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Erectile Dysfunction and Penile Rehabilitation after Pelvic Fracture – a Systematic Review and Meta-Analysis

Systematic Review

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Abstract

Objective

To investigate the rate of erectile dysfunction after pelvic ring fracture.

Design

Systematic review, and meta-analysis

Methods

A systematic literature search of the Cochrane, EMBASE, MEDLINE, Scopus and Web of Science Library databases was conducted. Included were original studies performed on humans assessing ED after PRF according the 5-item International Index of Erectile Function (IIEF-5) questionnaire and fracture classification following Young & Burgess, Tile or AO/OTA. Further, interventional cohort studies assessing the effect of penile rehabilitation therapy with phosphodiesterase-5-inhibitors (PDE-5-I) on IIEF-5 scores compared before and after treatment were included. Results were presented as forest plots of proportions of patients with ED after PRF or mean changes on IIEF-5 questionnaires before and after penile rehabilitation. Studies not included in the quantitative analysis were narratively summarized. Risk of bias assessment was conducted using the revised tool for the Quality Assessment on Diagnostic Accuracy studies (QUADAS-2).

Results

The systematic literature search retrieved 617 articles. Seven articles were included in the qualitative analysis and the meta-analysis. Pooled proportions revealed 37% of patients with ED after suffering any form of PRF (result on probability scale pr = 0.37, 95% CI: 0.26 to 0.50). Patients after 3 months of penile rehabilitation therapy reported a higher IIEF-5 score than before (change score [CS] = 6.5 points, 95% CI: 2.54 to 10.46, p-value = 0.0013).

Conclusion

Patients suffering from any type of PRF have an increased risk of developing ED. Oral intake of PDE-5-I for the purpose of penile rehabilitation therapy increases IIEF-5 scores and may relevantly influence QoL in these patients.

Trial registration number

PROSPERO ID: CRD42020169699

Strengths and limitations

- Despite strict definition of PRF and ED, there is still an inevitable variability due to the heterogeneous methodological nature of available studies and study populations from different centers worldwide
- Resulting from the lack of standardization, a broad variety of classifications for PRF and different definitions and questionnaires for the evaluation of ED were used
- Included studies provide a certain risk o bias
- The included results were consistent across studies

Introduction

Pelvic ring fractures (PRF) result from high-energy injuries and are associated with devastating acute and chronic complications as severe and life-threatening hemorrhage or chronic pain and impaired ambulation [1-5]. The initial treatment of PRF is guided by the fracture morphology, pathophysiologic reaction of the organism to the trauma and concomitant injuries [6-9]. After initial hemodynamic stabilization and fixation of the PRF, an interdisciplinary team-approach aims to improve long-term outcomes and to reduce complications [10 11]. In male patients suffering from PRF, erectile dysfunction (ED) is one of the main long-term complications. ED ranks among the adverse effects after PRF that severely impair the quality of life (QoL) in these patients, especially when urogenital damage is involved [12-14]. The treatment of ED depends on the underlying pathogenesis and on patient-specific factors – it ranges from psychological behavior therapy and pharmacological support until surgical interventions [15]. The incidence of ED after PRF varies across the published literature, indicating a potentially high number of missed cases. It further remains unclear, whether patients with PRF benefit from early pharmacological penile rehabilitation therapy with phosphodiesterase-5-inhibitors (PDE-5-I). Therefore, this meta-analysis aims to answer the following questions: A) Is the incidence of ED associated with the severity of PRF? B) What is the treatment effect of penile rehabilitation after PRF with the help of PDE-5-I? We hypothesize, that the rate of ED is associated with the increasing severity of PRFs and that pharmacological penile rehabilitation improves blood circulation in the pelvic organ region and therefore reduces the chances of persistent ED.

Methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16 17]. It was recorded on PROSPERO, the prospective register of systematic reviews, under the registration ID: CRD42020169699.

Search strategy and definitions

A scientific librarian and information expert, specialized in medical research, conducted a systematic literature search of the Cochrane, EMBASE, MEDLINE, Scopus and Web of Science Library databases. PRF are classified following Young and Burgess [18], Tile [19] or the AO/OTA classification [20]. ED was evaluated based on the 5-item International Index of Erectile Function (IIEF-5) questionnaire [21 22]. Presence of ED was defined as a score between 5 and 21 (severe-mild ED) according to results on IIEF-5 questionnaires. Categorization according to the achieved IIEF-5 score leads to the following subgrouping: “Severe” (5-7 points), “moderate” (8-11 points), “mild to moderate” (12-16 points), “mild” (17-21 points) and “no” (22-25 points) ED [23]. The term “penile rehabilitation” refers to the treatment of ED with PDE-5-I.

Inclusion / exclusion criteria

Inclusion criteria were original studies performed on humans assessing ED after PRF written in French, Spanish, Italian, German and English language. To increase comparability, we only included articles that assessed ED based on IIEF-5 and classified the severity of PRF accordingly (see above). We included interventional cohort studies assessing the effect of PDE-5-I on ED after PRF with the reported change of the IIEF-5 scores prior and after PDE-5-I treatment as main outcome parameter. Articles assessing secondary ED after treatment of urethral injuries were excluded. Further, articles without full-text availability were excluded. Case reports, case series, narrative reviews, expert opinions, editorials, book chapters, conference abstracts, letters, commentaries, correspondences, in vitro and animal

experiments were completely excluded from the systematic review. The full search string is shown in the *Appendix 1*.

Data management

The export of de-duplicated publications from all sources were saved in an EndNote library. Two authors (FAS and SH) received the same library and independently screened and assorted all articles within the publicly available web-tool Rayyan [24].

Study selection

According to the PRISMA flow diagram, steps of screening were performed as follows [16]: 1.) title and abstract screening, 2.) full text screening, 3.) extraction and storage of data, 4.) qualitative and quantitative evidence synthesis. After title and abstract screening, full texts were obtained for formal inclusion or exclusion into our systematic review. Full text analysis was performed independently by two authors (FAS an SH). Discrepancies were resolved by consensus or, if necessary, until consensus was reached. Studies that did not provide the type of PRF and the subsequent proportion of patients with ED, as well as no baseline scores of IIEF-5 questionnaires (before PDE-5-I therapy) for the evaluation of penile rehabilitation, were not included in the quantitative analysis. However, some of these studies were summarized in a narrative way.

Data extraction

The following data was extracted from published articles: (i) general study information: author, year, country, study design (i.e. prospective or retrospective); (ii) patient characteristics: sample size, age, type of pelvic injury (category), follow-up time (months); (iii) outcome: rate of patients with ED (proportion), mean or median IIEF-5 score (absolute values) either after trauma and follow-up or before and after treatment, IIEF-5 category (categorical values); associated injuries (iv): urogenital injuries (proportion) or urethral injury (proportion), other

injury sites (amount); treatment (v): medication (type of PDE-5-I), dosage (mg) and treatment duration (months).

The data was extracted independently and in duplicate by two authors (FAS and SH) on separate copies of an Excel spreadsheet. These were compared and discrepancies were resolved by consensus.

Risk of bias

Risk of bias assessment was conducted using the revised tool for the Quality Assessment on Diagnostic Accuracy studies (QUADAS-2) [25]. Each study was assessed for risk of bias through four key domains: patient selection, usage of standardized IIEF-5 questionnaires, grouping into internationally accepted pelvic fracture classifications and flow & timing. For each domain, the two authors (FAS and SH) independently assigned a rating of low, high or unclear risk of bias. Again, discrepancies were resolved through discussion or until consensus was reached.

Statistical analysis

Descriptive statistics on study level were reported as means and proportions. For evidence synthesis for continuous outcomes, means with standard deviations (SD) were used for pooling in a random effects model. If studies reported means with standard errors (SE), the SD was computed using the formula provided by the Cochrane Collaboration: SD = SE * $\sqrt{N}$ [26]. For studies which reported values as median with range or interquartile range (IQR), we estimated the mean and SD according to the formulas by Wan et al. [27]. To confirm the reliability of these estimations, we performed them in duplicate using the formulas by Luo et al. [28], and compared the results of the two methods. Both methods have in general shown good reliability for these estimations, even in presence of deviation from the normal distribution [29]. Evidence synthesis for binary outcomes was done by dividing reported numbers of patients with the condition over total number of patients in each study, and these proportions were used for

pooling in a random effects logistic regression model. The random effects model computes exact 95% confidence intervals (CI) based on the binomial distribution for the overall effect. Results were presented as forest plots of mean changes of IIEF-5 questionnaires before and after penile rehabilitation, or proportions of patients with ED including 95% CI. In one forest plot, studies were ordered by subtypes of pelvic ring fractures. To quantify heterogeneity, the Q-test (total between-study variance), I^2- (proportion of total variation) and H^2-statistic (ratio of total amount of variability and amount of sampling variance) was calculated for all meta-analyses . All statistical analyses were performed using R (version 3.4.2) [30].

Results

Study selection and characteristics

According to the systematic literature research and after removal of duplicates, 617 articles were found. The initial screening process for title and abstract excluded 556 articles. The full-text analysis of the remaining 61 articles led to the exclusion of further 54 articles. We included four articles assessing the incidence of ED after PRF based on IIEF-5 and three articles investigating the treatment effect of PDE-5-I on ED after PRF (*Figure 1)*. Articles included for qualitative and quantitative analysis were published between the years 2000 and 2019 and were all retrospective cohort studies (*Table 1).*

Incidence of ED after PRF

The analysis for the incidence of ED after PRF included 181 male patients with mean age 42 years. Out of these, 65 patients (35.9%) reported ED based on IIEF-5 score of ≤ 21 points. The mean follow-up was 24.01 ± 10.91 months. The overall mean IIEF-5 score was 20.01 ± 2.01 points. The rate of ED after anterior-posterior compression (APC) fracture or Type A fractures was 29.27%. The rate of ED after lateral compression (LC) or Type B PRF was 17.86%. After vertical shear (VS) or Type C PRF 48% of patients suffered from ED. PRF with associated pelvic fracture urethral injury (PFUI) led to a higher percentage of ED than PRF without PFUI (58.6 % vs. 38.1%). Pooling the proportions with the random effects model resulted in 37% of patients with ED after suffering any form of PRF (result on probability scale pr = 0.37, 95% CI: 0.26 to 0.50). As a measure of heterogeneity, the percentage of variability (I^2) was moderate with 44.2% (p-value = 0.021).

Elevated probabilities for the development of ED after PRF was described in Tile fractures type B and C (pr = 0.62; 95% CI: 0.28 to 0.87 and pr = 0.80; 95% CI: 0.31 to 0.97, respectively) as well as with injuries associated with PFUI (pr = 0.59; 95% CI: 0.40 to 0.75). Duramaz et al.

reported higher proportions of ED in patients with APC and VS (pr = 0.42; 95% CI: 0.18 to 0.69 and pr = 0.40; 95% CI: 0.21 to 0.62, respectively) compared to LC fractures (pr = 0.02; 95% CI: 0.00 to 0.29) according Young & Burgess. Fanjalalaina and colleagues reported the highest proportion of ED with 80% of patients affected after PRF Tile C (pr = 0.80; 95% CI: 0.31 to 0.97). The lowest proportion of ED was demonstrated by Duramaz et al. in LC fractures with 0% of patients developing ED after a follow up of 27 months (pr = 0.02; 95% CI: 0.00 to 0.29). Further, the type A fractures presented by Fanjalalaina et al. and the overall chances to develop ED in a combined group of A, B and C fractures from Malavaud reported all lower probabilities than the studies of comparison (pr = 0.24; 95% CI: 0.12 to 0.43 and OR = 0.30; 95% CI: 0.17 to 0.46, respectively). For overall results, please see forest plot in *Figure 2.*

Effect of penile rehabilitation in patients with PRF

Three studies with cumulative 67 patients investigated the effect of penile rehabilitation using PDE-5-I for the treatment of ED after PRF with concomitant PFUI. The mean age of patients across studies was 33 years. Either Sildenafil (50 mg) or Tadalafil (5 mg) were used for a treatment duration of three months. The mean IIEF-score after PRF and before treatment was 6.69 ± 1.16 points and increased to 13.3 ± 4.5 points after PDE-5-I treatment. There was strong evidence that the IIEF-5 score in patients after penile rehabilitation therapy was higher than the IIEF-5 score before treatment (change score [CS] = 6.5 points increase, 95% CI: 2.54 to 10.46, p-value = 0.0013). The largest difference in IIEF-5 scores before and after 3 months of Tadalafil treatment (5 mg) was reported by Nieto et al. (CS = 10.75, 95% CI: 8.04 to 13.46). Peng and colleagues published in 2014 the smallest effect of penile rehabilitation therapy after 3 months of Sildenafil (50 mg) with a statistically higher IIEF-score, comparing before and after treatment (CS = 4.00, 95% CI: 3.01 to 4.99). A considerable heterogeneity was observed between the studies in this meta-analysis, justifying the use of a random effects model (I^2 = 93%, p < 0.0001). For summarized results, please see forest plot in *Figure 3*.

Study quality

The assessment of study quality is depicted in *Figure 4*. The overall quality of the included studies was low due to a rather high risk of bias. We found selection bias to be a concern for more than half of the included studies. This was due to studies not following consecutive recruitment, no or partial definition of inclusion and exclusion criteria as well as time and/or place of recruitment. Either no or only sparse information was available on the different types of fractures that were subdivided into groups of internationally accepted classifications. Finally yet importantly, flow & timing of the study was associated with a high risk of bias in almost all cases, except for Fanjalalaina and colleagues [31].

Discussion

PRF resulting from high-energy trauma is associated with increased mortality [3], impaired QoL [32-34] and concomitant injuries of pelvic organs [35]. Amongst other adverse effects, ED is an underestimated functional complication in male patients after PRF [36]. The aim of this article was to assess the rate of ED after PRF and the effect of pharmacological penile rehabilitation with PDE-5-I on assessed, standardized IIEF-5 questionnaires. The following three points can be regarded as quintessence of this systematic review and the underlying meta-analysis: A) Males after PRF have a significant risk (37%) of developing any form of ED according to IIEF-5 scores, independent of injury severity. B) Pharmacological penile rehabilitation with PDE-5-I improves the individual IIEF-5 score by 6.5 points after a consecutive treatment of 3 months following injury in a male cohort with PRF and PFUI.

The rate of ED after PRF is subject of substantial research activities. In one of the first published manuscripts dealing with this topic in 1975, King et al. reviewed 90 patients and noted an incidence of 5-42% of ED after pelvic trauma, already claiming that ED was more commonly associated with concomitant urethral injury [37]. In 2007, Metze and colleagues investigated the rate of ED after PRF in 77 men utilizing a the long version of the IIEF questionnaire for evaluation: They reported 61% of patients with limitations in sexual function, 19% with persistent impairment and an increased risk of persistence with associated posterior ring disruptions (Tile C) [38]. The IIEF is known to be a simple questionnaire that meets established criteria, is consistent and reliable regarding test-retest reproducibility. Its' validity to evaluate improvement of EF after ED treatment is further justified [39]. Another study noted the rate of moderate and severe ED based on the IIEF-5 score to be 46.1%, increasing in line with the complexity of the fractures (Tile B and C), whereas mild and moderate forms of ED were present in 53.9% of patients affected from type A fractures [40]. A recent publication concluded, similar to our observed results, that APC and VS fractures according Young&Burgess are more associated with ED in men and sexual dysfunction in both sexes,

than LC fractures [41]. In a review article from Harwood and colleagues, the rate of ED after pelvic fractures without PFUI ranges from 5 to 24% and from 9 to 72% with PFUI [42].They discussed the broad variance of assessment tools for ED as well as concomitant injuries as relevant reasons for the broad variability of the gathered data [42]. Several studies investigated the pathogenesis of ED following pelvic fractures, identifying vasculogenic [43-47], neurogenic [43-46 48] and psychogenic [44 47] etiologies. One of the most commonly investigated risk factor for developing ED following PRF is the presence and severity of urethral injuries as collateral damage [13 46 49-51]. However, the management and the relevance of early vs. delayed surgical or conservative treatment approaches after PFUI is still controversially discussed [52-55]. Excluding PFUI, the present study concludes an incidence of ED based on standardized IIEF-5 questionnaires of 41.5% ranging from 29.7 to 71.4%, whereas the broad variance of incidence is mostly depending on injury severity. According to our meta-analysis, there is a visible trend for an increased rate of ED among higher classifications of PRF injuries. The severity of PRFs are associated with concomitant injuries such as vascular [56], nerve [57] as well as abdominal and urogenital organ damage [35]. Wright and colleagues identified that patients with sacroiliac fractures to have at least a four times higher risk for sexual and excretory dysfunction [58]. Further, it has been demonstrated, that patients suffer from a decreased QoL after more severe forms of PRFs [33 59 60]. All these risk factors, including higher trauma energy, are therefore associated with the development of persistent ED [42 61].

Strategies to treat ED as consequence of PRF include pharmacological, mechanical and invasive treatment approaches. Initial attempts in Italy used Papaverine and Prostaglandin E1 as vasodilatative, intracavernous injections [62]. In 2004, Shenfield et al. treated patients with ED after PFUI with 100mg oral Sildenafil (PDE-5-I) on demand for 3-6 months. Forty-seven percent responded favorably to treatment, of which one third reported resumption of normal spontaneous erections during the follow-up of 18 months [63]. Oral PDE-5-I therapy is regarded as standard of care and serves as initial reference treatment in men suffering from ED [64-66]. Both Sildenafil and Tadalafil are commonly used representatives of PDE5-I in the treatment of

ED with comparable safety and efficacy [67]. The management of concomitant injuries following PRF includes the early diagnostics and exclusion or treatment of organic damages in order to prevent or reduce the risk of ED [13 14 42]. According the results of our meta-analysis, the treatment with PDE-5-I increases the IIEF-5 score by 6.5 points in patients with ED after PRF with urethral injury. However, it remains unclear whether it also supports the permanent recovery of spontaneous erectile function. Similarly, the data for the efficacy of penile rehabilitation after radical prostatectomy is still controversially discussed [68 69]. The effect seems to be ameliorated with a regular treatment regime compared to on-demand use of PDE-5-I in patients with ED after radical prostatectomy [70]. The current limited evidence demonstrates, that daily oral intake of PDE-5-I seems to have also a relevant positive effect on ED in 55-88% of patients after PRF with or without associated PFUI [71-74]. Further, the efficacy of pharmacological therapy can also be supported with mechanical aids, such as the use of vacuum erection devices or low-intensity shock-wave therapy. Both have shown to ameliorate IIEF-5 score and erection quality when used in combination with PDE-5-I, compared to stand-alone treatment [75-77]. Finally, the implantation of penile prosthesis or revascularization surgery are both regarded as last resort options in ED treatment of patients after perineal or pelvic surgery or trauma [78].

Conclusion

Patients who suffer from PRF have an increased risk of developing ED, regardless of the classification severity and the concomitant injuries. Early beginning of penile rehabilitation with the pharmacological help of PDE-5-I on a daily basis and a treatment duration of at least 3 months may relevantly reduce ED after PRF and therefore ameliorate QoL in these patients.

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Conflicts of interest

None of the authors has any conflicts of interest to declare

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Author Statement

FA and SH contributed equally to this work: They developed the research idea and led the research team; both authors screened independently all articles, and found consent in cases of disagreement, both authors extracted and analyzed the data; They wrote the original draft of the manuscript

UH supported and supervised the methodology and the statistical analysis of the meta data; UH read and reviewed the manuscript critically

DE and HCP supervised the entire project, provided the infrastructure for conducting this research and critically reviewed the manuscript

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Figures Legend

Figure 1

PRISMA flow diagram of study selection

Figure 2

Weighted forest plot displaying the proportion of patients developing ED according to PRF classification.

Abbreviations: ABC = Tile A, B and C fractures; APC = anteroposterior compression, LC = lateral compression and VS = vertical shear according Young & Burgess; PFUI = pelvic fracture urethral injury.

Figure 3

Forest plot displaying the treatment effect as mean change score between IIEF-5 scores before and after penile rehabilitation treatment with PDE-5-I.

Abbreviations: PFUI = pelvic fracture urethral injury.

Figure 4

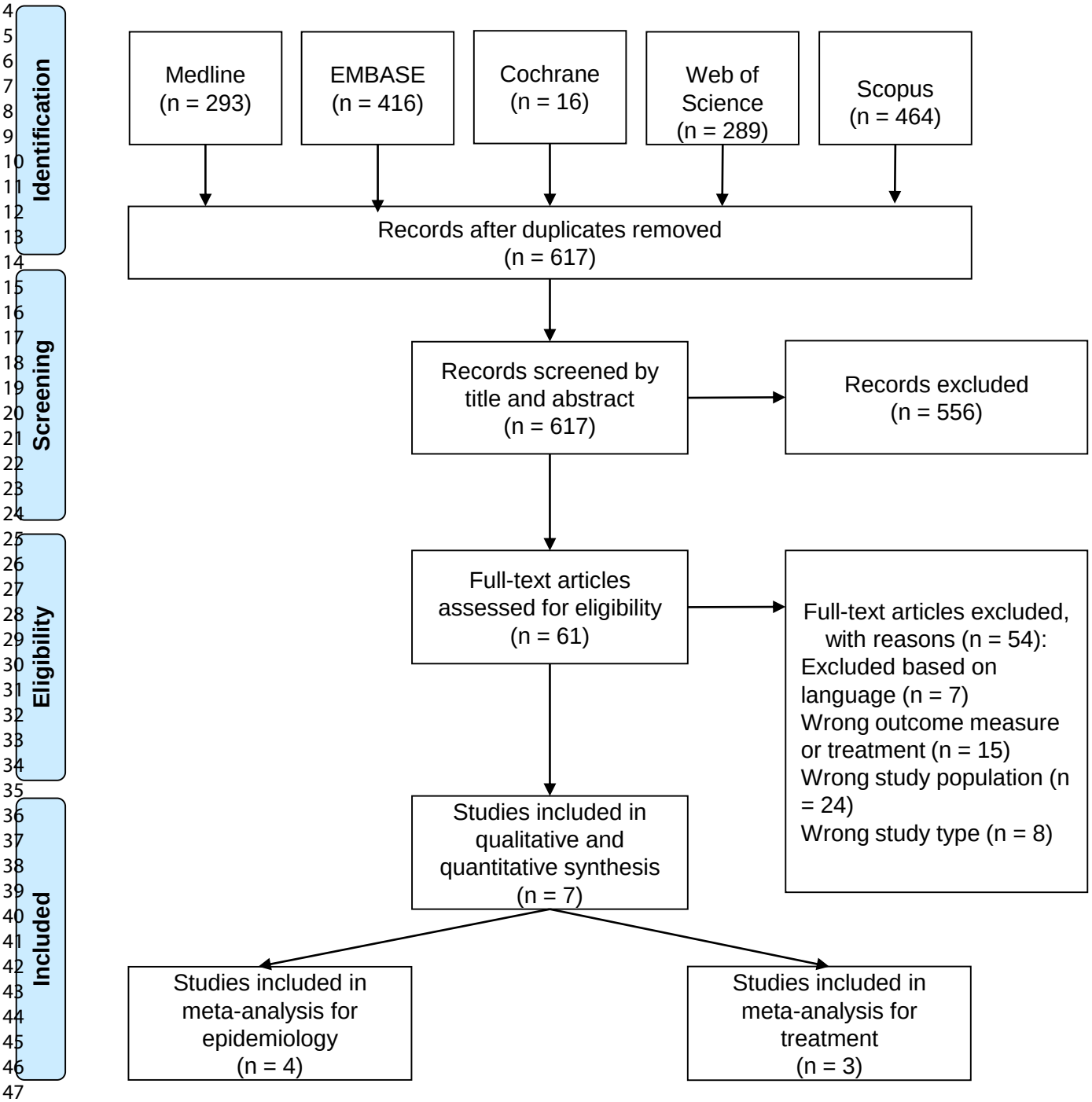
Domains in risk of bias of all included studies according to QUADAS-2 tool. Traffic light plot (A) and weighted summary plot (B).

Table 1: Included articles

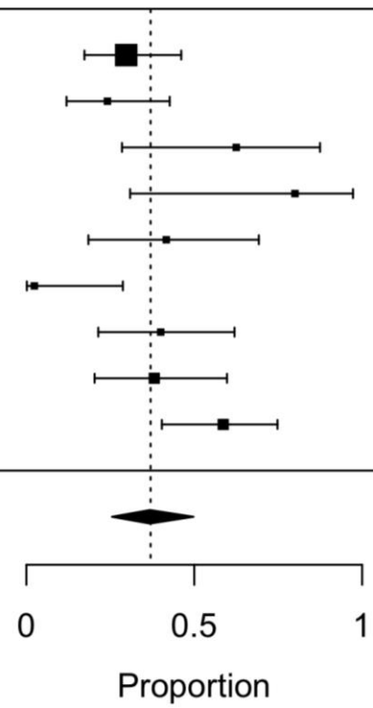
Author	Year	Country	Study Design	n	mean age	Inclusion	DOI
Nieto	2017	Mexico	Retrospective Cohort Study	8	32.5	Treatment effect PDE-5-I	10.1016/j.androl.2017.02.004
Peng	2014	China	Retrospective Cohort Study	31	33.1	Treatment effect PDE-5-I	10.1111/and.12548
Peng	2015	China	NFS	28	34	Treatment effect PDE-5-I	10.1016/j.urology.2014.08.006
Chung	2018	USA	Retrospective Cohort Study	29	52	Incidence of ED after PRF	10.1016/j.urology.2018.01.035
Duramaz	2019	Turkey	Retrospective Cohort Study	52	35	Incidence of ED after PRF	10.1007/s00068-018-01067-0
Fanjalalaina	2019	Madagaskar	Retrospective Cohort Study	42	39.6	Incidence of ED after PRF	10.1016/j.otsr.2019.01.026
Malavaud	2000	France	Retrospective Cohort Study	37	37.8	Incidence of ED after PRF	10.1016/s0090-4295(00)00492-1

n = number of patients
PMID = PubMed ID
PDE-5-I = Phosphodiesterase 5 inhibitor
PRF = Pelvic ring fracture
ED = Erectile dysfunction

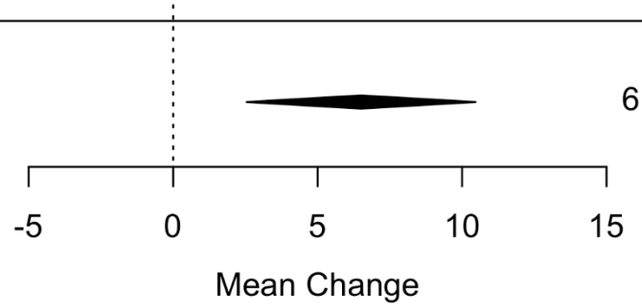
Figure 1: PRISMA flow diagram of study selection



Injury	Author	Year	Country	N	Months of Follow-up	Proportion [95% CI]
ABC	Malavaud	2000	France	37	26.8	0.30 [0.17, 0.46]
A	Fanjalalaina	2019	Madagaskar	29	12.5	0.24 [0.12, 0.43]
B	Fanjalalaina	2019	Madagaskar	8	12.5	0.62 [0.28, 0.87]
C	Fanjalalaina	2019	Madagaskar	5	12.5	0.80 [0.31, 0.97]
APC	Duramaz	2019	Turkey	12	27	0.42 [0.18, 0.69]
LC	Duramaz	2019	Turkey	20	27	0.02 [0.00, 0.29]
VS	Duramaz	2019	Turkey	20	27	0.40 [0.21, 0.62]
no_PFUI	Chung	2018	USA	21	56.4	0.38 [0.20, 0.60]
PFUI	Chung	2018	USA	29	46.8	0.59 [0.40, 0.75]
RE Model	(Q = 18.01, p = 0.021; I^2 = 44.2%, H^2 = 1.8)			181		0.37 [0.26, 0.50]

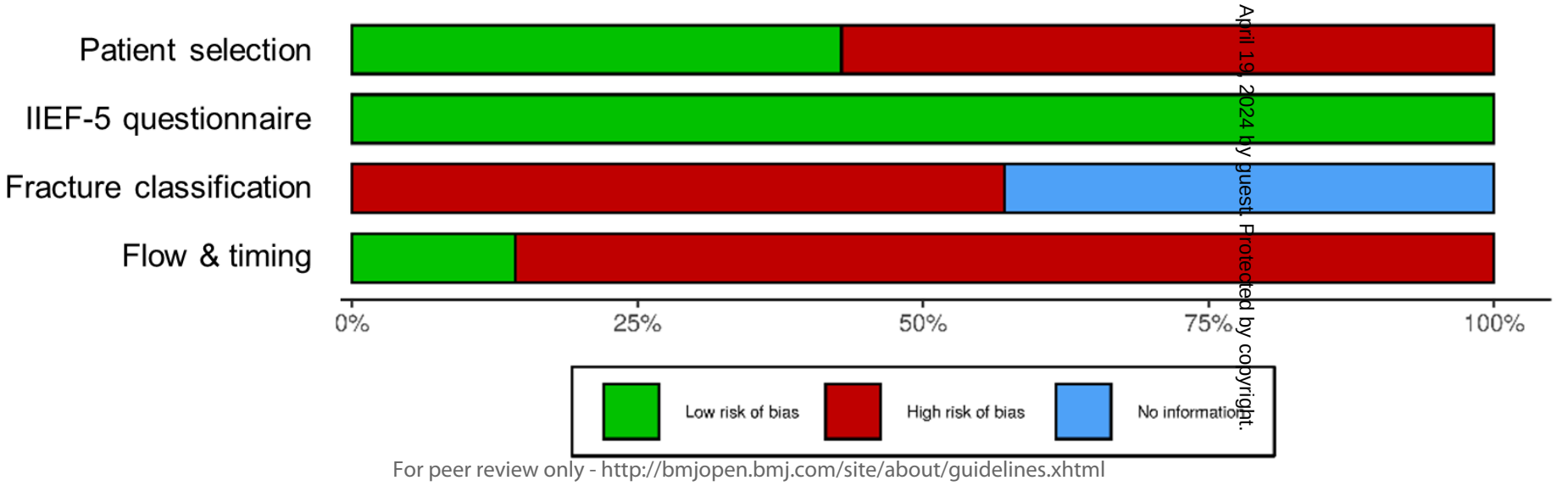


Author, Year	Injury	Country	N	Treatment	Months of Treatment	IIEF-5 post-pre	Change Score [95% CI]
Nieto, 2017	PFUI	Mexico	8	Tadalafil, 5mg	3		10.75 [8.04, 13.46]
Peng, 2014	PFUI	China	31	Sildenafil, 50mg	3		4.00 [3.01, 4.99]
Peng, 2015	PFUI	China	28	Sildenafil, 50mg	3		5.22 [3.25, 7.19]
RE Model	(Q = 21.14, p < 0.0001; I^2 = 93.0%, H^2 = 14.3)		67				6.50 [2.54, 10.46]



A

B



Search Strategy

COCHRANE

((pelvic OR pelvis OR acetabular OR acetabulum) NEAR/3 (fracture* OR trauma*)):ti,ab,kw AND erectile NEAR/3 (dysfunction OR function OR process OR failure OR capacity OR disorder* OR problem*)):ti,ab,kw OR (sexual NEAR/3 dysfunction):ti,ab,kw OR (erection OR impotence OR iief):ti,ab,kw

EMBASE

('pelvis fracture'/exp OR (((pelvic OR pelvis OR acetabular OR acetabulum) NEAR/3 (fracture* OR trauma*)):ti,ab)) NOT ([conference abstract]/lim AND [1974-2014]/py)
AND 'erectile dysfunction'/exp OR 'penis erection'/exp OR 'international index of erectile function'/exp OR ((erectile NEAR/3 (dysfunction OR function OR process OR failure OR capacity OR disorder* OR problem*)):ti,ab) OR ((sexual NEAR/3 dysfunction):ti,ab) OR erection:ti,ab OR impotence:ti,ab OR 'iief':ti,ab

MEDLINE

(exp Pelvic Bones/ and Fractures, Bone/) or exp Pelvic Bones/in or ((pelvic or pelvis or acetabular or acetabulum) adj3 (fracture* or trauma*)).ti,ab. AND exp Erectile Dysfunction/ or Penile Erection/ or (erectile adj3 (dysfunction or function or process or failure or capacity or disorder* or problem*)).ti,ab. or (sexual adj3 dysfunction).ti,ab. or (erection or impotence or 'iief').ti,ab.

SCOPUS

(TITLE-ABS-KEY((pelvic OR pelvis OR acetabular OR acetabulum) W/3 (fracture* OR trauma*))) AND (TITLE-ABS-KEY(erectile W/3 (dysfunction OR function OR process OR failure OR capacity OR disorder* OR problem*)) OR TITLE-ABS-KEY(sexual W/3 dysfunction) OR TITLE-ABS-KEY(erection OR impotence OR iief))

WEB OF SCIENCE

TS=((pelvic OR pelvis OR acetabular OR acetabulum) NEAR/3 (fracture* OR trauma*)) AND TS=(erectile NEAR/3 (dysfunction OR function OR process OR failure OR capacity OR disorder* OR problem*)) OR TS=(sexual NEAR/3 dysfunction) OR TS=(erection OR impotence OR iief)

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Erectile Dysfunction and Penile Rehabilitation after Pelvic Fracture – a Systematic Review and Meta-Analysis

Systematic Review

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Manuscript word count: 3358

Abstract

Objective

To investigate the rate of erectile dysfunction (ED) after pelvic ring fracture (PRF).

Design

Systematic review, and meta-analysis.

Methods

A systematic literature search of the Cochrane, EMBASE, MEDLINE, Scopus and Web of Science Library databases was conducted in January 2020. Included were original studies performed on humans assessing ED after PRF according the 5-item International Index of Erectile Function (IIEF-5) questionnaire and fracture classification following Young & Burgess, Tile or AO/OTA (Arbeitsgemeinschaft für Osteosynthesefragen / Orthopedic Trauma Association). Further, interventional cohort studies assessing the effect of penile rehabilitation therapy with phosphodiesterase-5-inhibitors (PDE-5-I) on IIEF-5 scores compared before and after treatment were included. Results were presented as forest plots of proportions of patients with ED after PRF or mean changes on IIEF-5 questionnaires before and after penile rehabilitation. Studies not included in the quantitative analysis were narratively summarized. Risk of bias assessment was conducted using the revised tool for the Quality Assessment on Diagnostic Accuracy studies (QUADAS-2).

Results

The systematic literature search retrieved 617 articles. Seven articles were included in the qualitative analysis and the meta-analysis. Pooled proportions revealed 37% of patients with ED after suffering any form of PRF (result on probability scale pr = 0.37, 95% CI: 0.26 to 0.50). Patients after 3 months of penile rehabilitation therapy reported a higher IIEF-5 score than before (change score [CS] = 6.5 points, 95% CI: 2.54 to 10.46, p-value = 0.0013).

Conclusion

Despite some heterogeneity and limited high quality research, this study concludes that patients suffering from any type of PRF have an increased risk of developing ED. Oral intake of PDE-5-I for the purpose of penile rehabilitation therapy increases IIEF-5 scores and may relevantly influence Quality of Life (QoL) in these patients.

Trial registration number

PROSPERO ID: CRD42020169699

Strengths and limitations

- Despite strict definition of PRF and ED, there is still an inevitable variability due to the heterogeneous methodological nature of available studies and study populations from different centers worldwide.
- Resulting from the lack of standardization, a broad variety of classifications for PRF and different definitions and questionnaires for the evaluation of ED were used.
- Included studies provide a certain risk of bias.
- The included results were consistent across studies.

Introduction

Pelvic ring fractures (PRF) result from high-energy injuries and are associated with devastating acute and chronic complications as severe and life-threatening hemorrhage or chronic pain and impaired ambulation [1-5]. The initial treatment of PRF is guided by the fracture morphology, pathophysiologic reaction of the organism to the trauma and concomitant injuries [6-9]. After initial hemodynamic stabilization and fixation of the PRF, an interdisciplinary team-approach aims to improve long-term outcomes and to reduce complications [10 11]. In male patients suffering PRF, erectile dysfunction (ED) is one of the main long-term complications. ED ranks among the adverse effects after PRF that severely impair the quality of life (QoL) in these patients, especially when urogenital damage is involved [12-14]. The treatment of ED depends on the underlying pathogenesis and on patient-specific factors – it ranges from psychological behavior therapy and pharmacological support until surgical interventions [15]. The incidence of ED after PRF varies across the published literature due to a lack of epidemiologic studies investigating this subject, indicating a high number of unreported cases. It further remains unclear what the consequences of ED after PRF in the young male population is and whether patients with PRF benefit from early pharmacological penile rehabilitation therapy with phosphodiesterase-5-inhibitors (PDE-5-I). Therefore, this meta-analysis aims to answer the following questions: A) Is the incidence of ED associated with the severity of PRF? B) What is the treatment effect of penile rehabilitation after PRF with the help of PDE-5-I? We hypothesize, that the rate of ED is associated with the increasing severity of PRFs and that pharmacological penile rehabilitation improves blood circulation in the pelvic organ region and therefore reduces the chances of persistent ED.

Methods

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16 17]. It was recorded on PROSPERO, the prospective register of systematic reviews, under the registration ID: CRD42020169699.

Search strategy and definitions

A scientific librarian and information expert, specialized in medical research, conducted a systematic literature search of the Cochrane, EMBASE, MEDLINE, Scopus and Web of Science Library databases in January 2020. PRF are classified following Young and Burgess [18], Tile [19] or the AO/OTA classification [20]. ED was evaluated based on the 5-item International Index of Erectile Function (IIEF-5) questionnaire [21 22]. Presence of ED was defined as a score between 5 and 21 (severe-mild ED) according to results on IIEF-5 questionnaires. Categorization according to the achieved IIEF-5 score leads to the following subgrouping: “Severe” (5-7 points), “moderate” (8-11 points), “mild to moderate” (12-16 points), “mild” (17-21 points) and “no” (22-25 points) ED [23]. The term “penile rehabilitation” refers to the treatment of ED with PDE-5-I. Penile rehabilitation is a urological concept to enhance ED in patients after nerve-sparing radical prostatectomy due to prostate cancer. The idea of this treatment is to enhance blood circulation in the postoperative period (3-6 months) after the intervention in order to ameliorate neurovascular regeneration and to avoid cavernous fibrosis. Although penile rehabilitation has been subject to some debate, this concept might be also helpful in young male patients after trauma to the pelvis. PRFs frequently lead to damage in the neurovascular structures of the pelvis. As a consequence, male patients may experience ED and therefore a severely reduced quality of life.

Inclusion / exclusion criteria

Inclusion criteria were original studies performed on humans assessing ED after PRF written in French, Spanish, Italian, German and English language. No specific time limits were used. To increase comparability, we only included articles that assessed ED based on IIEF-5 and classified the severity of PRF accordingly (see above). We included interventional cohort studies assessing the effect of PDE-5-I on ED after PRF with the reported change of the IIEF-5 scores prior and after PDE-5-I treatment as main outcome parameter. Articles assessing secondary ED after treatment of urethral injuries were excluded. Further, articles without full-text availability were excluded. Case reports, case series, narrative reviews, expert opinions, editorials, book chapters, conference abstracts, letters, commentaries, correspondences, in vitro and animal experiments were completely excluded from the systematic review. The full search string is shown in the *Supplementary*.

Data management

The export of de-duplicated publications from all sources were saved in an EndNote library. Two authors (FAS and SH) received the same library and independently screened and assorted all articles within the publicly available web-tool Rayyan [24].

Study selection

According to the PRISMA flow diagram, steps of screening were performed as follows [16]: 1.) title and abstract screening, 2.) full text screening, 3.) extraction and storage of data, 4.) qualitative and quantitative evidence synthesis. After title and abstract screening, full texts were obtained for formal inclusion or exclusion into our systematic review. Full text analysis was performed independently by two authors (FAS an SH). Discrepancies were resolved by consensus or, if necessary, until consensus was reached. Studies that did not provide the type of PRF and the subsequent proportion of patients with ED, as well as no baseline scores of IIEF-5 questionnaires (before PDE-5-I therapy) for the evaluation of penile rehabilitation, were not included in the quantitative analysis. However, some of these studies were summarized in a narrative way.

Data extraction

The following data was extracted from published articles: (i) general study information: author, year, country, study design (i.e. prospective or retrospective); (ii) patient characteristics: sample size, age, type of pelvic injury (category), follow-up time (months); (iii) outcome: rate of patients with ED (proportion), mean or median IIEF-5 score (absolute values) either after trauma and follow-up or before and after treatment, IIEF-5 category (categorical values); associated injuries (iv): urogenital injuries (proportion) or urethral injury (proportion), other injury sites (amount); treatment (v): medication (type of PDE-5-I), dosage (mg) and treatment duration (months).

The data was extracted independently and in duplicate by two authors (FAS and SH) on separate copies of an Excel spreadsheet. These were compared and discrepancies were resolved by consensus.

Risk of bias

Risk of bias assessment was conducted using the revised tool for the Quality Assessment on Diagnostic Accuracy studies (QUADAS-2) [25]. Each study was assessed for risk of bias through four key domains: patient selection, usage of standardized IIEF-5 questionnaires, grouping into internationally accepted pelvic fracture classifications and flow & timing. For each domain, the two authors (FAS and SH) independently assigned a rating of low, high or unclear risk of bias. Again, discrepancies were resolved through discussion or until consensus was reached.

Statistical analysis

Descriptive statistics on study level were reported as means and proportions. For evidence synthesis for continuous outcomes, means with standard deviations (SD) were used for

pooling in a random effects model. If studies reported means with standard errors (SE), the SD was computed using the formula provided by the Cochrane Collaboration: SD = SE * √N [26]. For studies which reported values as median with range or interquartile range (IQR), we estimated the mean and SD according to the formulas by Wan et al. [27]. To confirm the reliability of these estimations, we performed them in duplicate using the formulas by Luo et al. [28], and compared the results of the two methods. Both methods have in general shown good reliability for these estimations, even in presence of deviation from the normal distribution [29]. Evidence synthesis for binary outcomes was done by dividing reported numbers of patients with the condition over total number of patients in each study, and these proportions were used for pooling in a random effects logistic regression model. The random effects model computes exact 95% confidence intervals (CI) based on the binomial distribution for the overall effect. Results were presented as forest plots of mean changes of IIEF-5 questionnaires before and after penile rehabilitation, or proportions of patients with ED including 95% CI. In one forest plot, studies were ordered by subtypes of pelvic ring fractures. To quantify heterogeneity, the Q-test (total between-study variance), I^2- (proportion of total variation) and H^2-statistic (ratio of total amount of variability and amount of sampling variance) was calculated for all meta-analyses . All statistical analyses were performed using R (version 3.4.2) [30].

Patient and Public Involvement

No patient involved

Results

Study selection and characteristics

According to the systematic literature research and after removal of duplicates, 617 articles were found. The initial screening process for title and abstract excluded 556 articles. The full-text analysis of the remaining 61 articles led to the exclusion of further 54 articles. We included four articles assessing the incidence of ED after PRF based on IIEF-5 and three articles investigating the treatment effect of PDE-5-I on ED after PRF (*Figure 1)*. Articles included for qualitative and quantitative analysis were published between the years 2000 and 2019 and were all retrospective cohort studies (*Table 1).*

Incidence of ED after PRF

The analysis for the incidence of ED after PRF included 181 male patients with mean age 42 years. Out of these, 65 patients (35.9%) reported ED based on IIEF-5 score of ≤ 21 points. The mean follow-up was 24.01 ± 10.91 months. The overall mean IIEF-5 score was 20.01 ± 2.01 points. The rate of ED after anterior-posterior compression (APC) fracture or Type A fractures was 29.27%. The rate of ED after lateral compression (LC) or Type B PRF was 17.86%. After vertical shear (VS) or Type C PRF 48% of patients suffered from ED. PRF with associated pelvic fracture urethral injury (PFUI) led to a higher percentage of ED than PRF without PFUI (58.6 % vs. 38.1%). Pooling the proportions with the random effects model resulted in 37% of patients with ED after suffering any form of PRF (result on probability scale

pr = 0.37, 95% CI: 0.26 to 0.50). As a measure of heterogeneity, the percentage of variability (I^2) was moderate with 44.2% (p-value = 0.021).

Elevated probabilities for the development of ED after PRF was described in Tile fractures type B and C (pr = 0.62; 95% CI: 0.28 to 0.87 and pr = 0.80; 95% CI: 0.31 to 0.97, respectively) as well as with injuries associated with PFUI (pr = 0.59; 95% CI: 0.40 to 0.75). Duramaz et al. reported higher proportions of ED in patients with APC and VS (pr = 0.42; 95% CI: 0.18 to 0.69 and pr = 0.40; 95% CI: 0.21 to 0.62, respectively) compared to LC fractures (pr = 0.02; 95% CI: 0.00 to 0.29) according Young & Burgess. Fanjalalaina and colleagues reported the highest proportion of ED with 80% of patients affected after PRF Tile C (pr = 0.80; 95% CI: 0.31 to 0.97). The lowest proportion of ED was demonstrated by Duramaz et al. in LC fractures with 0% of patients developing ED after a follow up of 27 months (pr = 0.02; 95% CI: 0.00 to 0.29). Further, the type A fractures presented by Fanjalalaina et al. and the overall chances to develop ED in a combined group of A, B and C fractures from Malavaud reported all lower probabilities than the studies of comparison (pr = 0.24; 95% CI: 0.12 to 0.43 and OR = 0.30; 95% CI: 0.17 to 0.46, respectively). For overall results, please see forest plot in *Figure 2.*

Effect of penile rehabilitation in patients with PRF

Three studies with cumulative 67 patients investigated the effect of penile rehabilitation using PDE-5-I for the treatment of ED after PRF with concomitant PFUI. The mean age of patients across studies was 33 years. Either Sildenafil (50 mg) or Tadalafil (5 mg) were used for a treatment duration of three months. The mean IIEF-score after PRF and before treatment was 6.69 ± 1.16 points and increased to 13.3 ± 4.5 points after PDE-5-I treatment. There was strong evidence that the IIEF-5 score in patients after penile rehabilitation therapy was higher than the IIEF-5 score before treatment (change score [CS] = 6.5 points increase, 95% CI: 2.54 to 10.46, p-value = 0.0013). The largest difference in IIEF-5 scores before and after 3 months of

Tadalafil treatment (5 mg) was reported by Nieto et al. (CS = 10.75, 95% CI: 8.04 to 13.46). Peng and colleagues published in 2014 the smallest effect of penile rehabilitation therapy after 3 months of Sildenafil (50 mg) with a statistically higher IIEF-score, comparing before and after treatment (CS = 4.00, 95% CI: 3.01 to 4.99). A considerable heterogeneity was observed between the studies in this meta-analysis, justifying the use of a random effects model (I^2 = 93%, $p < 0.0001$). For summarized results, please see forest plot in *Figure 3*.

Study quality

The assessment of study quality is depicted in *Figure 4*. The overall quality of the included studies was low due to a rather high risk of bias. We found selection bias to be a concern for more than half of the included studies. This was due to studies not following consecutive recruitment, no or partial definition of inclusion and exclusion criteria as well as time and/or place of recruitment. Either no or only sparse information was available on the different types of fractures that were subdivided into groups of internationally accepted classifications. Finally yet importantly, flow & timing of the study was associated with a high risk of bias in almost all cases, except for Fanjalalaina and colleagues [31].

Discussion

PRF resulting from high-energy trauma is associated with increased mortality [3], impaired QoL [32-34] and concomitant injuries of pelvic organs [35]. Amongst other adverse effects, ED is an underestimated functional complication in male patients after PRF [36]. The aim of this article was to assess the rate of ED after PRF and the effect of pharmacological penile rehabilitation with PDE-5-I on assessed, standardized IIEF-5 questionnaires. The following three points can be regarded as quintessence of this systematic review and the underlying meta-analysis: A) Males after PRF have a significant risk (37%) of developing any form of ED according to IIEF-5 scores, independent of injury severity. B) Pharmacological penile rehabilitation with PDE-5-I improves the individual IIEF-5 score by 6.5 points after a consecutive treatment of 3 months following injury in a male cohort with PRF and PFUI.

Rate of ED after PRF

The rate of ED after PRF is subject of substantial research activities. In one of the first published manuscripts dealing with this topic in 1975, King et al. reviewed 90 patients and noted an incidence of 5-42% of ED after pelvic trauma, already claiming that ED was more commonly associated with concomitant urethral injury [37]. In 2007, Metze and colleagues investigated the rate of ED after PRF in 77 men utilizing a the long version of the IIEF questionnaire for evaluation: They reported 61% of patients with limitations in sexual function, 19% with persistent impairment and an increased risk of persistence with associated posterior ring disruptions (Tile C) [38]. The IIEF is known to be a simple questionnaire that meets established criteria, is consistent and reliable regarding test-retest reproducibility. Its' validity to evaluate improvement of EF after ED treatment is further justified [39]. Another study noted the rate of moderate and severe ED based on the IIEF-5 score to be 46.1%, increasing in line with the complexity of the fractures (Tile B and C), whereas mild and moderate forms of ED were present in 53.9% of patients affected from type A fractures [40]. A recent publication concluded, similar to our observed results, that APC and VS fractures according to Young &

Burgess are more associated with ED in men and sexual dysfunction in both sexes, than LC fractures [41]. In a review article from Harwood and colleagues, the rate of ED after pelvic fractures without PFUI ranges from 5 to 24% and from 9 to 72% with PFUI [42].They discussed the broad variance of assessment tools for ED as well as concomitant injuries as relevant reasons for the broad variability of the gathered data [42]. Several studies investigated the pathogenesis of ED following pelvic fractures, identifying vasculogenic [43-47], neurogenic [43-46 48] and psychogenic [44 47] etiologies. One of the most commonly investigated risk factor for developing ED following PRF is the presence and severity of urethral injuries as collateral damage [13 46 49-51]. However, the management and the relevance of early vs. delayed surgical or conservative treatment approaches after PFUI is still controversially discussed [52-55]. Excluding PFUI, the present study concludes an incidence of ED based on standardized IIEF-5 questionnaires of 41.5% ranging from 29.7 to 71.4%, whereas the broad variance of incidence is mostly depending on injury severity. According to our meta-analysis, there is a visible trend for an increased rate of ED among higher classifications of PRF injuries. The severity of PRFs are associated with concomitant injuries such as vascular [56], nerve [57] as well as abdominal and urogenital organ damage [35]. Wright and colleagues identified that patients with sacroiliac fractures to have at least a four times higher risk for sexual and excretory dysfunction [58]. Further, it has been demonstrated, that patients suffer from a decreased QoL after more severe forms of PRFs [33 59 60]. All these risk factors, including higher trauma energy, are therefore associated with the development of persistent ED [42 61].

Treatment of ED after PRF

Strategies to treat ED as a consequence of PRF include pharmacological, mechanical and invasive treatment approaches. Initial attempts in Italy used Papaverine and Prostaglandin E1 as vasodilatative, intracavernous injections [62]. In 2004, Shenfield et al. treated patients with ED after PFUI with 100mg oral Sildenafil (PDE-5-I) on demand for 3-6 months. Forty-seven percent responded favorably to treatment, of which one third reported resumption of normal

spontaneous erections during the follow-up of 18 months [63]. Oral PDE-5-I therapy is regarded as standard of care and serves as initial reference treatment in men suffering from ED [64-66]. Both Sildenafil and Tadalafil are commonly used representatives of PDE5-I in the treatment of ED with comparable safety and efficacy [67]. The management of concomitant injuries following PRF includes the early diagnostics and exclusion or treatment of organic damages in order to prevent or reduce the risk of ED [13 14 42]. According the results of our meta-analysis, the treatment with PDE-5-I increases the IIEF-5 score by 6.5 points in patients with ED after PRF with urethral injury. However, it remains unclear whether it also supports the permanent recovery of spontaneous erectile function. Similarly, the data for the efficacy of penile rehabilitation after radical prostatectomy is still controversially discussed [68 69]. The effect seems to be ameliorated with a regular treatment regime compared to on-demand use of PDE-5-I in patients with ED after radical prostatectomy [70]. The current limited evidence demonstrates, that daily oral intake of PDE-5-I seems to have also a relevant positive effect on ED in 55-88% of patients after PRF with or without associated PFUI [71-74]. Further, the efficacy of pharmacological therapy can also be supported with mechanical aids, such as the use of vacuum erection devices or low-intensity shock-wave therapy. Both have shown to ameliorate IIEF-5 score and erection quality when used in combination with PDE-5-I, compared to stand-alone treatment [75-77]. Finally, the implantation of penile prosthesis or revascularization surgery are both regarded as last resort options in ED treatment of patients after perineal or pelvic surgery or trauma [78].

Limitations & strengths

This systematic review and its meta-analysis has some limitations. Despite the strict definition of PRF and ED, all of the included studies present an inevitable variability due to their heterogeneous methodology and study populations coming from different centers worldwide. Therefore and due to the lack of standardization, a broad variety of PRF classifications and different definitions as well as questionnaires for the evaluation of ED were used. Further, all

of the included studies provide a considerable risk of bias (*Figure 4*). In addition, there are general limitations to systematic reviews regarding the search algorithm and the potential to miss relevant articles (selection bias, publication bias, language bias, time lag bias, etc.). However, all of the included studies showed consistent and overall comparable outcomes, which implicates a representative cohort with reliable and repeatable results included in this analysis.

Conclusion

Patients who suffer from PRF have an increased risk of developing ED, regardless of the classification severity and the concomitant injuries. Early beginning of penile rehabilitation with the pharmacological help of PDE-5-I on a daily basis and a treatment duration of at least 3 months may relevantly reduce ED after PRF and therefore ameliorate QoL in these patients.

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Ethics approval statement

Not applicable.

Conflicts of interest

None of the authors has any conflicts of interest to declare

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Author Statement

FAS and SH contributed equally to this work: They developed the research idea and led the research team; both authors screened independently all articles, and found consent in cases of disagreement, both authors extracted and analyzed the data; They wrote the original draft of the manuscript

UH supported and supervised the methodology and the statistical analysis of the meta data; UH read and reviewed the manuscript critically

DE and HCP supervised the entire project, provided the infrastructure for conducting this research and critically reviewed the manuscript

Data Availability Statement

Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi: 10.5061/dryad.mpg4f4r06

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Figures Legend

Figure 1

PRISMA flow diagram of study selection

Figure 2

Weighted forest plot displaying the proportion of patients developing ED according to PRF classification.

Abbreviations: ABC = Tile A, B and C fractures; APC = anteroposterior compression, LC = lateral compression and VS = vertical shear according Young & Burgess; PFUI = pelvic fracture urethral injury.

Figure 3

Forest plot displaying the treatment effect as mean change score between IIEF-5 scores before and after penile rehabilitation treatment with PDE-5-I.

Abbreviations: PFUI = pelvic fracture urethral injury.

Figure 4

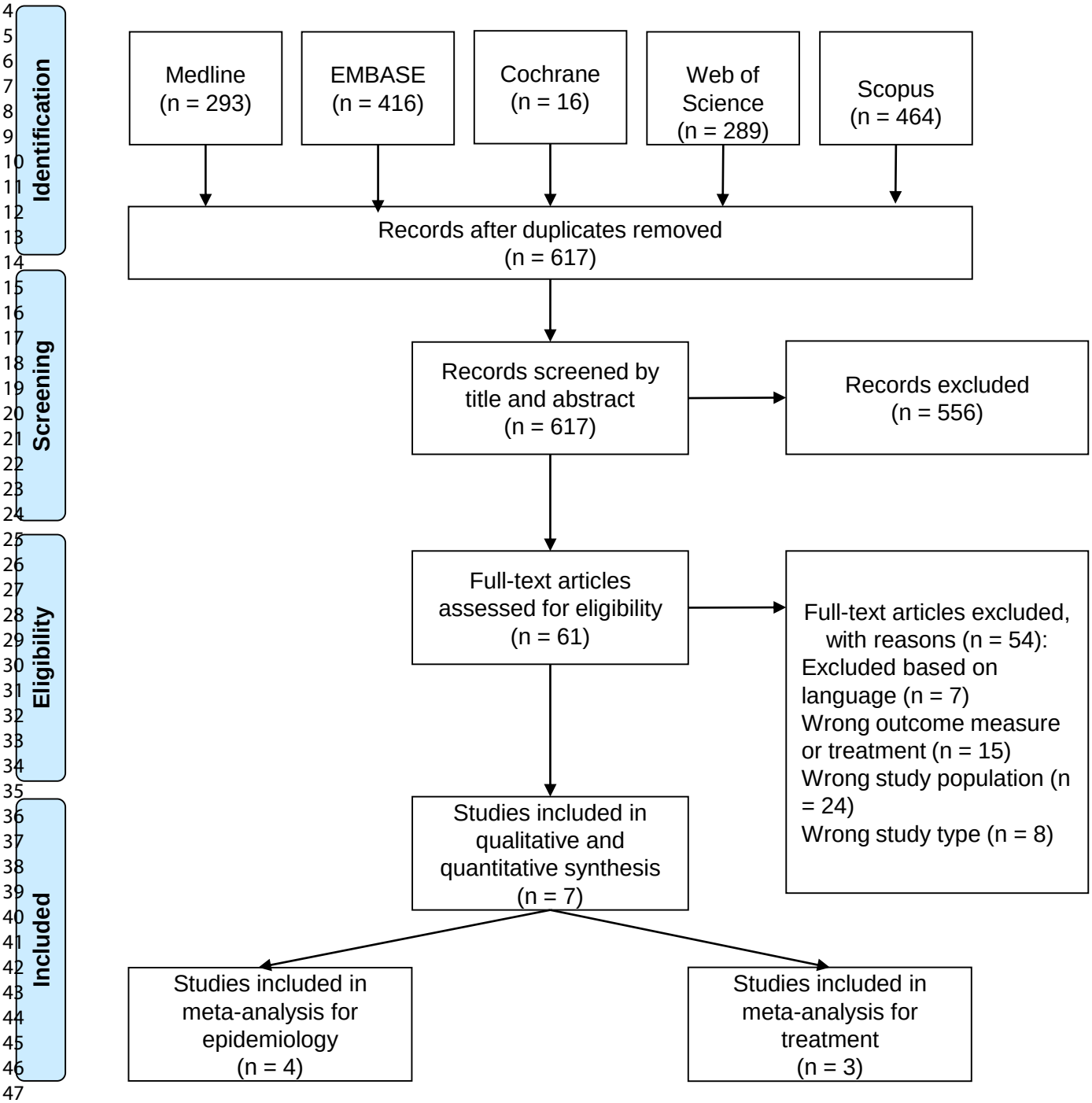
Domains in risk of bias of all included studies according to QUADAS-2 tool. Traffic light plot (A) and weighted summary plot (B).

Table 1: Included articles

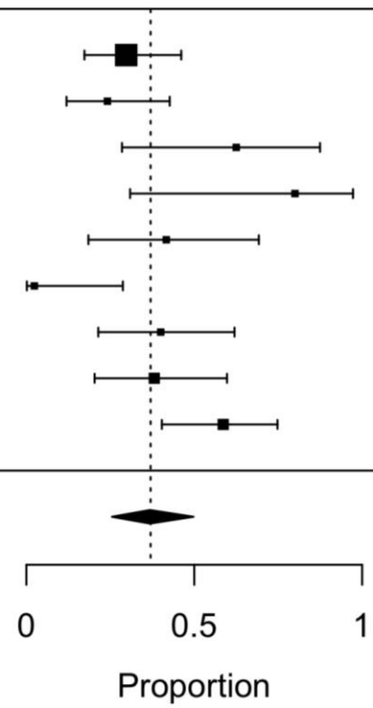
Author	Year	Country	Study Design	n	mean age (range)	Inclusion	Main result
Nieto	2017	Mexico	Retrospective Cohort Study	8	32.5 (26 - 56)	Treatment effect PDE-5-I	Nearly all patients (87.5%) had a positive effect on IIEF-5 questionnaires after penile rehabilitation treatment with Tadalafil 5mg for 3 months.
Peng	2014	China	Retrospective Cohort Study	31	33.1 (26 - 46)	Treatment effect PDE-5-I	More than half of the patients (54.8%) reported a successful penile rehabilitation with better IIEF-5 score after 3 months treatment with Sildenafil 50mg.
Peng	2015	China	NFS	28	34 (22 - 49)	Treatment effect PDE-5-I	Almost two-thirds of the patients (61.5%) witnessed a positive effect on IIEF-5 scores after penile rehabilitation with Sildenafil 50mg for 3 months.
Chung	2018	USA	Retrospective Cohort Study	29	52 (18 - >70)	Incidence of ED after PRF	ED was reported in 47.5% of all patients following PRF according to IIEF-5 scores.
Duramaz	2019	Turkey	Retrospective Cohort Study	52	35 (19 - 50)	Incidence of ED after PRF	Vertical shear injuries were the most common type of PRF in patients who suffered ED according to IIEF-5 scores.
Fanjalalaina	2019	Madagaskar	Retrospective Cohort Study	42	39.6 (18 - >66)	Incidence of ED after PRF	One in three patients (33.3%) suffered ED following PRF according to IIEF-5 scores.
Malavaud	2000	France	Retrospective Cohort Study	37	37.8 (16 - 76)	Incidence of ED after PRF	Nearly one in three patients (29.7%) reported ED following PRF according to IIEF-5 scores.

n = number of patients
NFS = Not further specified
IIEF-5 = International Index of Erectile Function 5 Questionnaire
PDE-5-I = Phosphodiesterase 5 inhibitor
PRF = Pelvic ring fracture
ED = Erectile dysfunction

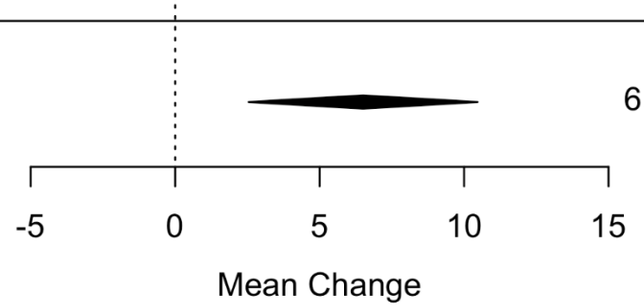
Figure 1: PRISMA flow diagram of study selection



Injury	Author	Year	Country	N	Months of Follow-up	Proportion [95% CI]
ABC	Malavaud	2000	France	37	26.8	0.30 [0.17, 0.46]
A	Fanjalalaina	2019	Madagaskar	29	12.5	0.24 [0.12, 0.43]
B	Fanjalalaina	2019	Madagaskar	8	12.5	0.62 [0.28, 0.87]
C	Fanjalalaina	2019	Madagaskar	5	12.5	0.80 [0.31, 0.97]
APC	Duramaz	2019	Turkey	12	27	0.42 [0.18, 0.69]
LC	Duramaz	2019	Turkey	20	27	0.02 [0.00, 0.29]
VS	Duramaz	2019	Turkey	20	27	0.40 [0.21, 0.62]
no_PFUI	Chung	2018	USA	21	56.4	0.38 [0.20, 0.60]
PFUI	Chung	2018	USA	29	46.8	0.59 [0.40, 0.75]
RE Model	(Q = 18.01, p = 0.021; I^2 = 44.2%, H^2 = 1.8)			181		0.37 [0.26, 0.50]



Author, Year	Injury	Country	N	Treatment	Months of Treatment	IIEF-5 post-pre	Change Score [95% CI]
Nieto, 2017	PFUI	Mexico	8	Tadalafil, 5mg	3		10.75 [8.04, 13.46]
Peng, 2014	PFUI	China	31	Sildenafil, 50mg	3		4.00 [3.01, 4.99]
Peng, 2015	PFUI	China	28	Sildenafil, 50mg	3		5.22 [3.25, 7.19]
RE Model	(Q = 21.14, p < 0.0001; I^2 = 93.0%, H^2 = 14.3)		67				6.50 [2.54, 10.46]



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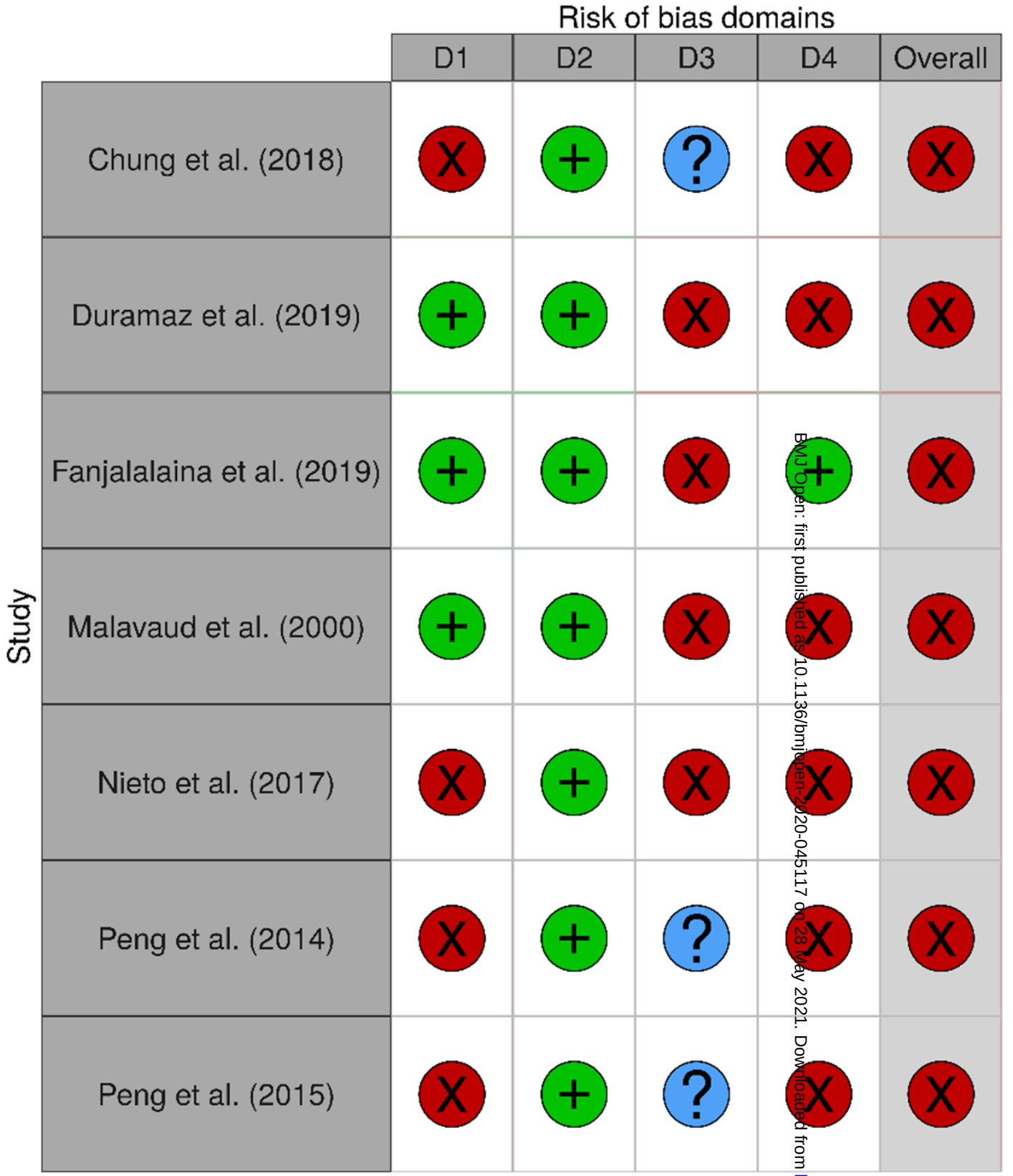
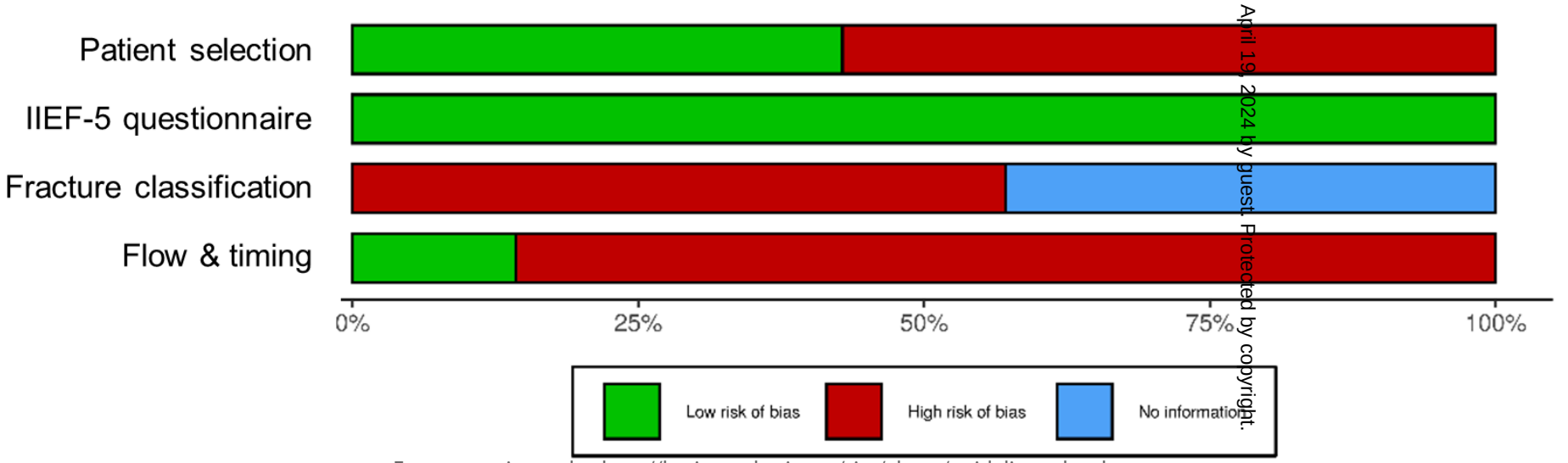


B



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Search Strategy:

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2	exp Erectile Dysfunction/ or Penile Erection/ or (erectile adj3 (dysfunction or function or process or failure or capacity or disorder* or problem*)).ti,ab. or (sexual adj3 dysfunction).ti,ab. or (erection or impotence or 'iief').ti,ab.	39893
3	1 and 2	293
4	exp Erectile Dysfunction/rh, th or (rehab* or therap* or treat*).mp.	8890204
5	3 and 4	182

1. Etiology of **Erectile Dysfunction** and Duration of Symptoms in Patients Undergoing Penile Prosthesis: A Systematic Review. [Review]

   Bajic P; Mahon J; Faraday M; Sadeghi-Nejad H; Hakim L; McVary KT.

   Sexual Medicine Reviews. 2019 Jul 02.

   [Journal Article. Review]

   UI: 31278064

   Authors Full Name
   Bajic, Petar; Mahon, Joseph; Faraday, Martha; Sadeghi-Nejad, Hossein; Hakim, Lawrence; McVary, Kevin T.

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No.	Query	Results
#6	#3 NOT #5	146
#5	#3 AND #4	270
#4	'erectile dysfunction'/exp/dm_dm,dm_dt,dm_rh,dm_th OR rehab*:ti,ab,de OR therap*:ti,ab,de OR treat*:ti,ab,de	11040498
#3	#1 AND #2	416
#2	'erectile dysfunction'/exp OR 'penis erection'/exp OR 'international index of erectile function'/exp OR ((erectile NEAR/3 (dysfunction OR function OR process OR failure OR capacity OR disorder* OR problem*)):ti,ab) OR ((sexual NEAR/3 dysfunction):ti,ab) OR erection:ti,ab OR impotence:ti,ab OR 'iief':ti,ab	65289
#1	('pelvis fracture'/exp OR (((pelvic OR pelvis OR acetabular OR acetabulum) NEAR/3 (fracture* OR trauma*)):ti,ab)) NOT ([conference abstract]/lim AND [1974-2014]/py)	12784

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#1	((pelvic OR pelvis OR acetabular OR acetabulum) NEAR/3 (fracture* OR trauma*)):ti,ab,kw	Limits	382	
#2	(erectile NEAR/3 (dysfunction OR function OR process OR failure OR capacity OR disorder* OR problem*)):ti,ab,kw OR (sexual NEAR/3 dysfunction):ti,ab,kw OR (erection OR impotence OR iief):ti,ab,kw	Limits	6630	
#3	#1 AND #2	Limits	16	
#4	Type a search term or use the S or MeSH buttons to compose	S	MeSH	Limits N/A

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1 ☑

Vardenafil and Cognitive-behavioral Sex Therapy for the Treatment of Erectile Dysfunction (STEDOV)

NCT02450188

https://clinicaltrials.gov/show/NCT02450188, **2014** | added to CENTRAL: 31 Mai 2018 | 2018 Issue 5

CT.gov

2 ☑

Erectile function improvement with oral sildenafil versus placebo in posterior urethroplasty: double blind randomized controlled trial

MM Mazloomfard, J Hosseini, M Jabbari

International journal of urology, **2014**, 21, A257-A258 | added to CENTRAL: 31 März 2015 | 2015 Issue 3

Embase

3 ☑

The role of vacuum erection devices in penile rehabilitation after posterior urethral anastomotic urethroplasty; A pilot study

L Song, T Liu, Q Fu

Journal of sexual medicine, **2017**, 14(1), S29- | added to CENTRAL: 31 Januar 2018 | 2018 Issue 1

Embase

4 ☑

The role of vacuum erection devices in penile rehabilitation after posterior urethral anastomotic urethroplasty: a pilot study

L Song, Q Fu

Journal of urology, **2017**, 197(4), e1224-e1225 | added to CENTRAL: 30 Juni 2017 | 2017 Issue 6

Embase

5 ☑

The role of vacuum erection devices in penile rehabilitation after posterior urethral anastomotic urethroplasty: a pilot study

L Song, T Liu, Q Fu

International journal of urology. Conference: 14th asian congress of urology of the urological association of asia, ACU 2016. Singapore singapore. Conference start: 20160720. Conference end: 20160724. Conference publication: (var.pagings), **2016**, 23, 6 | added to CENTRAL: 31 Mai 2018 | 2018 Issue 5

Embase

6 ☑

Comparison of Subcutaneous INFIX and EXFIX for Anterior Pelvic Ring Fractures Requiring Stabilization

NCT02403154

https://clinicaltrials.gov/show/NCT02403154, **2015** | added to CENTRAL: 31 Mai 2018 | 2018 Issue 5

CT.gov

7 ☑

Reconstructive surgery, primary realignment

F Mirkazemi

International journal of urology, **2014**, 21, A59- | added to CENTRAL: 31 März 2015 | 2015 Issue 3

Embase

8 ☑

A preliminary clinical study on non-transecting urethroplasty for the treatment of posterior urethral stricture caused by pelvic fractures

ChiCTR-INR-16010132

http://www.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-INR-16010132, **2016** | added to CENTRAL: 31 März 2019 | 2019 Issue 3

ICTRP

9 ☑

Not applicable

EUCTR2011-005333-39-GR

http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-005333-39-GR, **2011** | added to CENTRAL: 31 März 2019 | 2019 Issue 3

ICTRP

10 ☑

Primary Urethral Realignment Versus Suprapubic Cystostomy After Pelvic Fracture Urethral Injury

NCT03195179

https://clinicaltrials.gov/show/NCT03195179, **2017** | added to CENTRAL: 31 Mai 2018 | 2018 Issue 5

CT.gov

11 ☑

Is on demand use of tramadol more effective than selective serotonin reuptake inhibitors and/or sildenafil and/or topical penile anesthetics in treating premature ejaculation (PE)?

V Boulos, A Hassanin, MF Roaiah

European urology, supplements., **2015**, 14(2), e242 | added to CENTRAL: 31 August 2015 | 2015 Issue 8

Embase

12 ☑

Preexisting vascular pathology in donor and recipient vessels during penile microvascular arterial bypass surgery

DG Hatzichristou, I Goldstein, WC Quist

Journal of urology, **1994**, 151(5), 1217-1224 | added to CENTRAL: 31 März 2019 | 2019 Issue 3

PubMed Embase

13 ☑

Surgical management for Chinese children urethral injury: a systematic review

B-S Gong, G-B Xiong, M-X Qiu

Chinese journal of evidence-based medicine, **2010**, 10(9), 1063-1071 | added to CENTRAL: 31 März 2019 | 2019 Issue 3

Embase

14 ☑

Comparison of the effect of two intervention methods (pelvic floor exercise and moisturizing cream) on sexual function and disparity in women undergoing systemic cancer

IRCT20190619043952N1

http://www.who.int/trialsearch/Trial2.aspx?TrialID=IRCT20190619043952N1, **2019** | added to CENTRAL: 30 September 2019 | 2019 Issue 09

ICTRP

15 ☑

Relationship of episiotomy to perineal trauma and morbidity, sexual dysfunction, and pelvic floor relaxation

MC Klein, RJ Gauthier, JM Robbins, J Kaczorowski, SH Jorgensen, ED Franco, B Johnson, K Waghorn, MM Gelfand, MS Guralnick

American journal of obstetrics and gynecology, **1994**, 171(3), 591-598 | added to CENTRAL: 31 Januar 1998 | 1998 Issue 1

PubMed

16 ☑

A Phase II study of acute toxicity for Celebrex™ (celecoxib) and chemoradiation in patients with locally advanced cervical cancer: primary endpoint analysis of RTOG 0128

DK Gaffney, K Winter, AP Dicker, B Miller, PJ Eifel, J Ryu, V Avizonis, M Fromm, K Greven

International journal of radiation oncology biology physics, **2007**, 67(1), 104-109 | added to CENTRAL: 31 März 2019 | 2019 Issue 3

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# 2	46,855	TS=(erectile NEAR/3 (dysfunction OR function OR process OR failure OR capacity OR disorder* OR problem*)) OR TS=(sexual NEAR/3 dysfunction) OR TS=(erection OR impotence OR iief) *Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years*	Edit		
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4	TITLE-ABS-KEY (rehab* OR therap* OR treat*)	12,028,692 document results
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2	TITLE-ABS-KEY (erectile W/3 (dysfunction OR function OR process OR failure OR capacity OR disorder* OR problem*)) OR TITLE-ABS-KEY (sexual W/3 dysfunction) OR TITLE-ABS-KEY (erection OR impotence OR iief)	87,771 document results

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5/6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplement
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 7
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page7/8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page7/8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page7/8
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page7/8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page7/8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page7/8
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page7/8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 7
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7/8

PRISMA 2020 Checklist

assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 9
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figures 2 and 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figure 2 and 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Figures 2 and 3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 11
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 9/10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 12
	23b	Discuss any limitations of the evidence included in the review.	Page 14/15
	23c	Discuss any limitations of the review processes used.	Page 14/15
	23d	Discuss implications of the results for practice, policy, and future research.	Page 13-16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 5
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 16
Competing interests	26	Declare any competing interests of review authors.	Page 16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

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