs versus RPDPs for SDAs in the lower jaw. Two included studies from the UK and Denmark assessed comparison 1 ^{33,34,37,39-43}.

Comparison 2: RPDPs versus no treatment (SDA). five studies from Germany and Ireland assessed comparison 2 44-54

Comparison 3: SDA versus CDA. Only one study from the Netherlands assessed comparison 3^{10,55,56}.

3.3 Quality assessment of included studies:-

Table(4) specifies the quality assessment of the included studies and these are summarized in the 'risk of bias table' and 'risk of bias graph' where judgements are categorized to indicate a low, high, or unclear risk of bias following the Cochrane guidelines. Below we give a detailed explanation of these results: Sequence Generation: Three of the eight trials were reported as having been randomized. For sequence generation, two clinical trials used computer-generated numbers and a third trial used randomly permuted block randomization for generating the allocation sequence, which we judged as having a low risk of bias ^{39–42,46–48,52–54}.

The Witter et al (2001) clinical trial invited subjects to join the department for a study, and no attempt was made to randomize patients, thus it is judged as having a high risk of bias 55-57. The Budtz-Jorgensen and Isidor and Shoi et

al. (2014) trials did not mention how the sequence was generated and provided insufficient information to enable us to judge whether there was ahigh or low risk of bias, and we thus rated it as having an unclear risk of bias 33,34,37,49 .

Allocation Concealment: The Moynihan et al (2000), Wolfart et al (2005) and Mc Kenna (2012) studies are described as having a low risk of bias for allocation concealment, as they indicated that the clinician was not involved in the allocation and that concealment was warranted following a central randomization process after patient enrolment ^{39–42,46–48,50–54}. For the Budtz- Jorgensen and Isidor (1987), Witter et al (2001) and Aras et al. (2009) studies, there is no indication as to how intervention allocation was concealed and these were judged as having an unclear risk of bias ^{33,34,37,44,55–57}, but ^{45,49} have high risk of bias for allocation.

Blinding: The Moynihan et al (2000) study was referred to as a double blinded study with the clinician blinded to allocation of intervention and statistician being blinded to treatment and thus it is judged as having a low risk of bias ^{39–42}. The Witter et al (2001) study can be considered as a single blinded study because evaluation of outcomes was completed by a calibrated observer at all intervals, but it was not stated as such, thus it is judged as having an unclear risk of bias ^{55–57}. Mc Kenna (2012) indicated that the researcher was not involved in the intervention allocation, making it a single-blinded study, thus it is judged as having a low risk of bias ^{47,48}. The Wolfart et al (2005) study indicated that it was impossible to blind the dentist and patient due to discrepancies of the treatments; thus it was judged as having a high risk of bias, whereas Budtz-Jorgensen and Isidor (1987) provided insufficient information related to blinding and it was regarded as having an unclear risk of bias ^{33,34,46,50–54}. in the studies of Arce-Tumbay et al. (2011); Shoi et al. (2014); Aras et al. (2009) no mentioned of way of bliding so we can mentioned that there are unclear ^{44,45,49}.

Incomplete Outcome Data: Analyses for the Moynihan et al (2000), Wolfart et al (2005) and Mc Kenna (2012) studies were conducted on the "intention-to-treat" (ITT) principle; and the studies reported proportionate numbers of losses to follow-up (which were small) and some having no losses between the intervention and control $^{39-42,46-48,50-54}$. Witter et al (2001) indicated that regression models accounted for the subjects lost during the study ⁵⁶. Thus, all 4 studies above were judged as having a low risk of bias $^{39-42,46-48,50-54}$. On the other hand, Budtz-Jorgensen and Isidor (1987) did not indicate and specify how the analysis was completed, but all pre-specified outcomes were reported, and the number of losses to follow-up was small, thus it was judged as having a low risk of bias 33,34,37 . In the Budtz-Jorgensen and Isidor (1987) and Witter et al (2001) studies all outcomes were reported but outcomes were not prespecified as primary or secondary outcomes $^{33,34,37,55-57}$ Both these studies were thus judged as having a high risk of bias. The three remaining RCTs specified the outcomes as primary and secondary and reported these as such, thus these were judged as having a low risk of bias $^{39-42,46-48,50-54}$. Other potential sources of bias: No other sources of bias were detected with four of the five included studies. The Budtz- Jorgensen and Isidor (1987) study was judged as having high risk of bias because there were six patients who did not wear the RPDP at all during the study 33,34,37 .

Comparison 1: Fixed Denture Prosthesis vs Removable Partial Denture Prosthesis.

1. Oral Health Related Quality of Life (OHRQoL: This outcome was not reported in the one study assessing this comparison.

2. Biological Effects: (caries; tooth loss; interdental spacing).

Caries: Both studies are in agreement regarding the development of caries lesions with FDPs and RPDPs where: Jepson et al (2001) found that treatment with FDPs showed a significant increase in number of patients with no caries experience compared to the RPDP patients (RR 1.89, 95% CI: 1.09 to 3.30, 50 participants) ⁴¹. Similarly, Isidor and Budtz-Jorgensen (1990) observed 22 dental carious lesions in the RPDP group compared with only two lesions in the FDP group; however we could not calculate a treatment effect since the respective number of patients was not reported. Our unit of analysis was individual patients and not individual teeth ³⁷.

Tooth Loss: In the Isidor and Budtz-Jorgensen (1990) study, 11 teeth were extracted in the RPDP group compared with only one tooth in the FDP group during the five years of observation. However, no treatment effect could be calculated because the respective numbers of patients were not reported ³⁷.

Comparison 2: Removable Partial Denture Prosthesis versus no treatment (SDA).

1. Oral Health Related Quality of Life (OHRQoL):

Mc Kenna (2012) reported a non-significant difference in the OHRQoL scores from baseline to the end of treatment (month 1) for the two treatment groups 48 . The author used the oral health impact profile (OHIP-14) to give a score

ranging from 0 (minimum) to 56 (maximum). A high score indicated a poor OHRQoL with low scales indicating good OHRQoL.

However, no treatment effect could be calculated to compare the change in the OHIP-14 scores between the two treatment groups because standard deviations of change were not given and also because exact p-values were not reported.

For the Wolfart et al. (2012) study, the median OHIP-49 scores for pre-treatment, baseline, 1 and 5 years follow-up showed significant reduction of impacts (p,0.05). Before treatment, the median OHIP-49 total score was 38.0 for the RPDP group and 40.0 for the SDA group. Most significant reductions occurred at baseline (27.0; p,0.0001) and 1 year on (13.0; p,0.0002) for the RPDP group (compared to the Mc Kenna study after 1 month).For the SDA group, a significant change in impacts (19.0; p,0.05) were observed only at baseline, no further significant changes were reported 52 .

2. Biological Effects:

Tooth loss: The Walter et al study (2013) showed no significant difference in the number of patients experiencing first tooth loss within 38 months of observation after treatment between the RPDP and SDA groups (RR 1.23, 95% CI: 0.56 to 2.70, 150 participants) ⁵¹. The respective Kaplan-Meier survival rates at 38 months were 0.83 (95% CI: 0.74 to 0.91) in the RPDP group and 0.86 (95% CI: 0.78 to 0.95) in the SDA group, the difference is not significant (as reported by study authors) ⁵¹.

Interdental spacing: Kern et al. (2016) described a comparison of the mean scores of interdental spacing per region According to the authors, A significant difference between the mean score changes was found in the mandible comparing the PRDP group and the SDA group. The respective mean score changes from baseline to 5 years were 0.23 (SD 0.49) for the PRDP group and 0.02 (SD 0.30) for the SDA group(p 0.023)⁵⁸.

Comparison 3: Shortened Dental Arches (SDA) versus Complete Dental Arches (CDA).

1. Oral Health Related Quality of Life (OHRQoL): This outcome was not reported in the one study assessing this comparison.

2. Biological Effects:

Interdental spacing: Witter et al (2001) described a comparison of the mean scores of interdental spacing per region 57 . According to the authors, the premolar regions of the SDA subgroups had significantly higher means [mean (SD): 0.4(0.1) and 0.5(0.1)] than the CDA group [mean (SD): 0.1(0), p, 0.01 as reported by authors]. For the anterior regions, the spacing was not significantly different for SDA [mean (SD) range from 0.2(0.1) to 0.5(0.1)]; CDA group [mean (SD) range from 0.1(0.0) to 0.3(0.1)]. They also reported that spacing remained the same in all regions over time in the SDA group 56 . No treatment effect could be calculated because the results were given per region and also because the respective number of patients were not specified in the results.

Excluded study characteristics: All non-RCTs and reviews were excluded from this SR. Other SRs and summary articles were viewed as potentially included studies, but these were however later not considered for inclusion (Table2)

Discussion:-

Studies comparing treatment outcomes within subjects before and after treatment indicated that RPD improved masticatory function, patient satisfaction and OHRQoL. However, studies that compared the outcomes between subjects found that patients with RPDs did not show significantly greater masticatory performance, patient satisfaction and OHRQoL than for those with CFPDs (premolar occlusion) or no restoration for missing molars. Furthermore, treatment with RPDs showed higher risk for caries incidence, gingival inflammation and poor oral hygiene than treatment with CFPDs. Survival rate and tooth loss in patients with CFPDs were not significantly less than in patients with RPDs, but more visits for maintenance after treatment were required in patients with RPDs. These suggest that treatment with RPDs does not have significant advantage over treatment with CFPDs. Risks for TMD and occlusal instability without restoration of missing molars were not higher than for treatment with RPDs.

Therefore, the SDA concept seems to be a more favorable option than treatment with RPDs when considering a minimum intervention approach. However, it should be noted that the SDA concept may be contraindicated in

patients under 50 years of age and with malocclusion such as Angle's Class III or a sever Class II relationship, evidence for parafunction, pre-existing TMD and a marked reduction in alveolar bone support for remaining teeth ⁵⁹.

Jepson et al (2001) and Isidor and Budtz-Jorgensen (1987, 1990) regarding an increase in caries incidence as reported 2 and 5 years post treatment 37,41,43 . In addition, the increase in caries incidence for the RPDP group also concurred with the research of Bergman et al, (1964), cited in Budtz-Jorgensen (1990) 33 .

other studies ^{33,34,39,43}. For patient satisfaction, the small sample size does not allow us to generalize our results to other settings, thus it is advised to conduct these studies amongst different populations.

For the patient satisfaction outcome, the summary scores of the pilot study were similar to another German study (John and Micheelis, 2003, cited in Walter et al (2012)⁵². For temporomandibular disease (TMD) pain scores, the instrument used in other studies was more reliable (Dworkin, 2002, cited in Walter et al (2012)⁵¹. Tooth loss as a primary outcome is questioned due to extended time periods, thus it was advised to use caries and periodontal attachment loss as outcomes instead⁵¹.

The Mc Kenna study (2012), which is the most recently conducted RCT; the results are similar to other RCTs completed in the past, where small sample sizes would not necessarily show a significant difference between interventions given the follow-up ^{47,48}. In this case, follow-up after only one month of treatment was too short to show any difference between interventions^{47,48}. But the cost-effectiveness reported with this RCT has been noted as researchers and clinicians are under the impression that the cost for FDPs far outweighs that of RPDP treatment ^{22,47,60}. And this has been in line with the findings of the Danish study published some years ago ^{33,37}.

The quality of the evidence is indicative of the integrity of the study and the research conducted. With reference to the quality assessment of the included studies, this has been described in detail above. More importantly, this quality is determined by the study designs. Study designs are graded according to the quality of evidence that they provide. Systematic reviews and RCTs are considered to be designs of the highest quality ^{38,61}.

Only RCTs were included in this systematic review which provides stronger evidence and increases the strength of the recommendations. After completing the quality assessment (using the GRADE approach) of the included studies, it clearly showed that some of the studies had not followed the exact guidelines for RCTs, but nevertheless had the features thereof ^{38,61}. These can be regarded as downgraded RCTs. These downgraded RCTs did not use randomization, allocation concealment or blinding, and failed to specify the outcomes as primary or secondary. These downgraded RCTs could thus affect the quality of evidence only slightly ^{38,61}. For example, the Budtz-Jorgensen (1987, 1990) and Witter et al (2001) studies could be regarded as downgraded CTs ^{10,33,34,37,55–57}.

Conclusion:-

The results from this SR related to SDAs as a treatment option, it would have strengthened the recommendation of the SDA as a treatment option for partially edentulous patient.

Table 1:- Characteristics of included studies											
Study ID	Countr y	follow- up month	(Gende r)	Age	Proble m	Outco mes measur ed	No. of subject	Interve ntions	Subject s per group		
BUDTZ-	Arhus,	two	69		mandibula	Periodontal	53	Distally	27		
JORGENSEan	Denmark.	and			r SDA and	condition(GI/PI)		extended	Femal		
d		five			complete	, caries,		cantilever	e 14		
ISIDOR8 ^{33,34,37}		years			maxillary	prosthetic		bridges	Male		
					arch	conditions,			13		

Jepson et al, 25,30,41,42	Newcastle, united kingdom (UK)	Two and five years	67 23female and 25 male	mandibula r SDA	masticatory system(TMJ) and patient opinion Primary outcomes survival time of prosthesis, influence of diet and nutrition intake secondary	60	Removabl e partial dentures Resin bonded bridges Removabl e partial dentures	26 Femal e 14 Male 12 30 30
					outcomes Caries incidence, periodontal conditions and patient satisfaction			
Walter et al, 46,50–54,62	Germany	Five years	59 107femal e and 108	mandibula r SDA or maxillary	Primary first Tooth loss Secondary	21 5	Removabl e partial dentures	109
			male	SDA	second tooth loss, survival of treatment OHRQoL, TMD problem, tooth mobility and GI/PI		No treatment SDA	106
McKenna et al ⁴⁸	Cork. Ireland	One years	68 28female 16 male	mandibula r SDA or maxillary SDA	Primary OHRQoL, Nutritional status measured using haematological biomarkers. secondary cost effectiveness	44	RPDS SDA	<u>21</u> 23
Witter et al ^{8,10,18,55,56}	Netherland s	9 years	82 females and 64 males	Mandibula r SDA or maxillary SDA	Occlusal contact; Overbite; occlusal wear and TMJ problems	14 6	CDA SDA	72 74
Arce-Tumbay	Sao Paulo,	8	Not	Mandibula		20		
et al, ⁻³	Brazil	month s	recorded	r SDA or maxillary SDA	Masticatory performance and time		SDA RPDs	10
Aras ⁴⁴	Turkey	1 years	45-56	Mandibula	Masticatory	20	Iu Do	10
	-	-	16	r SDA	Performance,		SDA	10
			females 14 males		Maximum Occlusal Force, and Occlusal Contact Area		RPDs	10
SHOI ⁴⁹	Tokyo			Mandibula	Masticatory	11	RPD	11

Japan	66.1	r SDA	function and	SDA	11
	1 male 10	(cross	brain activity	SDA	53
	female	over)			

Table 2:- Excluded study

study	Reason for exclusion
ANTUNES ⁶³	Cross sectional study
Armellini ⁶⁴	Cross sectional study
Astrand ⁶⁵	Combination of natural teeth with implant
Onur Cakir ⁶⁶	Implant supported prosthesis
Roger A. ⁶⁷	Case control
GONCALVES ⁶⁸	Implant supported prosthesis
IVAN TANASIĆ ⁶⁹	In vitro study
NISSAN ⁷⁰	Not SDA
Ohkubo ⁷¹	Pilot study
Sanchez ⁷²	Not RCT
FUEKI ⁷³	Not RCT

Table 3:- Data extraction

Study			One				Tw	0			Five				nin	e		
ID			year	s			yea	rs			year	5			yea	rs		
	interven tion	No. of particip ant	OHIP	caries	Tooth loss	Interdental	OHIP	caries	Tooth loos	Interdental	OHIP	caries	Tooth loss	Interdental snacino	OHIP	Caries	Tooth loss	Interdental spacing
uztz- jorgen	CFPDs	27										2	1					
sen and isidor 37	RPDs	25										2 2	1 1					
Jepson	CFPDs	30						1 1										
et al. ⁴¹	RPDs	30						5 1										
Walfa rt et al .2012- 2014 ^{52,53}	SDA	106	15. 5 (6. 0, 39. 0)								18. 0 (7. 0, 42. 0)							
	RPDs	109	13. 0 (6. 0, 35. 0)								13. 0 (7. 0, 37. 0)							
Walte r et	SDA	106											1 7					
al2013	RPD	109											2 2					
Kern et al 2016 ⁵⁸	SDA	106												0.0 2 (S				

								D 0.3		
	RPD	109						0.2 3 (S D		
Witter	SDA	74						0.4 9)		0.4(0
et al 2001 ⁵⁶	5DA	/-								0.4(0 .1) and 0.5(0 .1)
	CDA	72								0.1(0), p, 0.01

Table 4:- risk of assessment

Study ID	Random	Allocation	Blinding	Incomplete	Selective	Others
	sequence	concealment	Detection and	outcome	reporting	
	(Selection	(Selection	performance bias	assessment	(Reporting	
	bias)	bias)	-	(attrition	bias)	
				bias)		
BUDTZ-	unclear	Unclear	High risk	Low risk	High risk	High
JORGENSEand						risk
ISIDOR8 ^{33,34,37}						
	unclear	unclear	High risk	Low risk	Low risk	Low risk
Jepson et al, 25,30,41,42						
	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Walter et al, 46,50–54,62					-	
McKenna et al ⁴⁸	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	unclear	unclear	unclear	Low risk	High risk	Low risk
Witter et al ^{8,10,18,55,56}					-	
Arce-Tumbay	high	high	unclear	Low risk	Low risk	High
et al, ⁴⁵	-					risk
Aras ⁴⁴	High	unclear	unclear	Low risk	Low risk	Low risk
SHOI ⁴⁹	unclear	High	unclear	Low risk	Low risk	Low risk



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