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Erectile Dysfunction is a Transient Complication of Prostate Biopsy: A Systematic Review and Meta-Analysis

J. Fainberg,* C. D. Gaffney,* H. Pierce, A. Aboukhshaba, B. Chughtai, P. Christos† and J. A. Kashanian‡

From the Department of Urology (JF, CDG, HP, AA, BC, JAK), Weill Cornell Medical College, New York-Presbyterian Hospital, New York, New York, and Department of Health Policy and Research (PC), Weill Cornell Medical College, New York, New York

Abbreviations and Acronyms

ED = erectile dysfunction

IIEF-5 = International Index of Erectile Function 5

MRI = magnetic resonance imaging

PB = prostate biopsy

TPBx = transperineal prostate biopsy

TRUS-PBx = transrectal ultrasound guided prostate biopsy

WOS = Web of Science

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‡ Correspondence: Department of Urology, Weill Cornell Medical College, New York-Presbyterian Hospital, 525 E. 68th Street, Starr 900, New York, New York 10065 (email: jak9111@med.cornell.edu).

Purpose: Because the association between erectile dysfunction and prostate biopsy is variable in the available literature, we sought to perform a systematic review and meta-analysis of sexual dysfunction in males within 6 months of prostate biopsy.

Materials and Methods: We conducted a systematic literature search in 4 databases: MEDLINE® (via PubMed®), Embase® (via Ovid®), Web of Science™ and the Cochrane Library. We included studies focused on sexual dysfunction in men of all age groups undergoing transrectal or transperineal prostate biopsy for suspicion of prostate cancer. We included studies with International Index of Erectile Function 5 scores pre-biopsy and post-biopsy at 1, 3 or 6 months. We performed an effect size meta-analysis comparing patient baseline International Index of Erectile Function 5 (IIEF-5) scores with post-biopsy IIEF-5 scores.

Results: We identified 9 studies that met our inclusion criteria, of which 6 examined transrectal prostate biopsy, 2 examined transperineal prostate biopsy and 1 examined both. At 1 month after biopsy, the mean IIEF-5 score decreased by approximately 2.2 points as determined by the effect size (−0.43, p=0.002). However, at 3 and 6 months after biopsy, there was no difference compared to baseline (effect size=−0.08, p=0.52 and effect size=−0.11, p=0.18, respectively). An exploratory subgroup analysis examining transrectal prostate biopsy at 3 months showed a statistically significantly lower mean IIEF-5 score compared to baseline (p=0.047), corresponding to an approximately 1.25-point decrease in IIEF-5.

Conclusions: Prostate biopsy does cause a mild, transient decrease in average IIEF-5 scores at 1-month post-biopsy. However, this resolves at 3 months on average, and average IIEF-5 remains at baseline at 6 months post-biopsy.

Key Words: prostate, biopsy, erectile dysfunction, ultrasonography, systematic review

Prostate biopsy is the gold standard procedure used to diagnose prostate cancer, the most common non-dermatological malignancy in men. Frequent adverse events following this procedure are well known and include hematospermia, hematuria, urinary tract infection, rectal bleeding and rectal discomfort. More severe complications such as serious infection and sepsis are less common.[1]

Penile erection is a complex process that occurs through a cascade of vascular, neurological, and psychological events. Therefore, any damage or disruption of normal physiological sequences in those processes, such as aging, drug side effects, comorbid

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disease or psychological stress, may affect the quality of a patient's erections.[2]

Erectile dysfunction has been reported following prostate biopsy. However, there has been significant controversy as to whether prostate biopsies predispose patients to erectile dysfunction. Some well studied factors that may influence erectile dysfunction after prostate biopsy include patient age,[3] neurovascular bundle damage during injection of local anesthesia,[4] compression of the neurovascular bundle from hematoma formation or edema,[5] the number of biopsies taken,[6] anxiety related to the biopsy,[5] the type of biopsy (either transperineal or transrectal) and time interval after the procedure.[7]

The diagnosis of prostate cancer itself is associated with psychological stress, anxiety and depression, which in turn may cause ED. International Index of Erectile Function 5 scores post-prostate biopsy may take longer to return to baseline in men diagnosed with cancer than those with benign pathology.[8]

The literature on erectile dysfunction after prostate biopsy is heterogeneous and rife with conflicting results. Therefore, for counseling and patient management, there is a need to better understand the association between PB and ED. We hypothesized that prostate biopsy is associated with ED, but that this effect is likely transient. To provide clear evidence concerning the duration and degree of ED following biopsy, we performed a systematic review and meta-analysis of validated measures of sexual function at 1, 3 and 6 months after prostate biopsy.

METHODS

Objective

Our primary aim was to systematically evaluate rates of ED at 1 month following PB as defined by the change in IIEF-5 score. Additionally, we assessed rates of ED at 3 months and 6 months as secondary endpoints.

Search Methods

Systematic literature searches were conducted (October 29, 2018) in 4 databases for human-only research studies with no specified date, age, or language filters. The databases searched were MEDLINE (via PubMed), Embase (via Ovid), WOS and the Cochrane Library. Controlled vocabularies and text words were used in the development of the search strategies in all databases except for WOS, as this resource does not employ controlled terminology. We combined search results in a bibliographic management tool (EndNote). Duplicates were eliminated both electronically and through manual review. Search results were then imported into the systematic review support tool, Covidence (Veritas Health Innovation, Melbourne, Australia, www.covidence.org), for further reference management and screening.

The search terminology included 2 major components. Both concepts were linked together with the AND operator: prostate biopsy, including transrectal ultrasound-guided biopsy, fusion biopsy, and MRI guided biopsy; erectile dysfunction, including ED and impotence. We investigated the grey literature perspective of this review topic by conducting comprehensive searches in Embase and WOS that included all publication types such as conference proceedings, research and other reports, and theses/dissertations. Search terms are detailed in the supplementary Appendix (https://www.jurology.com). For a complete list of MeSH and keyword terms used, please refer to the MEDLINE search strategy accompanying this paper (supplementary Appendix, https://www.jurology.com). The search was extended through May 2020 in order to ensure that current data were included at the time of publication and no suitable papers for inclusion were identified.

Inclusion and Exclusion Criteria

Included studies focus on sexual dysfunction in men of all age groups undergoing PB for suspicion of prostate cancer. We included studies in English with both pre-biopsy and post-biopsy IIEF-5 scores. Regarding followup, we only included studies that reported 1, 3 or 6-month IIEF-5 scores post-biopsy. Studies examining erectile function following TRUS-Bx, TPBx and MRI targeted biopsy were all included. We excluded abstracts, case reports, and editorials. We excluded studies that did not report quantitative IIEF-5 scores and studies that lacked a transparent methodology.

Data Extraction

Two independent reviewers (HP and AA) scanned abstract content of retrieved records to determine which studies to assess in further detail. We extracted data using predefined data fields, including information on study characteristics, study population, and sexual function outcomes. We recorded followup time, biopsy type, and the number of cores taken from each study. Outcomes reviewed in this meta-analysis were as compared to pre-biopsy IIEF-5 scores, 1-month post-biopsy scores, 3-month post-biopsy scores and/or 6-month post-biopsy scores as available within each study.

Assessment of Risk of Bias and Study Quality

Two reviewers (HP and AA) assessed included study quality independently using the Newcastle-Ottawa Scale (NOS) tool (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The NOS tool assesses quality of cohort studies via 3 main criteria: selection, comparability and outcome. The scale consists of 8 items summing to a total score of 9, with a maximum of 4 points for selection, 2 points for comparability, and 3 points for outcome. Scores of 0–3 were considered poor quality, 4–6 fair quality, and 7–9 high quality. If scores were not concordant between the 2 independent reviewers, a joint reevaluation of the study was conducted.

Statistical Analysis

Studies that quantitatively reported the erectile dysfunction score pre-biopsy and 1-month post-biopsy

were used for the meta-analysis. Reported means and standard deviations for the pre-biopsy and 1-month post-biopsy assessments in each study were used to calculate Cohen's effect size (d), which is the standardized mean difference (ie mean difference between 1-month post-biopsy erectile dysfunction score and pre-biopsy erectile dysfunction score, divided by the pooled standard deviation). Cohen's effect size is the preferred measure when combining mean differences across studies in meta-analysis. It should be noted, however, that a side-by-side "paired" comparison of the IIEF-5 between the pre-biopsy and 1-month post-biopsy assessments within the same patient was not possible because the individual studies did not provide the standard deviation of the differences (in erectile dysfunction score) between the pre-biopsy and 1-month post-biopsy assessments (required to compute Cohen's effect size for paired data). As a result, we assumed independence of the pre-biopsy and 1-month post-biopsy assessments within a patient (ie to be conservative) and calculated the effect size as the mean difference between the 1-month post-biopsy assessment and pre-biopsy assessment divided by the pooled standard deviation. We then combined the individual study effect sizes into a pooled effect size. We used the median instead of the mean and estimated the standard deviation from the range in studies where the median and range were reported rather than the mean and standard deviation. Due to the significant heterogeneity in the effect sizes across the studies, a random-effects (DerSimonian-Laird) model was used to pool the effect sizes. Statistical heterogeneity was measured using Cochran's Q. p Value ≤ 0.20 was used to indicate the presence of heterogeneity. We tested statistical heterogeneity using an inconsistency measure (the I^2 statistic). An I^2 percentage $\geq 50\%$ was used to indicate the presence of heterogeneity. Publication bias was statistically tested with the Begg-Mazumdar rank-correlation test and Egger's test. We then repeated the meta-analysis using the 3-month and 6-month post-biopsy IIEF-5 compared to pre-biopsy (for the subset of studies that had available 3-month data and 6-month data). Meta-analysis was conducted with the use of StatsDirect statistical software (version 3.2.9).

RESULTS

We identified 1,892 records using our search criteria. Figure 1 details the application of the inclusion and exclusion criteria. Nine studies were eligible for inclusion after applying exclusion criteria. All studies received a score of 6 after quality assessment using the NOS tool, indicating acceptable quality. The main weaknesses for each study on assessment were lack of control groups and poor comparability on the basis of study design, in particular controlling for confounders. All studies were of good quality regarding representativeness, intervention ascertainment, outcome assessment, followup time and adequacy of followup.

From these 9 included studies published from 2006 to 2019, we identified a total of 525 men for analysis. Six studies examined erectile function after TRUS-Bx, 2 following TPBx and 1 examined both. The TPBx and TRUS saturation biopsies took more cores than standard TRUS biopsies. No papers on MRI targeted biopsies met the inclusion criteria. The table details individual data regarding methodology, biopsy type, study population, and sexual function outcomes.

The individual effect size estimates for each study at 1, 3, and 6 months, as well as the pooled effect sizes at those time points, are detailed in figure 2. At 1 month post-biopsy, 9 studies reported IIEF-5 scores compared to baseline: 2 TPBx, 6 TRUS-Bx, and 1 both. These men had a statistically significant decline in mean IIEF-5 score with an overall effect size of -0.43 (95% CI -0.70, -0.16, $p=0.0021$), which corresponds to a mean decrease in IIEF-5 of approximately 2.2 points (95% CI 3.5 points, -0.8 points). This effect was not seen at 3 or 6 months post-prostate biopsy at which point the overall effect sizes were -0.08 (95% CI -0.34, 0.17, $p=0.52$) and -0.11 (95% CI -0.27, 0.05, $p=0.18$), respectively. The Begg-Mazumdar test for publication bias at the 1, 3 and 6-month meta-analyses were $p=0.08$, 0.56, and 0.75, respectively, indicating low evidence of publication bias; however, these analyses were likely underpowered to detect publication bias given the small number of component studies in each analysis.

When we excluded the 3 studies that included transperineal biopsy studies, we found, in an exploratory analysis of TRUS-Bx at 1 and 3 months, that the remaining 4 studies showed a statistically significantly lower mean IIEF-5 compared to their pre-biopsy mean IIEF-5 score (effect size -0.27, 95% CI -0.53, -0.003, $p=0.047$) at 3 months (fig. 3. This effect size translates to an approximate 1.25-point decrease in IIEF-5 score from baseline at 3 months post-biopsy (95% CI $=-2.7$ points, -0.02 points). We could not perform this analysis at 6 months because there are too few studies available.

DISCUSSION

We conducted a systematic review and meta-analysis examining erectile dysfunction post-prostate biopsy. Our results suggest that prostate biopsy is associated with a mild decrease in IIEF-5 scores, but that the effect is time-dependent. We found that at 1 month post-biopsy there was a statistically significant decrease in the mean IIEF-5 score, which appeared to resolve at 3 months. The net decrease in IIEF-5 score at 1 month from the combined analysis of TRUS-Bx and TPBx studies was 2.2 points (95% CI $=-3.5$ points, -0.8 points). Notably, the minimally clinically important difference for the IIEF is 4 points

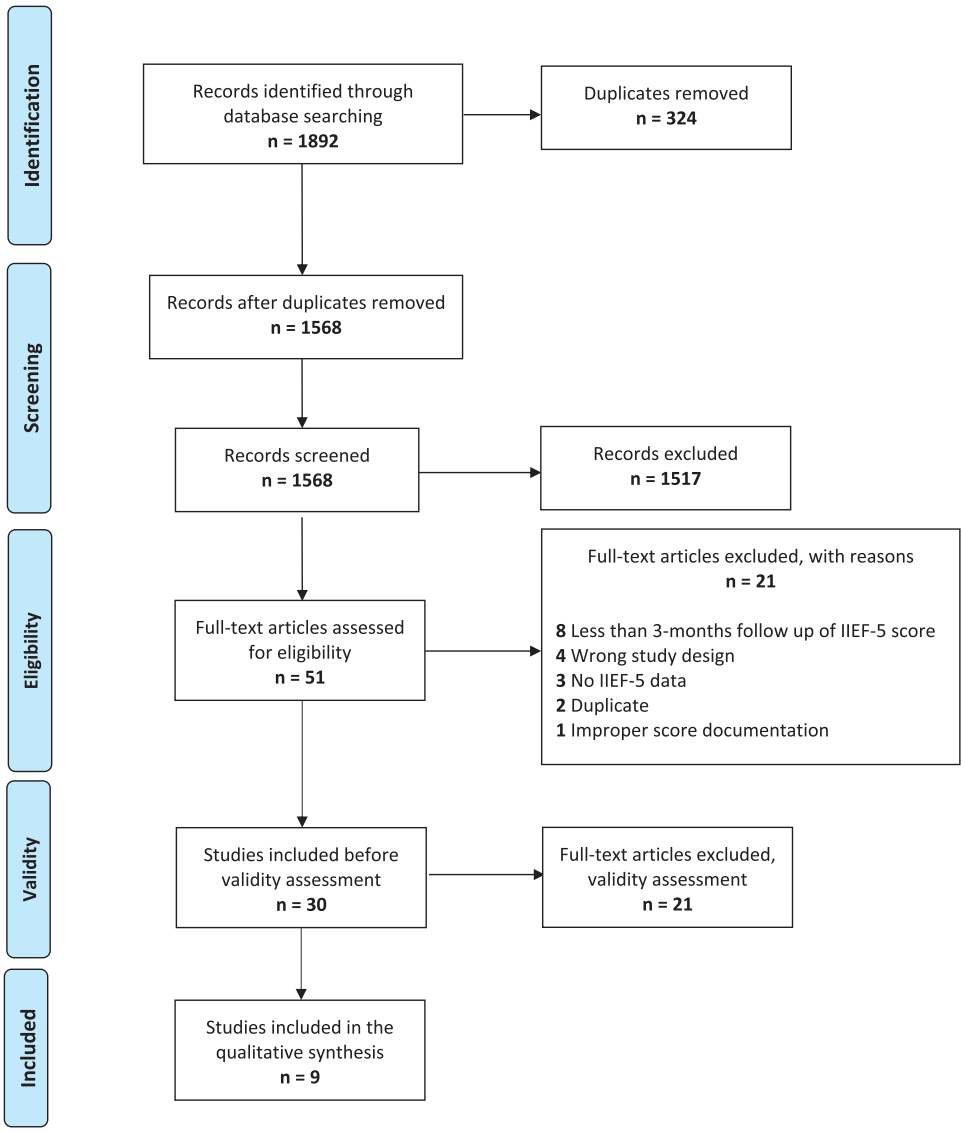

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram of literature search and study selection.

overall, but ranges from 2 to 7 points depending on the severity of a patient's existing ED.[9] This suggests that a 2-point change on average could result in significant clinical bother for patients, especially those with mild symptoms to begin with. At 3 months, the mean change in the IIEF-5 score was no longer statistically significant. This effect persisted at 6 months after biopsy. For men who had TRUS-Bx, IIEF-5 scores remained mildly decreased at 3 months, suggesting that some men continue to have decreased IIEF-5 scores at 3 months, which they did not have before biopsy.

The etiology of ED after prostate biopsy is likely multifactorial. Klein et al investigated whether periprostatic nerve block could result in ED post-biopsy by randomizing patients to receive traditional periprostatic nerve block vs lidocaine gel as the primary analgesic for prostate biopsy.[4] Mechanistically, they were concerned that the process of injection could potentially damage the nerves responsible for erection. They found that IIEF-5 scores decreased at 1 month in patients undergoing 10-core biopsy with and without periprostatic nerve block. Both groups saw a resolution of ED at 3 months. They found no correlation between the number of cores and post-biopsy ED. The authors concluded that ED might be associated with prostate biopsy regardless of periprostatic nerve block or number of cores, but that impairment is reversible within 3 months.[4]

Aktoz et al examined a cohort of 136 men undergoing prostate biopsy and reported transient ED in 3 patients.[10] They postulated that lateral sampling in a large prostate could result in accidental

damage to the neurovascular bundles. Zisman et al evaluated 211 consecutive men and found that 15% of men had new ED at 30 days.[5] This study suggested secondary trauma involving nerve compression from hematoma or edema could lead to transient ED and that anxiety related to the diagnosis of prostate cancer or related to the procedure led to ED in 7% of the overall sample. Data from Tuncel et al 2014 provided data that support nerve injury as a mechanism of post-biopsy ED.[11] They used power Doppler ultrasonography to evaluate the impact of TRUS-Bx on the prostate and neurovascular bundles. They showed inflammation of prostate parenchyma and bilateral neurovascular bundles in the 4/10 men in their sample with ED after prostate biopsy.

The data have been more consistent in TPBx. Chong et al analyzed 64 men undergoing TPBx and found that IIEF-5 decreased by 10 points at 1nmonth post-biopsy, 0.8 points at 3 months post-biopsy and normalized at 6 months post-biopsy.[12] Akbal et al also examined TPBx and found that 11.6% of patients had ED at 1 month post-biopsy, but that this resolved by 6 months.[6] The largest study which explored ED after prostate biopsy looked at 1,050 men who had extended, saturation, or saturation plus MRI targeted TPBx at baseline, 1 month, 3 months, and 6 months.[13] This single center series found no change in erectile function after TPBx overall. For men reporting mild ED at 1 month, symptoms resolved by 3 months. While these results were encouraging, they are less applicable to the majority of patients who get TRUS-Bx.

While ED after prostate biopsy may be caused by nerve injury from mechanical or chemical causes directly related to the biopsy itself, there is evidence that the diagnosis of prostate cancer, anxiety related to the diagnosis of prostate cancer and eventual choice of treatment for prostate cancer can affect erectile function. Helfand et al 2013 found, in 134 men evaluated with TRUS-Bx, that men with a diagnosis of had an increased odds ratio of 7.2 for developing ED as compared to men without a diagnosis of prostate cancer.[8] Importantly, the men who were not diagnosed with prostate cancer had no change in IIEF-5 at followup.[8] Therefore, as one would expect mechanical causes of post-biopsy ED to resolve with time, one might expect psychogenic ED related to a diagnosis of prostate cancer to improve with time as well.

To our knowledge, this is the first systematic review and meta-analysis that evaluates the impact of prostate biopsies on erectile function as a comprehensive analysis and as a single adverse effect of this procedure. ED is a significant quality of life concern for men. It is essential to understand the effect and the outcome of prostate biopsy in this

Included studies on prostate biopsy and erectile function at 1, 3 and 6 months

		Before Biopsy				1 Mo after Biopsy				3 Mos after Biopsy				6 Mos after Biopsy			
PubMed ID	No.	Biopsy Type	No. Cores	IIEF-5	SD or Range	IIEF-5	SD or Range	No.	p Value	IIEF	SD or Range	No.	p Value	IIEF-5	SD or Range	No.	p Value
24656160[10]	42	TRUS	10	20.8	3.7					17.4	5.5	42	**< 0.001**				
18372025[3]	97	TRUS	10	19.1	5.8	17.1	5.9	97	**< 0.001**					16.8	7.5	97	**< 0.001**
16669915[7]	46	TRUS	9*	15.91*	5–25	14.33*	6–25	46	Not significant	14.81*	6–25	46	Not significant				
27350788[11]	64	TPBx	24–38†	19.5	6.11	10.5	5.4	64	**< 0.001**	18.7	5.6	64	**0.001**	19.6	5.4	64	0.7
20078514[9]	62	TRUS	10	13.58	5.48	12.9	5.58	62	**< 0.001**	13.43	5.25	62	0.16				
17619078[6]	88	TRUS	22.9	23*	9–25	22*	8–25	88	**0.01**					22.5*	5–25	88	Not significant
22639942[8]	85	TRUS	12	19.7	5.4					18.5	6.8	85	0.07				
26780550[13]	53	TPBx	24–32†	23*	18–25	22*	15.5–25	41	0.09	24*	24–25	36	0.86				
31475394[14]	90	TRUS	12.2	17.7	4.6	17.3	3.5	131‡	0.3	17.6	1.9		0.9	17.4	3.1	131‡	0.7
31475394[14]	45	TPBx	19.4	17.7	4.6	17.7	3.3		0.9	17.8	1.2		0.8	17.9	3.7		0.8

Pre-biopsy IIEF means are default. Number of cores is the number of cores taken at biopsy, with mean being the default value. Bold entries indicate signficant values.
* Median.
† Range.
‡ Total number for both TRUS and TPBx as individual values are not reported in the manuscript.

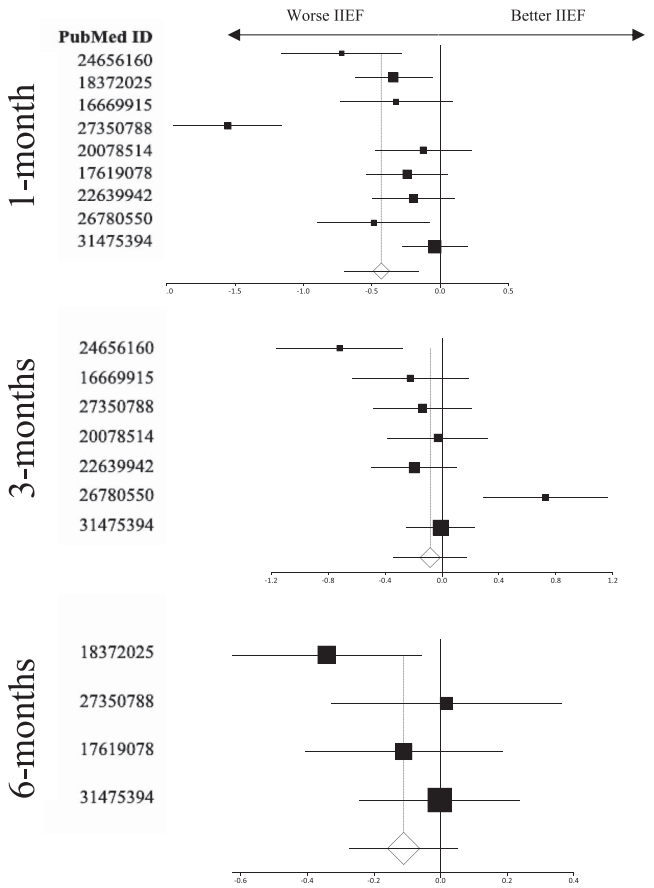

Figure 2. Effect size at 1, 3 and 6 months after prostate biopsy. Effect sizes less than 0.0 imply that relevant post-biopsy assessment had lower mean erectile dysfunction score compared to pre-biopsy assessment. Effect sizes at 1, 3 and 6 months after prostate biopsy were −0.43 (95% CI −0.70, −0.16, p=0.0021), −0.08 (95% CI −0.34, 0.17, p=0.52) and −0.11 (95% CI −0.27, 0.05, p=0.18), respectively.

population to be transparent in terms of counseling, consent and followup plan. As urologists manage more men with active surveillance, we may begin to see more patients who have multiple biopsies over many years. The effects of repeated biopsy on erectile function remain unclear.

This study is not without its limitations. We used IIEF-5, which does not include questions about sexual desire or libido. However, it is a validated questionnaire for patient-reported erection quality. Means and standard deviations on the IIEF-5 were not consistently reported and occasionally medians and ranges were reported (presumably due to lack of normality in the individual component study). In these situations, we had to use the median in place of the mean and estimated the standard deviation from the range to facilitate pooled SMD calculations in the meta-analyses. In addition, Cohen's effect size for paired data could not be calculated because the individual component studies did not report the standard deviation of the paired differences, and, as a result, we had to assume independence of the pre and post measurements to facilitate computation of the pooled effect size (note, however, that this is more conservative when assessing statistical significance). We were not able to control for men who had a new diagnosis of prostate cancer, which is known to be associated with anxiety-related ED. As this analysis is limited to Cohen's effect size (an aggregate measure, by definition), we cannot conclude whether changes in IIEF-5 post-PB are global or driven by more dramatic change in specific individuals. Furthermore, we were not able to control for medical comorbidities that might put patients at higher risk of prostate biopsy associated ED or treatment of patients who developed ED with medications or injections. This study is bolstered by its relative sample size as compared to included cohort studies, strict inclusion and exclusion criteria, and direct applicability to patient care and counseling.

CONCLUSIONS

Prostate biopsy is associated with a decrease in IIEF-5, a measurement of erectile function, although this appears to improve with time. We found that overall IIEF-5 scores were lower at 1 month post-prostate biopsy as compared to baseline, but that the difference resolved at 3 months and remained stable at 6 months. Men who undergo transrectal prostate biopsy may still have a decline in erectile function at 3 months. However, given that this slight decrease does not translate into a meaningful minimally clinically important difference, symptomatic erectile function change at 3 months after TRUS-Bx is likely negligible. Providers should inform men that transient ED is an expected complication of prostate biopsy, but that symptoms tend to resolve by 3–6 months.

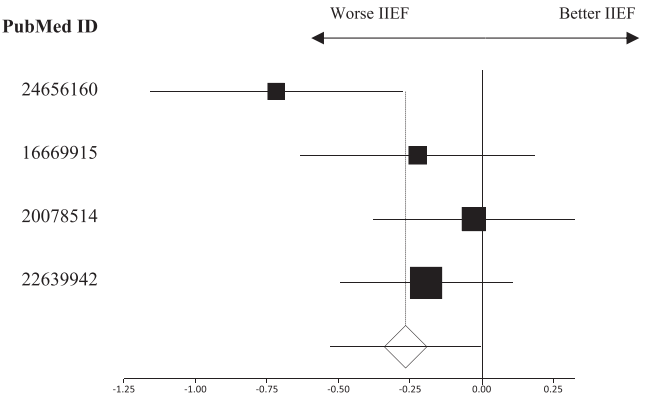

Figure 3 Effect size at 3 months after TRUS-Bx. Effect sizes less than 0.0 imply that 3-month post-biopsy assessment had lower mean erectile dysfunction score compared to pre-biopsy assessment. Effect size here was −0.27 (95% CI −0.53, −0.003, p=0.047).

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