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MRI-targeted biopsy versus systematic biopsy in the detection of prostate cancer: a systematic review and meta-analysis

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Competing Interests
Authors report no relevant conflicts of interest

Keywords
MRI-targeted biopsy; systematic biopsy; prostate cancer; diagnosis; clinically significant; clinically insignificant; meta-analysis; systematic review.

Abstract

Context: MRI-targeted prostate biopsy (MRI-TB) may be an alternative to systematic biopsy for diagnosing prostate cancer.

Objective: The primary aims of this systematic review and meta-analysis were to compare the detection rates of clinically significant and clinically insignificant cancer by MRI-TB to systematic biopsy in men undergoing prostate biopsy to identify prostate cancer.

Evidence acquisition: A literature search was conducted using the PubMed, Embase, Web of Science, Cochrane library and Clinicaltrials.gov databases. We included prospective and retrospective paired studies where the index test was MRI-TB and the comparator test was systematic biopsy. We also included randomized controlled trials (RCTs) if one arm included MRI-TB and another arm included systematic biopsy. The risk of bias was assessed using a modified Quality Assessment of Diagnostic Accuracy Studies-2 checklist. In addition, the Cochrane risk of bias 2.0 tool was used for RCTs.

Evidence Synthesis: We included 68 studies with a paired design and 8 RCTs, comprising a total of 14709 men who received either both MRI-TB and systematic biopsy or were randomized to receive one of the tests.

MRI-TB detected more men with clinically significant cancer than systematic biopsy (Detection ratio (DR) 1.16 [95% CI 1.09-1.24], $p < 0.0001$) and fewer men with clinically insignificant cancer than systematic biopsy (DR 0.66 [95% CI 0.57-0.76], $p < 0.0001$). The proportion of cores positive for cancer was greater for MRI-TB than systematic biopsy, relative risk 3.17 [95% CI 2.82-3.56], $p<0.0001$.

Conclusions: MRI-TB is an attractive alternative diagnostic strategy to systematic biopsy.

Patient summary:
We evaluated the published literature, comparing two methods of diagnosing prostate cancer. We found that biopsies targeted to suspicious areas on an MRI (MRI-Targeted biopsy) were better at detecting prostate cancer that needs to be treated and at avoiding the diagnosis of disease that doesn't need treatment than the traditional systematic biopsy.

1. Introduction

Multiparametric magnetic resonance imaging (mpMRI) has an increasingly important role in the diagnosis of prostate cancer [1-3]. The MRI information can be used to guide prostate biopsy cores to suspicious areas in the prostate [4]. The traditional diagnostic pathway of systematic biopsy with 10-12 core transrectal ultrasound-guided prostate (TRUS) biopsy, in men with raised prostate specific antigen (PSA), has been challenged by evidence from systematic reviews and randomized controlled trials (RCTs). There is support for an alternative pathway where men with suspicious MRIs only undergo biopsy of MRI-suspicious areas, MRI-targeted biopsy (MRI-TB) [1, 5-8]. Potential advantages are maintaining or improving the rates of detection of clinically significant disease, using fewer biopsies in fewer men. In addition, detection of clinically insignificant disease, and associated overtreatment, are reduced [9-12]. This pathway has the potential to be cost-effective in a number of different healthcare settings [13-15].

The primary aim of this systematic review and meta-analysis was to compare the detection rates of clinically significant and clinically insignificant cancer by MRI-targeted biopsy versus systematic biopsy in men with a suspicion of clinically significant prostate cancer with raised PSA or abnormal digital rectal examination. The main focus of the review was to assess whether MRI-TB (with biopsies only to suspicious areas on MRI) could replace systematic biopsy as a diagnostic test for prostate cancer. Previous systematic reviews in this field highlighted limitations in the quality of reporting in the included studies [7]. The Standards of Reporting for MRI-targeted Biopsy Studies (START) of the Prostate Consortium aimed to address this and here, we review the published literature since these standards were released [4]. “Systematic biopsy” is a term that encompasses several different types of biopsy approaches. Though the most commonly used type of systematic biopsy is TRUS biopsy, transperineal template biopsy (TPM) is becoming an increasingly used systematic biopsy technique. A comparison of MRI-TB to transperineal template biopsy (TPM) has not been addressed in previous reviews and thus was also included in this review.

2. Evidence Acquisition

This systematic review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, and relevant aspects of the diagnostic test accuracy extension (PRISMA-DTA) [16]. The review was registered in the International prospective register of systematic reviews (PROSPERO), ID CRD42015017543.

2.1 Search strategy

A literature search was conducted with the assistance of an information specialist using the PubMed, Embase, Web of Science, Cochrane library and Clinicaltrials.gov databases (see Supplementary Appendix 1). We searched from inception of the databases up to the 28th July 2017. To capture the latest evidence, authors of studies identified in the Clinicaltrials.gov database search as ongoing were contacted, and if the full paper was available prior to completing data extraction on 8th July 2018, they were eligible for inclusion.

2.2 Inclusion and exclusion criteria

We included prospective and retrospective paired studies, where the index test was MRI-TB and the comparator test was systematic biopsy. We also included RCTs if one arm included MRI-TB and another arm included systematic biopsy. Studies needed to report the number of men with at least one of the target conditions (significant prostate cancer, insignificant prostate cancer or any prostate cancer based on histological definitions) in those with raised PSA or abnormal digital rectal examination. MRI-TB was defined as a biopsy in which mpMRI information was used to influence the conduct of the prostate biopsy. For a study to be eligible, it was necessary to be able to derive the cancer detection specifically from the biopsies taken from MRI suspicious areas. Systematic biopsy was defined as TRUS or TPM biopsy. Since there is no accepted definition of clinically significant or clinically insignificant cancer, definitions used in individual studies were permitted. If the definition was not specified but cancer detection was presented by Gleason grade, then cancer with Gleason grade 3+4 or greater was considered clinically significant and cancer with Gleason grade 3+3

was considered clinically insignificant [1]. Studies were not excluded on basis of language. When multiple publications including overlapping cohorts were reported, only the most recent or relevant cohort to the review objectives was included.

2.3 Study selection and data collection

Screening of studies was carried out using Covidence© software. Prior to screening, all reviewers underwent a pilot screening process to ensure consistency in reviewing. Each title and abstract was screened independently by two reviewers from a team of 10 (VK, AS, JN, FG, MV, YS, KC, DS, YP, DT). Reviewers were selected from the BURST Research collaborative [17] on the basis of expertise in MRI-targeted prostate biopsy and/or in the conduct of systematic reviews. Full text articles were reviewed for inclusion independently by two of the reviewers. Data from each study were extracted independently by two of the reviewers. Data were collected in line with the START criteria [4] and a list of items collected is given in Supplementary appendix 2. Where appropriate, authors were contacted to provide missing data and blank tables were sent to them for completion. After each stage of the screening, inclusion and extraction process, discrepancies between reviewers were resolved via consensus, adjudicated by a third reviewer (one of VK, JN).

2.4 Quality assessment of included studies

The risk of bias and applicability concern in individual studies was assessed independently, by two reviewers using a modified Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) checklist (Supplementary Appendix 3). RCTs were also assessed using the Cochrane risk of bias 2.0 tool for RCTs. Discrepancies between reviewers were resolved via consensus, adjudicated by a third reviewer (one of VK, JN).

2.5 Data synthesis

Since there is no ideal reference standard in prostate cancer diagnosis, we compared the detection rates of MRI-TB and systematic biopsy for each target condition. Our primary

analysis was the comparison of clinically significant cancer detection rates. Detection rates were calculated as the number of men with the target condition divided by the number of men who had the test. A detection ratio (DR) was calculated as the MRI-TB detection rate divided by the systematic biopsy detection rate. Thus, a DR > 1 indicates that MRI-TB detected more of the target condition than systematic biopsy. Studies with a paired design and RCTs were analysed separately. For meta-analyses of the DRs from paired studies, if both MRI-TB and systematic biopsy were performed on men in one arm of an RCT and paired data were available, we included the data as a paired study. The within-study variance was calculated for each paired study, taking into account the correlation between the detection rates of MRI-TB and systematic biopsy since both tests were performed on each patient. We synthesised detection ratios using the DerSimonian and Laird random effects approach [18]. Further details on data synthesis techniques are given in Supplementary Appendix 4.

Heterogeneity between studies was measured using the I^2 statistic and the between study variance (τ^2) from the random effects analyses. We performed the following planned sensitivity analyses:

i. Significant cancer detection rates defined as any Gleason 3+4 prostate cancer or greater.
ii. Significant cancer detection rates defined as any Gleason 4+3 prostate cancer or greater.
iii. Insignificant cancer detection defined as Gleason 3+3 prostate cancer.

In addition, we performed a post hoc sensitivity analysis, which limited analysis to studies with at least 100 men and 50 cancer cases diagnosed. For assessment of publication bias and small study effects, log-transformed values of the detection ratios were plotted against their standard error in a contour enhanced funnel plot.

To assess differences between subgroups, the following covariates were specified a priori:

i. Systematic biopsy type (TRUS-biopsy or TPM)
ii. Prior biopsy status (biopsy naïve, prior prostate biopsy negative for cancer and prior biopsy positive for cancer)

iii. Type of MRI-TB (cognitive registration/visual registration, software-assisted registration/fusion software, in-bore biopsy)

We performed univariable meta-regression analyses using random-effects models to statistically assess differences in detection ratios between subgroups.

We assessed three additional outcomes:

i. Proportion of cores positive for prostate cancer by MRI-TB compared to systematic biopsy
ii. Proportion of men having MRI-TB and systematic biopsy, who had cancer upgraded or downgraded on subsequent radical prostatectomy
iii. Proportion of clinically significant cancer missed by MRI-TB but detected by the addition of systematic biopsy

All statistical analyses were performed in Stata version 15.

3. Evidence Synthesis

3.1 Summary of studies

Figure 1 shows the flow of studies through the screening process. Of 7398 studies included in the screening phase, 76 studies were considered eligible for inclusion, of which 68 were studies with a paired design and 8 were RCTs, including a total of 14709 men who received either both MRI-TB and systematic biopsy or were randomized to receive only one of the tests. Study characteristics for paired studies are given in Table 1a [5, 19-89] and for the RCTs in Table 1b [1, 5, 6, 20, 21, 79, 90, 91].

3.2 Risk of bias within studies

The risk of bias and applicability concern is given in supplementary appendix 5a and 6. The overall methodological quality of the studies was moderate, with 14 having low risk of bias and applicability concern across all domains assessed. Supplementary appendix 5b summarises the additional items assessed for each RCT using the Cochrane risk of bias 2.0 tool. Overall methodological quality of the RCTs was good with 5 of the 8 studies rated as having low risk of bias across all domains and none of the studies having a domain at high risk of bias.

3.3 Studies with paired data

3.3.1 Clinically significant cancer detection

56 study cohorts including 4652 patients were included in the analysis. This includes data from the MRI arm of four RCTs where both MRI-TB and systematic biopsy were carried out in the same patient [5, 20, 21, 79]. The definition of clinically significant cancer in each study is given in Table 1a. MRI-TB detected more men with clinically significant cancer than systematic biopsy (DR 1.16 [95% CI 1.09-1.24], $p < 0.0001$) (Figure 2). This effect was also evident in sensitivity analyses where the definition of clinically significant cancer was

Gleason 3+4 or greater (DR 1.09 (95% CI 1.02-1.18), p = 0.018) (Supplementary Appendix 7) or where the stricter definition of Gleason grade 4+3 or greater was used (DR 1.38 (95% CI 1.14-1.68), p = 0.001) (Supplementary Appendix 8). Publication bias was assessed by visual inspection of a contour enhanced funnel plot (supplementary appendix 9). There was indication of funnel plot asymmetry though many studies differing in precision were in the regions of statistical non-significance (5% < p <10% and p > 10%). Therefore, publication bias or small study effects may be absent. A subsequent sensitivity analysis that included only studies with greater than 100 patients and 50 cancer cases showed results consistent with the primary analysis (DR 1.19 (95% CI 1.09-1.30), p < 0.0001) (Supplementary appendix 10).

There was some evidence in the meta-regression analysis to suggest that the superiority of MRI-TB relative to systematic biopsy may depend on the type of comparator, with MRI-TB performing better when the comparator was TRUS biopsy (DR 1.22 [95% CI 1.13-1.32]) than when the comparator was TPM biopsy (DR 0.99 [95% CI 0.91-1.07], difference between subgroups, p = 0.083). There was no evidence of differences by prior biopsy status (biopsy naïve DR 1.18 [95% CI 1.06-1.31]), prior biopsy negative DR 1.22 [95% CI 1.05-1.42], prior biopsy positive DR 1.09 [95% CI 0.92-1.30], difference between subgroups, p = 0.71) or by type of MRI-TB registration method (fusion biopsy DR 1.22 [95% CI 1.12-1.33], cognitive registration DR 1.11 [95% CI 0.94-1.31], difference between subgroups, p = 0.36). A summary of these results is given in Table 2.

3.3.2 Clinically insignificant cancer detection

46 study cohorts including 2124 patients were included in the analysis. MRI-TB detected fewer men with clinically insignificant cancer than systematic biopsy (DR 0.66 [95% CI 0.57-0.76], p < 0.0001) (Figure 3). This effect was also evident in the sensitivity analysis that defined clinically insignificant cancer as Gleason grade 3+3 (DR 0.74 (95% CI 0.65-0.84), p < 0.0001) (Supplementary Appendix 11).

There was no evidence from meta-regression analysis that this effect differed by systematic biopsy type (MRI-TB vs TRUS biopsy, DR 0.64 [95% CI 0.54-0.76], MRI-TB vs TPM biopsy, DR 0.74 [95% CI 0.60-91]), difference between subgroups, p = 0.61), by prior biopsy status

(biopsy naïve DR 0.71 [95% CI 0.51-0.96]), prior biopsy negative DR 0.48 [95% CI 035-0.66], prior biopsy positive DR 0.51 [95% CI 0.40-0.66], difference between subgroups, p=0.12) or by registration choice (cognitive registration (DR 0.81 [95% CI 0.56-1.17]) or fusion biopsy (DR 0.64 [95% CI 0.56-0.73]), difference between subgroups, p = 0.14). A summary of these results is given in Table 3.

3.3.3 Any cancer detection

61 study cohorts including 6742 patients were included in the analysis. There was no difference in any cancer detection by MRI-TB compared to systematic biopsy (DR 1.02 [95% CI 0.96-1.08], p = 0.49), Supplementary appendix 12.

3.4 Randomized controlled trials

Eight RCTs of 2635 patients (Table 1b) presented results for clinically significant cancer and insignificant cancer detection. The two RCTs which most directly addressed the review objectives used MRI-TB alone as the index test when the MRI was suspicious and compared this to a comparator arm of TRUS biopsy alone, showing a clear benefit for the MRI arm over the TRUS-biopsy arm (DR 1.46 [95% CI 1.12-1.90] and DR 2.43 [95% CI 1.53-3.84], Figure 4a) [[1, 6]. However, due to heterogeneity amongst the RCTs in how MRI information was used to influence a decision for biopsy, how that biopsy was conducted and in the choice of index and comparator tests, we did not conduct meta-analysis of all RCTs. We meta-analysed a subset of 5 RCTs which compared MRI-TB plus TRUS biopsy to TRUS biopsy alone. MRI-TB plus TRUS biopsy detected more men with clinically significant cancer than TRUS biopsy alone (DR 1.21 [95% CI 0.94-1.57], though this difference was not statistically significant (p = 0.14).

For clinically insignificant cancer detection (Figure 4b), the two RCTs of MRI-TB alone in MRI-suspicious men versus TRUS biopsy, showed lower detection rates for MRI-TB compared to TRUS biopsy [1, 6]. However, after meta-analysis of the 4 RCTs of MRI-TB plus TRUS biopsy versus TRUS biopsy alone, this benefit was no longer seen (DR 1.11 [95% CI 0.49-2.51], p = 0.80).

In 4 of the 8 RCTs, men with a negative MRI were biopsied and the proportion of clinically significant cancer were 0/23 (0%) [21], 0/130 (0%) [5], 1/26 (4%) [6] and 3/13 (23%) [79].

3.6 Proportion of cores positive for cancer

The proportion of cores positive for prostate cancer was reported in 18 studies comprising 2045 men. The proportion of cores positive for cancer was 2464 out of 7866 (31%) for MRI-TB and 3943 out of 35873 (11%) for systematic biopsy. The proportion of cores positive for cancer was greater for MRI-TB than systematic biopsy, RR 3.17 [95% CI 2.82-3.56], p <0.0001 (Supplementary Appendix 13).

3.7 Proportion of men with cancer upgraded or downgraded on radical prostatectomy

There was one study which reported both the proportion of men with cancer upgraded or downgraded by radical prostatectomy for MRI-TB and systematic biopsy [1]. In this study 4/27 (15%) men undergoing TRUS biopsy were upgraded compared to 5/30 (17%) men undergoing MRI-TB, who were upgraded. For downgrading, 4/27 (15%) men were downgraded from TRUS biopsy to radical prostatectomy and 6/30 (20%) were downgraded from MRI-TB to radical prostatectomy.

3.8 Proportion of men with clinically significant cancer missed by MRI-TB but detected by the addition of systematic biopsy

56 study cohorts including 4652 patients were included in the analysis. The definition of clinically significant cancer in each study is given in Table 1a. The proportion of men with clinically significant cancer missed by MRI-TB but detected by the addition of systematic biopsy was 13% [95% CI 10-16%], p < 0.0001 (Supplementary Appendix 14).

Discussion

The principal findings of this systematic review are that in men with suspected clinically significant prostate cancer with raised PSA or an abnormal digital rectal examination, MRI-TB detects more clinically significant cancer and less clinically insignificant cancer than systematic biopsy, requiring fewer cores than systematic biopsy to achieve this. These findings were consistent across a range of different thresholds for defining significant and insignificant cancer. The clinical implications are that using an MRI-targeted biopsy strategy could identify those men who will benefit from treatment, and allow men at lowest clinical risk to avoid unnecessary biopsy and potentially, overtreatment.

There was no evidence that these findings varied by whether men were biopsy naïve or had had a prior biopsy. Previously, international guidelines have recommended the use of MRI in men with a prior negative biopsy [92, 93], but the present findings support its role in all men who require further diagnostic testing. There was also no evidence that these findings varied whether MRI-TB was carried out with cognitive or image-fusion registration techniques. This is also consistent with findings from recent trials and systematic reviews [94-96].

Previous systematic reviews have not compared the performance of MRI-TB with systematic TPM biopsy. In this review, the comparative performance of MRI-TB appeared to be influenced by the choice of systematic biopsy, with MRI-TB performing better when the comparator was TRUS biopsy than when the comparator was TPM biopsy. This is consistent with what one might expect from the more intensive sampling approach of a TPM, which when compared directly to TRUS biopsy has been shown to identify more clinically significant cancer [2]. MRI-TB appeared to be comparable to the intensive sampling regime of TPM, as demonstrated in previous studies [48], but is far more efficient, requiring fewer cores. Fewer biopsy cores may avoid the significant side effects seen with TPM [97] whilst allowing the possibility of a local anaesthetic office-based approach [98].

In the one study reporting upgrading and downgrading by radical prostatectomy, MRI-TB and systematic biopsy appeared to have similar results, though further data in this area is needed to make any firm conclusions.

In the paired studies analysed, when performing MRI-TB and TRUS biopsy in the same biopsy session, it is possible that conduct of one test could have influenced the performance of the other. For example, knowledge of where the MRI-targets were could have improved the performance of the systematic biopsy. This review did identify RCTs which allowed us to explore the performance of MRI-TB independently of TRUS biopsy and vice versa; MRI-TB detected more clinically significant cancer than TRUS biopsy in the RCTs most relevant to the review's objectives [1, 6]. It was also evident from the 4 pooled RCTs, that combining MRI-TB with TRUS biopsy diminished the benefit of MRI-TB in reducing clinically insignificant cancer detection [21, 79, 90, 91].

The RCTs also presented an opportunity to explore cancer detection rates in men with non-suspicious MRIs. In 3 of the 4 RCTs where clinically significant cancer was reported, this was low (0-4%) [5, 6, 21] but was higher in the remaining study (3/13, 23%), albeit in a small sample [79]. Clearly if a strategy of avoiding biopsy in men with negative MRI and low clinical risk of prostate cancer is to be adopted, then further follow up in these men is important, though level 1 evidence would support the concept that a negative MRI has a higher negative predictive value than TRUS biopsy [2] and that a negative MRI is more reassuring to patients and clinicians than a negative TRUS biopsy [1]. Emerging data from key recently published studies, including the MRI-FIRST study, 4M Study and Panebianco *et al* also support the concept of incorporating MRI into the diagnostic pathway [3, 99, 100].

There are a number of limitations in this review. First, it is important to appreciate that there is a bias introduced by analysing studies with a paired design as the conclusions of such data are limited to men with MRIs with suspicious findings who underwent both MRI-TB and systematic biopsy. An RCT design would mitigate some of this bias and although this systematic review included several RCTs, the majority did not perfectly address the primary question of this review in terms of the index test and comparator.

Second, there was substantial between-study variability in most of the meta-analyses, as indicated by the magnitude of the I^2 statistic. Although there was variation in the direction of effect, confidence intervals for studies generally overlapped. Thus, the I^2 values may be misleading as I^2 is known to increase with the precision of the studies [101], and many studies in the main analysis of clinically significant cancer had high precision, as is evident on the funnel plot. Furthermore, due to the large number of included studies, we were able to perform several planned sensitivity analyses to assess the robustness of the findings and subgroup analyses to investigate potential sources of heterogeneity. These analyses did not contradict our main findings.

Third, the primary focus of this review was to evaluate MRI-TB as a replacement test [102] for systematic biopsy. We acknowledge that a strategy of using targeted biopsies as an additional test to systematic biopsy increases significant cancer detection, but note that it would also increase the detection of clinically insignificant disease. Identifying men with clinically important disease and avoiding the overdetection of clinically unimportant disease are both critical issues and there is no certainty as to where the optimal balance lies. Previous studies suggest that effort should be made to avoid the diagnosis of men with clinically unimportant disease who can otherwise be over treated and experience side effects of treatment [9-12]. The data presented in this study allow clinicians and patients to make informed decisions about the risks and benefits using MRI-TB as a replacement test or additional test to systematic biopsy.

Fourth, it is important to appreciate that the majority of centres conducting these studies are likely to be those with greater expertise in MRI-TB. Despite this, it is not known what the true quality of the MRI conduct, reporting and biopsy is at each centre. High detection rates of cancer by MRI-TB are dependent on high quality MRI so it is essential that centres wishing to adopt MRI-TB conduct high quality MRI, accurate MRI-TB and have clinicians with appropriate training performing these procedures. Minimum standards for MRI conduct and reporting have been recommended and should be adhered to [103-105]. Non-expert centres can optimise their prostate MRI imaging and reporting under the supervision of a centre experienced in prostate MRI. Further, centres using MRI should counsel patients, who are considering whether or not to undergo prostate biopsy, with the rates of detection

of clinically significant cancer from different MRI levels of suspicion at their centre. Centres should be confident about the negative predictive value of MRI at their own centre before considering omitting systematic biopsy.

In conclusion, this systematic review highlights that in men with clinical suspicion of prostate cancer, MRI-TB detects more clinically significant cancer and less clinically insignificant cancer than systematic biopsy and requires fewer biopsy cores. Thus, MRI-TB is an attractive alternative diagnostic strategy to systematic biopsy for the diagnosis of prostate cancer.

Take Home message

In men with suspected prostate cancer, MRI-targeted biopsy detects more clinically significant and less clinically insignificant cancer and requires fewer cores than systematic biopsy.

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Figure 1 – Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow chart

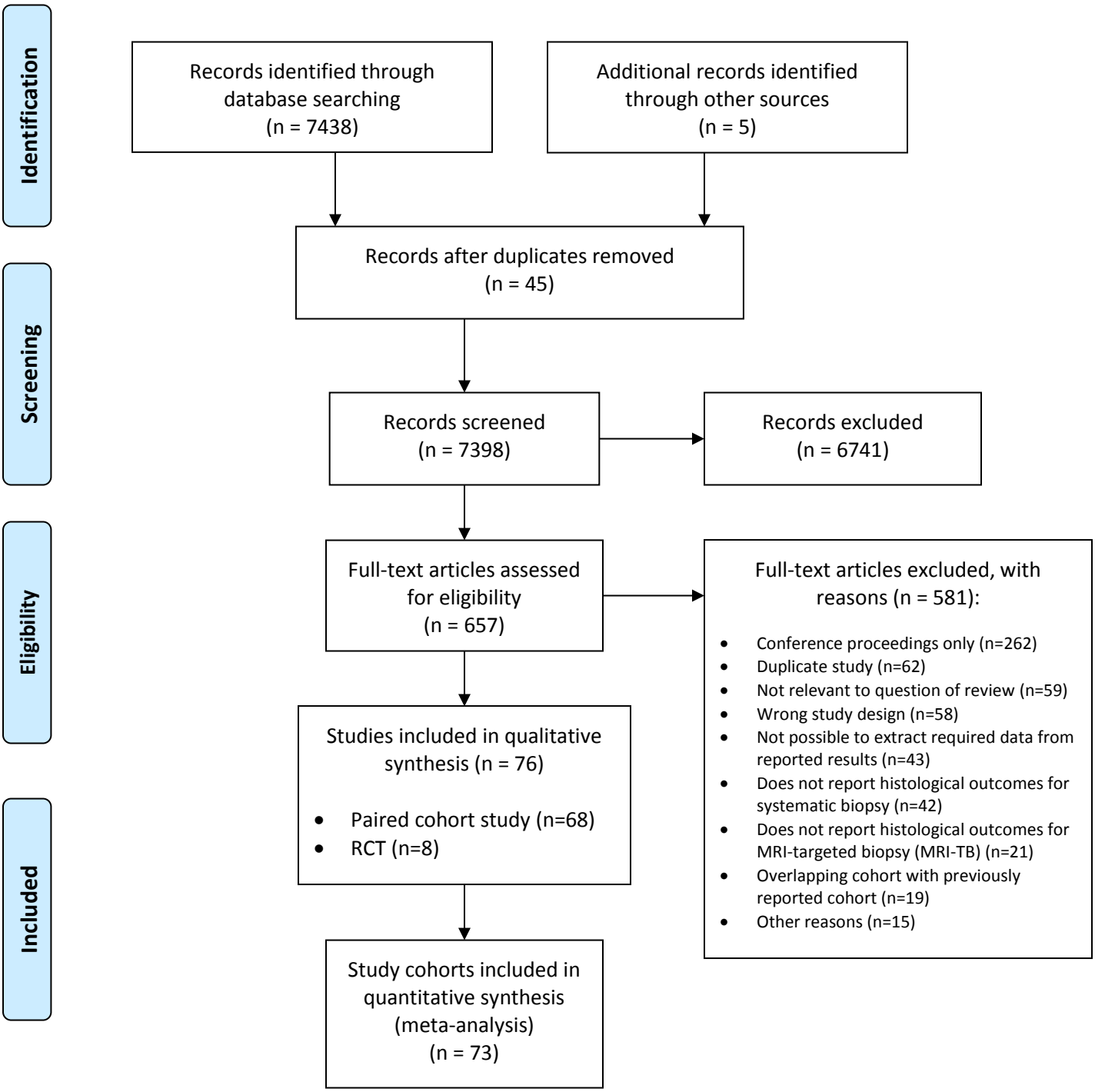


Figure 2 – Forest plot of the detection ratio of MRI-targeted biopsy (MRI-TB) versus systematic biopsy (SB) for clinically significant cancer (CsPCa)

The forest plot shows 56 study cohorts. Studies are grouped by type of comparator and sorted according to type of MRI TB, coil strength and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of non-overlapping cohorts in the same year. DR = detection ratio. TRUS = transrectal ultrasound guided prostate biopsy. Template = transperineal template prostate biopsy. Cognitive = cognitive / visual registration; fusion = MRI/US image fusion; In-bore = carried out in the MRI scanner; Mixed = more than one registration method used in the study. The pooled summary estimate indicated that MRI-TB detected more men with clinically significant cancer than systematic biopsy (DR 1.16 [95% CI 1.09-1.24], p < 0.0001).

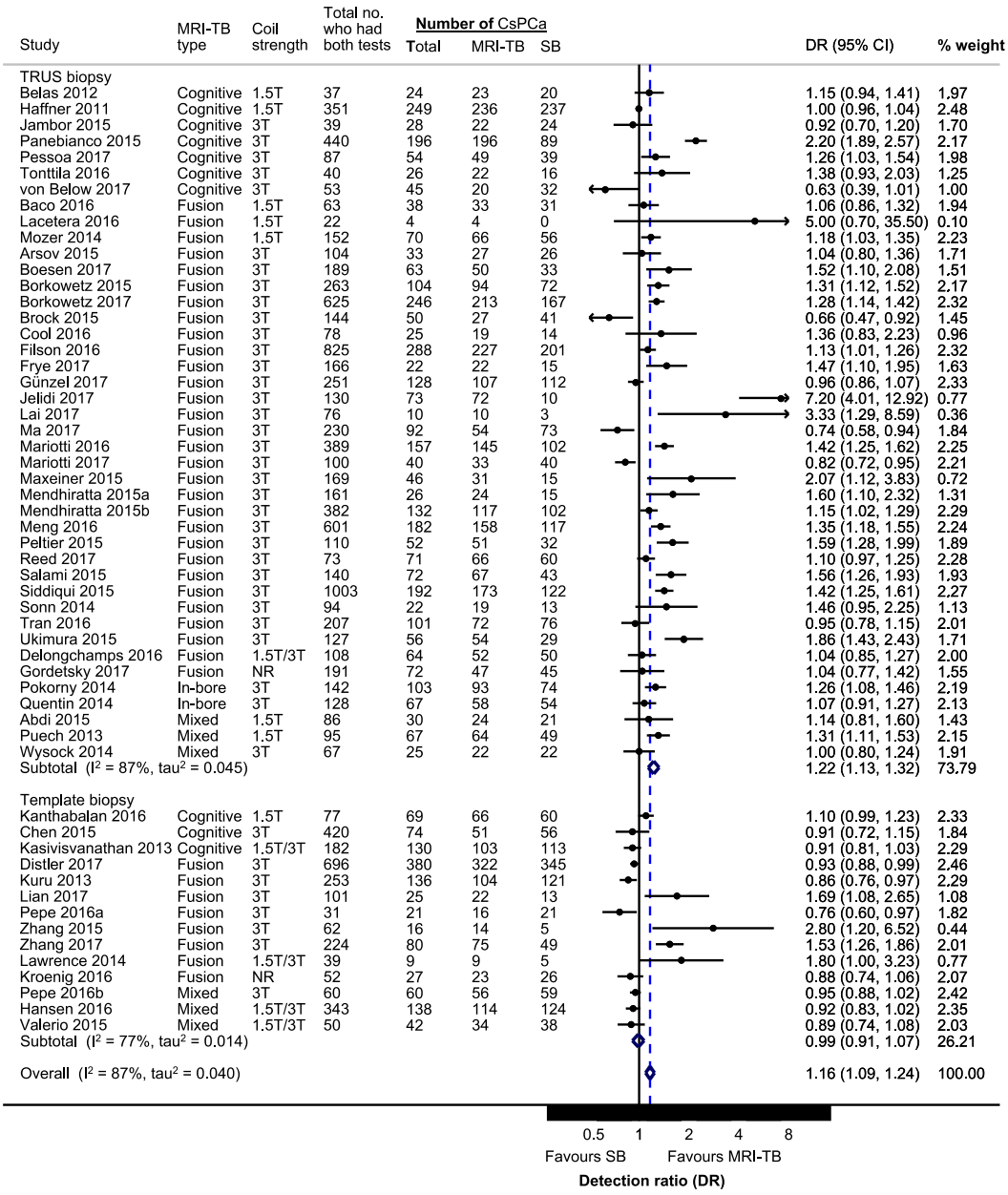


Figure 3 – Forest plot of the detection ratio of MRI-targeted biopsy (MRI-TB) versus systematic biopsy (SB) for clinically insignificant cancer (CiPCa)

The forest plot shows 46 study cohorts. Studies are grouped by type of comparator and sorted according to type of MRI-TB, coil strength and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of non-overlapping cohorts in the same year. The pooled summary estimate indicates that MRI-TB detected fewer men with clinically insignificant cancer than systematic biopsy, DR 0.66 [95% CI 0.57-0.76], p < 0.0001.

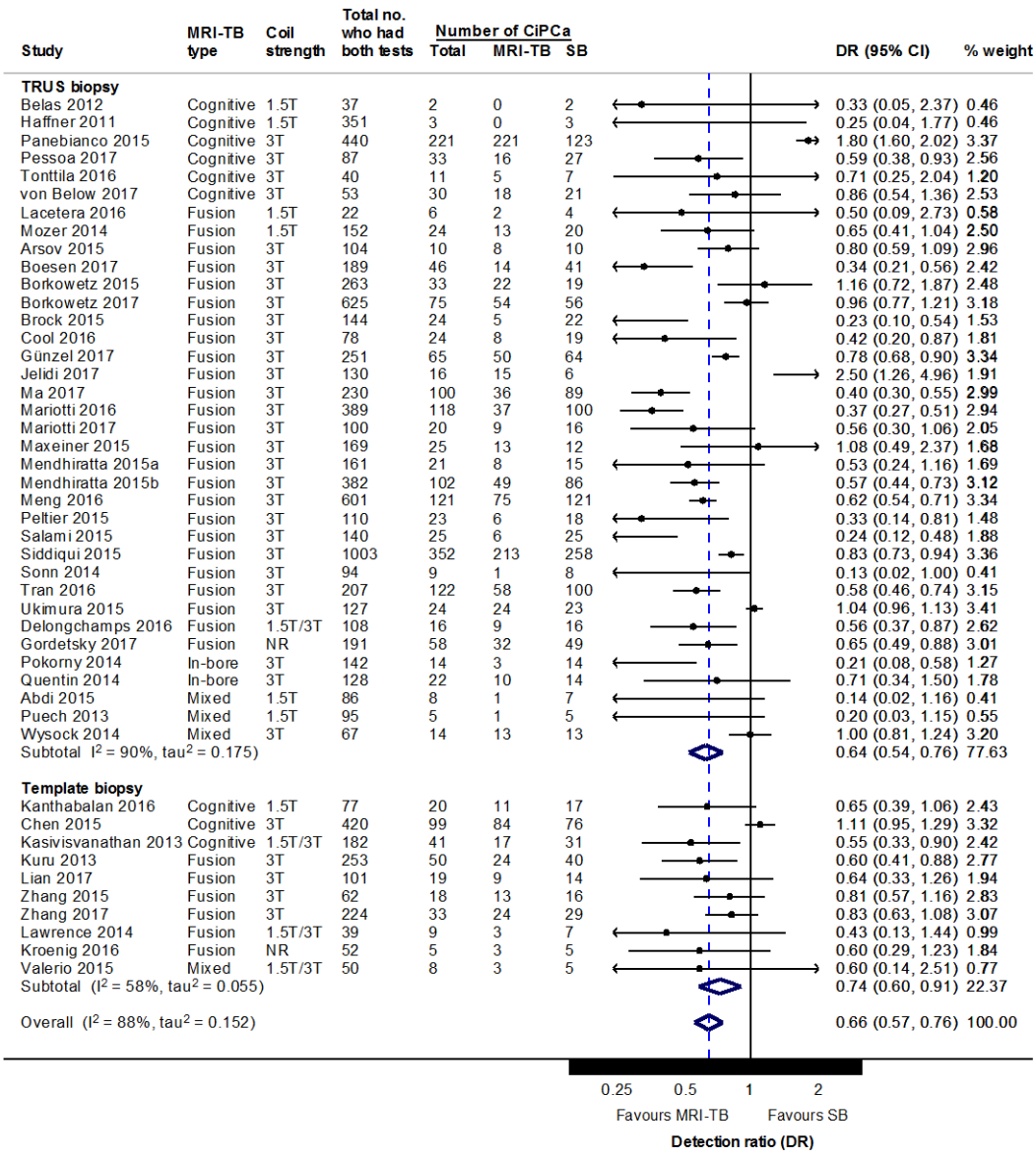


Figure 4a - Forest plot of the detection ratio for significant cancer detection (csPCa) for randomized controlled trials (RCTs) involving MRI-targeted biopsy (MRI-TB) and systematic biopsy (SB).

The forest plot shows 8 RCTs. Studies are grouped by study identifier and similarities in the index test (MRI-TB +/- additional biopsy) and comparator arm (systematic biopsy +/- additional biopsies). Where men with a non-suspicious MRI undergo systematic biopsy, the number with clinical significant prostate cancer are reported. Due to clinical heterogeneity of the included trials, meta-analysis was only carried out for the subset of 5 RCTs with similar index tests and comparators.

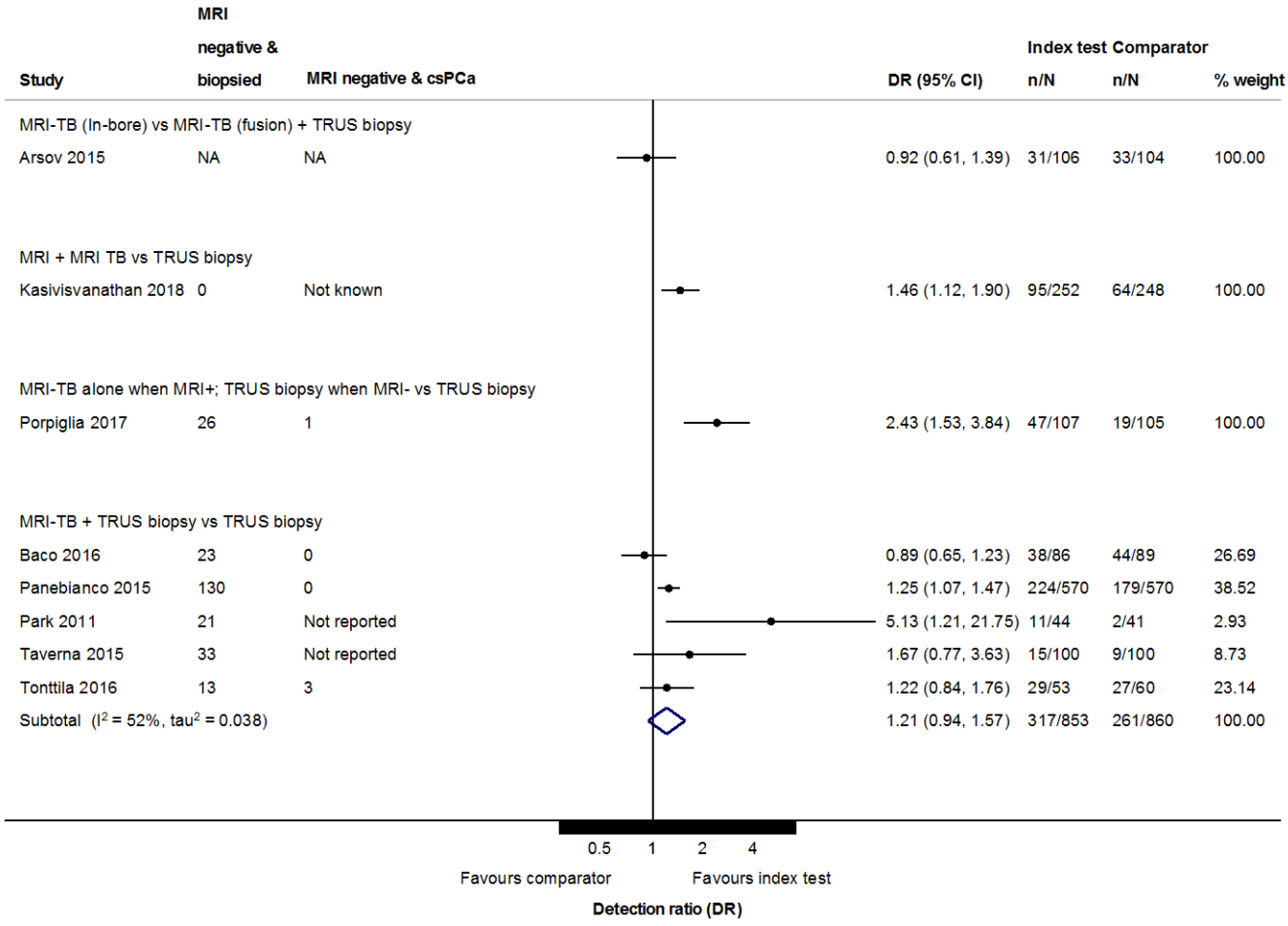


Figure 4b - Forest plot of the detection ratio for insignificant cancer detection (ciPCa) for randomized controlled trials (RCTs) involving MRI-targeted biopsy (MRI-TB) and systematic biopsy (SB).

The forest plot shows 8 RCTs. Studies are grouped by study identifier and similarities in the index test (MRI-TB +/- additional biopsy) and comparator arm (systematic biopsy +/- additional biopsies). Due to clinical heterogeneity of the included trials, meta-analysis was only carried out for the subset of 4 RCTs with similar index tests and comparators.

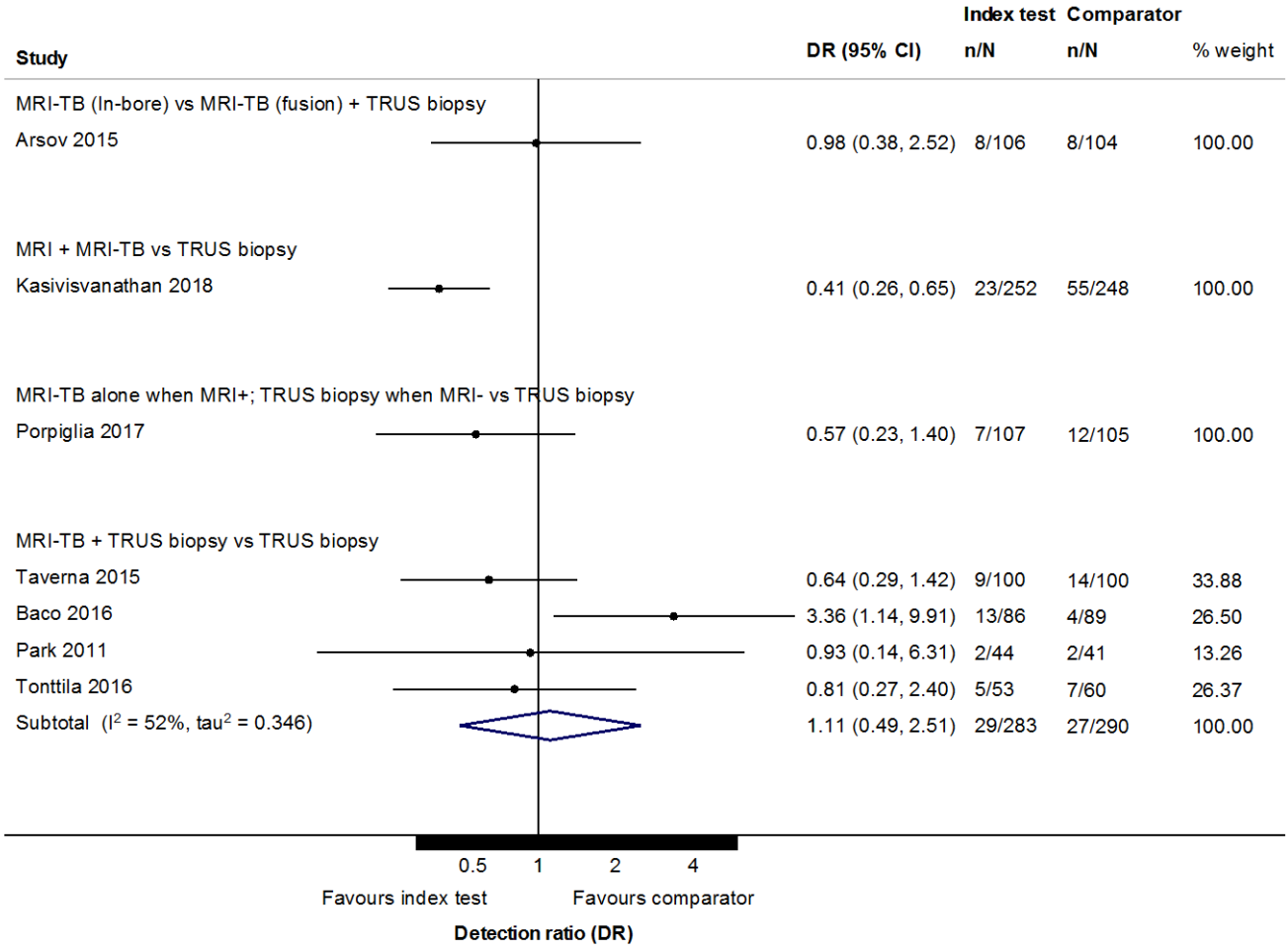


Table 1a: Characteristics of included studies with paired data

Author (ref)	Year	Population	N° of patients	Median age (years)	Median PSA (ng/ml)	Median prostate volume (cc)	Positive MRI	Field of strength (Tesla)	MRI sequences	Endorectal coil	Threshold for target	Target approach (cores per target)	Comparator (cores)	Definition of clinically significant PCa
Abdi et al. [19]	2015	Prior negative biopsy	86	65.4	10.9	48	86	1.5	T2, DWI, DCE	No	PI-RADS ≥ 3	Fusion-TBx (2)	TRUS-Bx (12)	Gleason >6 or > 2 cores, and > 50% of each core
Arsov et al. ‡ [20]	2015	Prior negative biopsy	210	68	10.8	60	104	3	T2, DWI, DCE	No	NR	In-bore TBx (2)	TRUS-Bx (12) + fusion-TBx	GS ≥ 3+4
Baco et al. ‡ [21]	2016	Biopsy naive	175	65	7.3	42	63	1.5	T1, T2, DWI	No	PI-RADS ≥ 3	Fusion-TBx (2)	TRUS-Bx (12) + targeted core to palpable lesions	GS = 6 and MCCL ≥ 5 or GS ≥ 7
Baco et al. [22]	2015	Biopsy naïve + prior negative biopsy + prior positive biopsy	135	64	8.7	38.4	128	1.5/3	T2, DWI, DCE	No	PI-RADS ≥ 3	Fusion-TBx (NR)	Prostatectomy	GS 6 volume ≥ 0.5ml and any GS ≥ 7
Bansal et al. [23]	2017	Biopsy naïve	96	64.4	8.6	41	NR	3	T2, DWI, DCE, MRSI	No	NR	Fusion-Bx (NR)	TRUS-Bx (12)	NR
Belas et al.[24]	2012	Prior negative biopsy + prior positive biopsy	71	66	7	45	37	1.5	T2, DWI, DCE	No	NR	Visual-TBx (3)	TRUS-Bx (NR)	NR
Boesen et al. [25]	2017	Biopsy negative	206	65	12.8	NR	189	3	T2, DWI, DCE	No	PI-RADS ≥ 2	Fusion-TBx (1-2)	TRUS-Bx (10)	GS ≥ 7
Borkowetz et al. [26]	2015	Biopsy naïve + prior negative biopsy	263	66	8.3	50	263	3	T2, DWI, DCE	No	PI-RADS ≥ 2	Fusion-TBx (8.9*)	TRUS-Bx (12)	GS > 6 or GS = 6 with 50% involvement of PCa in more than two cores
Borkowetz et al. [27]	2017	Biopsy naïve + prior negative biopsy + prior positive biopsy	625	66	8.17	50	625	3	T2, DWI, DCE	No	PI-RADS ≥ 2	Fusion-TBx (7)	TRUS-Bx (12)	GS ≥ 7
Brock et al. [28]	2015	Prior negative biopsy	168	64	9.2	55.4	144	3	T2, DWI, DCE	No	PI-RADS ≥ 8 (15 points)	Fusion-TBx (2.3*)	TRUS-Bx (12)	GS ≥ 7
Costa et al. [29]	2013	Prior negative biopsy	38	64	14.4	NR	22	3	T2, DCE	Yes	Likert ≥ 3/4	Visual-TBx (NR)	TRUS-Bx (NR)	Epstein grading
Chen et al. [30]	2015	Biopsy naïve	420	NR	9.73	44.82	420	3	T2, DWI	No	Likert ≥ 3	Visual-TBx (NR)	Transperineal template-Bx (12)	NR
Cool et al. [31]	2016	Biopsy naïve + prior negative biopsy	100	NR	NR	NR	78	3	T2, DWI, DCE	Yes	NR	Fusion-TBx (1-3**)	TRUS-Bx (12)	GS ≥ 7
De Gorski et al. [32]	2015	Biopsy naïve	232	64	6.5	47	232	1.5	NR	No	Likert ≥ 2	Fusion-TBx (2-3**)	TRUS-Bx (12)	At least 1 core with a Gleason score of 7 (3 + 4) or 6 with a maximum cancer core length of 4 mm or greater
Delongchamps et al.[33]	2015	Prior positive biopsy	125	65	7.2	40	125	1.5	T2, DWI, DCE	Yes	NR	Fusion-TBx (2)	Prostatectomy	NR
Delongchamps et al.[34]	2016	Biopsy naïve	108	65	7.2	46	108	1.5/3	T2, DWI, DCE	Yes	PI-RADS ≥ 3	Fusion-TBx (3)	TRUS-Bx (12)	GS ≥ 7 or GS = 6 and MCCL ≥ 5mm
Distler et al. [35]	2017	Biopsy naïve + prior negative biopsy	1040	65	7.2	45	696	3	T2, DWI, DCE	No	PI-RADS ≥ 3	Fusion-TBx (3)	Transperineal template-Bx (24)	GS ≥ 7
Filson et al. [36]	2016	Biopsy naïve + prior negative biopsy + prior positive biopsy	1042	NR	NR	NR	825	3	T2, DWI, DCE	No	PI-RADS ≥ 3	Fusion-TBx (NR)	TRUS-Bx (12)	GS ≥ 7
Frye et al^. [37]	2017	Prior positive biopsy	166	NR	NR	NR	166	3	T2, DWI, DCE	Yes	NR	Fusion-TBx (2)	TRUS-Bx (12)	GS ≥ 7
Garcia Bennet et al.[38]	2015	Biopsy naïve + prior negative biopsy	53	65	12.6	NR	53	1.5/3	T2, DWI, DCE	No	PI-RADS ≥ 2	Visual-TBx (3)	TRUS-Bx (9)	NR
Gordetsky et al. [39]	2017	Biopsy naïve	191	63.3	9.2	NR	191	NR	T2, DWI, DCE	NR	NR	Fusion-TBx (4.8*)	TRUS-Bx (12)	NR
Günzel et al. [41]	2017	Biopsy naïve + prior negative biopsy	251	68	8.42	49	251	3	T2, DWI	No	PI-RADS ≥ 3	Fusion-TBx (3)	TRUS-Bx (10)	NR
Haffner et al. [40]	2011	Biopsy naïve	555	64	6.75	46	351	1.5	T2, DCE	No	Suspicious vs non-suspicious (no scoring system)	Visual-TBx (3.8*)	TRUS-Bx (10)	Any MRI lesions biopsied which were positive for cancer irrespective of Gleason score. Or any other biopsy with >5mm total cancer length and/or gleason pattern >3
Hansen et al. [42]	2016	Prior negative biopsy	487	66	9	56	343	1.5/3	T2, DWI, DCE	No	PI-RADS ≥ 3	Fusion-TBx (3)	Transperineal template-Bx (24)	GS ≥ 7
Jambor et al. [43]	2015	Biopsy naïve	55	nR	NR	NR	39	3	T2, DWI, DCE, MRSI	No	PI-RADS ≥ 4	Visual-TBx (1-2**)	TRUS-Bx (12)	3mm core length of Gleason 3+3 or any Gleason grade 4
Jang et al. [44]	2015	Prior negative biopsy	42	65	9.77	39.5	NA	3	T2, DWI, DCE	No	NR	Visual-TBx (NR)	TRUS-Bx (12)	GS > 6 or GS 6 with > 50% PCa per core or > 2 cores
Jelidi et al. [45]	2017	Biopsy naïve + prior negative biopsy	130	62.9	9.5	45.9	130	3	T2, DWI, DCE	Yes	PI-RADS ≥ 2	Fusion-TBx (2-3**)	TRUS-Bx (16)	GS > 7 or GS = 6 with a CCL > 5 mm
Junker et al. [46]	2015	Prior negative biopsy	50	63.7	7.6	49.2	50	3	T2, DWI, DCE	No	PI-RADS ≥ 3	Fusion-TBx (4.5*)	TRUS-Bx (10)	NR
Kanthabalan et al. [47]	2016	Prior biopsy positive	77	70.5	14	NR	77	1.5T	T2, DWI, DCE	No	Likert ≥ 3	Visual-TBx (4.9*)	Transperineal template-Bx (31)	GS ≥ 3+4 and/or maximum cancer core length (MCCL) ≥4 mm
Kasivisvanathan et al. [48]	2013	Biopsy naïve + prior negative biopsy + prior positive biopsy	182	63.3	6.7	40.6	182	1.5T/3	T2, DWI, DCE	No	Likert ≥ 3	Visual-TBx (5)	Transperineal template-Bx (30)	GS ≥ 3+4 and/or maximum cancer core length (MCCL) ≥4 mm
Kaufmann et al. [49]	2015	Prior negative biopsy	287	66	9.7	52	234	1.5	T2, DWI, DCE	Yes	NR	In-bore TBx (2-5**)	Transperineal template-Bx (24)	GS ≥ 7
Kroenig et al. [50]	2016	Prior negative biopsy	52	66	8.75	49.3	52	NR	T2, DWI, DCE (partially	No	PI-RADS ≥ 2	Fusion-TBx (10.3*)	Transperineal template-Bx (32)	GS ≥ 7

Author (ref)	Year	Population	N° of patients	Median age (years)	Median PSA (ng/ml)	Median prostate volume (cc)	Positive MRI	Field of strength (Tesla)	MRI sequences	Endorectal coil	Threshold for target	Target approach (cores per target)	Comparator (cores)	Definition of clinically significant PCa
Kuru et al. [51]	2013	Prior negative biopsy	347	65.3	9.85	48.7	253	3	T2, DWI, DCE, MRSI	No	Suspicious vs non-suspicious (no scoring system)	Fusion-TBx (NR)	TRUS-Bx (12-6)	NR
Lacetera et al. [52]	2016	Biopsy naïve + prior negative biopsy	22	64	7.7	55	22	1.5	T2, DWI	No	PI-RADS ≥ 3	Fusion-TBx (3)	TRUS-Bx (12)	GS ≥ 7
Lai et al. [53]	2017	Prior positive biopsy	76	62.5	5.1	NR	76	3	T2, DWI, DCE	No	PI-RADS ≥ 3	Fusion-TBx (2.3*)	TRUS-Bx (12)	GS ≥ 7
Lawrence et al. [54]	2014	Prior negative biopsy	39	64	10	NR	39	1.5/3	T2, DWI	No	Suspicion score ≥ 6/10	Fusion-TBx (7)	TRUS-Bx (24-36)	GS ≥ 7
Lian et al. [55]	2017	Prior negative biopsy	101	68.9	10.8	42.1	101	3	T2, DWI, DCE	No	PI-RADS ≥ 2	Fusion-TBx (4.9*)	Transperineal template-Bx (12)	GS ≥ 7 or GS 6 with MCCL ≥ 4 mm
Ma et al.^ [56]	2017	Biopsy naïve + prior positive biopsy	230	NR	NR	NR	230	3	T2, DWI, DCE	Yes	PI-RADS ≥ 3	Fusion-TBx (3-4)	TRUS-Bx(12)	GS ≥ 7
Mariotti et al. [57]	2016	Biopsy naïve + prior negative biopsy	389	NR	NR	NR	389	3	T2, DWI, DCE	Yes	Likert ≥ 3	Fusion-TBx (2-3)	TRUS-Bx (12)	GS 3 + 4 with 50% or more of any core positive for cancer or 33% or more of standard biopsy cores positive for cancer or GS 4 + 3 or greater cancers
Mariotti et al. [58]	2017	Biopsy naïve + prior negative biopsy	100	62.5	5.3	48	100	3	T2, DWI, DCE	No	Likert ≥ 3	Fusion-TBx (2-3**)	TRUS-Bx (12)	GS ≥ 7
Maxeiner et al. [59]	2015	Biopsy naïve + prior negative biopsy	169	65.6	13.9	60.6	NR	3	T2, DWI	No	PI-RADS ≥ 2	Fusion-TBx (1.86*)	TRUS-Bx (10)	Gleason ≥ 4+3
Mendhiratta et al. [60]	2015a	Biopsy negative	161	64.9	8.9	72.5	161	3	T2, DWI, DCE	No	NR	Fusion-TBx (NR)	TRUS-Bx (12)	GS ≥ 7
Mendhiratta et al. [61]	2015b	Biopsy naïve	382	64.5	6.8	44	382	3	T2, DWI, DCE	No	Likert ≥ 2	Fusion-TBx (5.7*)	TRUS-Bx (12)	GS ≥ 7
Meng et al. [62]	2016	Biopsy naïve + prior negative biopsy + prior positive biopsy	601	65.2	6.7	59.9	601	3	T2, DWI, DCE	No	Likert ≥ 2	Fusion-TBx (4)	TRUS-Bx (12)	GS ≥ 7
Mozer et al. [63]	2014	Biopsy naïve	152	63	6	44	152	1.5	T2, DWI, DCE	No	Likert ≥ 2	Fusion-TBx (2)	TRUS-Bx (12)	At least one core with a Gleason score of 3 + 4 or 6 with a maximum cancer core length ≥4 mm
Okoro et al. [64]	2015	Prior positive biopsy	50	61.4	5.34	NR	50	3	T2, DWI, DCE, MRSI	Yes	NR	Fusion-TBx (1)	TRUS-Bx (12)	NR
Panebianco et al. ‡ [5]	2015	Biopsy naïve	1140	NR	NR	NR	NR	3	T2, DWI, DCE	Yes	PI-RADS ≥ 2	Visual-TBx (2)	TRUS-Bx (12)	GS ≥ 3+4
Peltier et al. [65]	2015	Biopsy naïve	110	65.1	8.4	49.3	110	3	T2, DWI, DCE, MRSI	Yes	NR	Fusion-TBx (2.4*)	TRUS-Bx (14.6)	GS ≥ 7 and/or MCCL ≥ 6mm
Pepe et al. [66]	2016a	Biopsy positive	75	NR	NR	NR	31	3	T2, DWI, DCE, MRSI	Yes	PI-RADS ≥ 3	Fusion-TBx (4)	Transperineal template-Bx (NR)	GS ≥ 7 and/or number of cores positive>2
Pepe et al. [67]	2016b	Prior negative biopsy	200	NR	8.6	NR	60	3	T2, DWI, DCE, MRSI	Yes	PI-RADS ≥ 4	Fusion-TBx (4)	Transperineal template-Bx (30)	GS ≥ 7 and/or number of cores positive > 2
Pessoa et al. [68]	2017	Prior positive biopsy	105	67	7.5	53	87	3	T2, DWI, DCE	No	PI-RADS ≥ 2	Fusion-TBx (2-6**)	TRUS-Bx (12)	GS ≥ 7 and/or core involvement >50%
Pokorny et al. [69]	2014	Biopsy naïve	223	63	5.3	41	142	3	T2, DWI, DCE	No	PI-RADS ≥ 3	In-bore TBx (2)	TRUS-Bx (12)	(i) GS 3+3 in > 2 cores or (ii) GS 3+3 >6mm in 1 core or (iii) GS 3+4 > 4mm in ≥ 1 core or (iv) GS 3+4 in ≥ 2 cores.
Puech et al. [70]	2013	Biopsy naïve + prior negative biopsy	95	65	10.1	52	95	1.5	T2, DWI, DCE	No	Likert ≥ 13 or ≥ 5	Fusion-TBx (1.5*)	TRUS-Bx (12)	Gleason ≥ 3+4; MCCL ≥ 3 mm
Quentin et al. [71]	2014	Biopsy naïve	128	66	8.7	54.7	128	3	T2, DWI, DCE	No	NR	In-bore TBx (2)	TRUS -Bx(12)	Gleason ≥ 3+4
Reed et al. [72]	2017	Prior positive biopsy	73	NR	NR	NR	73	3	T2, DWI, DCE	Yes	NR	Fusion-TBx (6)	TRUS-Bx (12)	NR
Salami et al. [73]	2015	Biopsy negative	140	NR	NR	NR	140	3	T2, DWI, DCE	Yes	NR	Fusion-TBx (NR)	TRUS-Bx (12)	Gleason ≥ 3+4 or Gleason 3+3 MCCL 50% or more than 2 cores positive
Shigemura et al. [74]	2012	Biopsy naïve + prior negative	96	67	8.58	31.9	96	1.5	T2, DWI, DCE (partially)	NR	Suspicious vs. non-suspicious	Fusion-TBx (NR)	TRUS-Bx (12)	NR
Shin et al. [75]	2017	Biopsy naïve + prior negative biopsy + prior positive biopsy	117	63	7.1	52.9	117	3	NR	NR	NR	Fusion-TBx (NR)	TRUS-Bx (10-12)	GS ≥ 7
Shoji et al. [76]	2015	Biopsy naïve	20	70	7.4	38	20	1.5	T2, DWI, DCE	No	PI-RADS ≥ 2	Fusion-TBx (NR)	Transperineal template biopsy (12)	Gleason ≥ 3+4 OR (Gleason 6 + MCCL≥4mm)
Siddiqui et al. [77]	2015	Biopsy naïve + prior negative biopsy	1003	62.1	6.7	49	1003	3	T2, DWI, DCE, MRSI	Yes	Score ≥ 1	Fusion-TBx (6.2*)	TRUS-Bx (12)	Gleason ≥ 4+3
Sonn et al. [78]	2014	Biopsy naïve + prior negative biopsy	105	65	7.5	58	101	3	T2, DWI, DCE	No	NR	Fusion-TBx (NR)	TRUS-Bx (12)	Gleason 3 + 4 or Gleason 6 with maximal cancer core length (MCL) ≥4mm
Tontilla et al. ‡ [79]	2016	Biopsy naïve	113	63	6.1	27.8	40	3	T2, DWI, DCE	No	Likert ≥ 2/4	Visual-TBx (2)	TRUS-Bx (10-12)	Gleason ≥ 3+4
Tran et al. [80]	2016	Prior positive biopsy	207	66.7	5.9	42	207	3	T2	Yes	NR	Fusion-TBx (2)	TRUS-Bx (14)	NR
Ukimura et al. [81]	2015	Biopsy naïve + prior negative biopsy	127	66	5.8	NR	127	3	T2, DWI, DCE	No	NR	Fusion-TBx (2.8*)	TRUS-Bx (11)	GS ≥ 7 and/or maximum cancer core length ≥5 mm
Valerio et al. [82]	2015	Biopsy naïve + prior negative	50	68	7.9	38	50	1.5/3	T2, DWI, DCE	No	Likert ≥ 3	Fusion-TBx (3)	Transperineal template-Bx	GS ≥ 3 + 4 and/or maximum cancer core length ≥4 mm

Author (ref)	Year	Population	N° of patients	Median age (years)	Median PSA (ng/ml)	Median prostate volume (cc)	Positive MRI	Field of strength (Tesla)	MRI sequences	Endorectal coil	Threshold for target	Target approach (cores per target)	Comparator (cores)	Definition of clinically significant PCa
		biopsy + prior positive biopsy											(32)	
Volkin et al. [83]	2014	Biopsy naïve + prior negative biopsy	42	64	12.6	53.5	42	3	T2, DWI, DCE, MRSI	Yes	Score ≥ 1	Fusion-TBx (NR)	TRUS-Bx (12)	NR
von Below et al. [84]	2017	Biopsy naïve + prior positive biopsy	53	64	6.4	33	53	3	T2, DWI, MRSI	Yes	Likert > 1	Fusion-TBx (2)	TRUS-Bx (12)	GS ≥ 7
Wang et al. [85]	2016	Biopsy negative	15	NR	NR	NR	15	NR	NR	NR	NR	Fusion-TBx (NR)	TRUS-Bx (NR)	NR
Wysock et al. [86]	2014	Biopsy naïve + prior negative biopsy + prior positive biopsy	125	65	5.1	40.5	67	3	T2, DWI, DCE	No	PI-RADS ≥ 2	Fusion-TBx (2)	TRUS-Bx (NR)	NR
Zhang et al. [87]	2014	Biopsy naïve	518	NR	NR	NR	254	3	T2, DWI, DCE, MRSI	No	Suspicious vs. non-suspicious	Fusion-TBx (NR)	TRUS-Bx (12)	NR
Zhang et al. [88]	2017	Biopsy naïve	224	69	10.05	45.5	224	3	T2, DWI, DCE	No	Likert ≥ 2	Fusion-TBx (3.54*)	Transperineal -Bx (12)	GS > 6 or GS 6 with 50% involvement of PCa per core
Zhang et al. [89]	2015	Biopsy naïve	62	68.38	10.21	34.05	62	3	T2, DWI, DCE	No	PI-RADS ≥ 2	Fusion-TBx (3.24*)	Transperineal -Bx (12)	GS of 7 (or more) or 6 with a MCCL > 4 mm

* Mean; ** Range; GS: gleason score; TBx: MRI targeted prostate biopsy; TRUS: transrectal ultrasound guided prostate biopsy; ^Represents a combination of cohorts by the same author. ‡Represents paired data from an arm of a randomized controlled trial

Table 1b: Characteristics of randomized controlled trials

Author, ref	Year	Population investigated	N° of patients	Investigation arm, (N)	Comparator arm, (N)	Sequences and coil strength	Threshold for target	Definition of clinically significant PCa	Key findings
Arsov et al. [20]	2015	Prior negative biopsy	210	In Bore-TBx (106)	MRI-fusion-TBx + 12-core TRUS-Bx (104)	T1, T2, DWI, DCE, 3T	NR	GS ≥ 3+4	I) No significant differences between combined biopsy approach over In Bore-TBx alone II) Only difference that fewer number of cores were taken in In Bore-TBx alone patients
Baco et al. [21]	2016	Biopsy naïve	175	MRI-fusion-TBx + 12-core TRUS-Bx (86)	12-core TRUS-Bx + target core on palpable lesions (89)	T1, T2, DWI, 1.5T	PI-RADS ≥ 3	GS = 6 and MCCL ≥ 5 or GS ≥ 7	I) Overall csPca detection rate was similar between the two groups II) Traditional 12-core TUR-Bx may be replaced by two-core MRI-TBx
Kasivisvanathan et al. [1]	2018	Biopsy naïve	500	MRI + MRI-TBx in MRI positive	10-12 core TRUS-Bx	T1, T2, DWI, DCE 1.5T/3T	PI-RADS ≥ 3	GS ≥ 3+4	The proportion of men with clinically significant cancer in the MRI arm was greater than TRUS-Bx and the proportion of men with clinically insignificant cancer was less in the MRI arm than tha TRUS-Bx arm
Panebianco et al. [5]	2015	Biopsy naïve	1140	TRUS-Bx + MRI-TBx in positive MRI (570)	12-core TRUS-Bx (570)	T1, T2, DWI, DCE 3T	PI-RADS ≥ 2	GS ≥ 3+4	The proportion of men with csPCa is higher among those randomized to MRI-TBx vs. those randomized to TRUS-Bx
Park et al. [90]	2011	Biopsy naïve	85	MRI-cognitive-TBx + 10-12-core TRUS-Bx (44)	10-12-core TRUS-Bx (41)	T1, T2, DWI, DCE 3T	NR	NR	MRI group had a significant higher detection rate of PCa
Porpiglia et al. [6]	2017	Biopsy naïve	212	MRI-fusion-TBx alone when positive MRI; TRUS-Bx when negative MRI (107)	12-core TRUS-Bx (105)	T1, T2, DWI, DCE 1.5T	PI-RADS ≥ 3	GS ≥ 7 or MCCL ≥ 5mm	A diagnostic pathway based on MRI had higher detection rate of both PCa and csPCa compared to standard pathway
Taverna et al. [91]	2015	Prior negative biopsy	200	MRI-cognitive-TBx + 13 core TRUS-Bx (100)	13 core TRUS-Bx (100)	T2 + others (NR) 3T	"MRI-positive lesion" using PI-RADSv2	GS ≥ 3+4	No difference in overall cancer detection between MRI-TBx and systematic biopsy
Tonttila et al. [79]	2016	Biopsy naïve	113	MRI-cognitive-TBx + 10-12-core TRUS-Bx (53)	10-12-core TRUS-Bx (60)	T1, T2, DWI, DCE 3T	Likert ≥ 2/4	GS ≥ 3+4	MRI-TBx did not improve PCa detection rate compared with TRUS-Bx alone

GS: Gleason score; MCCL: maximum score length; PCa: prostate cancer; csPCa: clinically significant prostate cancer; TBx: Targeted biopsy

Table 2: A summary of overall and subgroup analyses for the detection of clinically significant cancer

	Study cohorts (n)	Number of men with cancer	DR (95% CI)	P value	τ^2	I^2 (%)
Overall	56	4652	1.16 (1.09, 1.24)	<0.0001	0.040	87
Clinically significant cancer threshold						
≥ Gleason 3+4	31	3014	1.09 (1.02, 1.18)	0.018	0.027	80
≥ Gleason 4+3	14	752	1.38 (1.14, 1.68)	0.001	0.082	82
Subgroup analyses and meta-regression						
Type of systematic biopsy						
TRUS biopsy	42	3445	1.22 (1.13, 1.32)		0.045	87
Template biopsy	14	1207	0.99 (0.91, 1.07)		0.014	77
Difference				0.083		
Prior biopsy status						
Biopsy naïve	19	1548	1.18 (1.06, 1.31)		0.039	87
Prior biopsy negative	15	896	1.22 (1.05, 1.42)		0.064	84
Prior biopsy positive	10	493	1.09 (0.92, 1.30)		0.052	77
Difference				0.71		
MRI registration method						
Cognitive	10	895	1.11 (0.94, 1.31)		0.059	92
Fusion	38	3225	1.22 (1.12, 1.33)		0.050	87
Difference				0.36		

τ^2 is the between study variance, a measure of between study heterogeneity.
CI = confidence interval; DR = detection ratio; TRUS = transrectal ultrasound-guided.
Meta-regression was used to formally assess differences between subgroups.

Table 3: A summary of overall and subgroup analyses for the detection of clinically insignificant cancer

	Study cohorts (n)	Number of men with cancer	DR (95% CI)	P value	τ^2	I^2 (%)
Overall	46	2124	0.66 (0.57, 0.76)	<0.0001	0.152	88
Clinically insignificant cancer threshold						
≥ Gleason 3+3	25	1481	0.74 (0.65, 0.84)	<0.0001	0.069	79
Subgroup analyses and meta-regression						
Type of systematic biopsy						
TRUS biopsy	36	1822	0.64 (0.54, 0.76)		0.175	90
Template biopsy	10	302	0.74 (0.60, 0.91)		0.055	58
Difference				0.61		
Prior biopsy status						
Biopsy naïve	15	704	0.71 (0.52, 0.96)		0.289	92
Prior biopsy negative	12	312	0.48 (0.35, 0.66)		0.176	71
Prior biopsy positive	4	251	0.51 (0.40, 0.66)		0.026	40
Difference				0.12		
MRI registration method						
Cognitive	9	460	0.81 (0.56, 1.17)		0.207	89
Fusion	31	1593	0.64 (0.56, 0.73)		0.094	83
Difference				0.14		

τ^2 is the between study variance, a measure of between study heterogeneity.
CI = confidence interval; DR = detection ratio; TRUS = transrectal ultrasound-guided.
Meta-regression was used to formally assess differences between subgroups.

Supplementary Appendix 1

Search terms used in the systematic review

Searches were carried out on 28th July 2017.

Ovid (EMBASE and Medline)

1 exp Biopsy/
2 biopsy.mp. or biopsies.ti,ab.
3 biopsy.af.
4 1 or 2 or 3
5 MRI-TB.ti,ab.
6 MRI.ti,ab.
7 MRI*.ti,ab.
8 exp Magnetic Resonance Imaging/
9 magnetic resonance imag*.ti,ab.
10 magnetic resonance imaging.af.
11 or/5-10
12 prostate.ti,ab.
13 ((prostat*) adj2 (neoplasm* or cancer* or carcinoma* or tumor* or tumour*)).ti,ab.
14 exp Prostatic Neoplasms/
15 prostate.af.
16 or/12-15
17 4 and 11 and 16

Web of Science

TS=(((biops*)) AND (("magnetic resonance imaging" or MRI)) AND ((prostat*)) AND ((detection or diag*)))

Cochrane Library

(biops*):ab,ti and ('magnetic resonance' or mri) and (prostat*):ab,ti

Clinicaltrials.gov

Search terms included: “Prostate neoplasm” and Other Terms included “MRI, biopsy”. If a relevant trial was in progress at the time of the search, the trial contacts specified were contacted for study results and if the published paper was available prior to completing data extraction on the 8th July 2018, the study results were eligible to be included.

Reference searching

References of included studies were hand searched and relevant studies meeting eligibility criteria of the study were included.

Supplementary Appendix 2

The list of variables for which data were collected from studies include:

1. First Author Surname
2. Year of Publication (YYYY)
3. Study design (prospective vs retrospective; paired studies, case-control type studies, randomised controlled trials, other)
4. Inclusion and exclusion criteria
5. Total number of patients (n)
6. Average age of the patients (years)
7. Prior biopsy status of population (biopsy naïve, prior positive, prior negative, mixed)
8. Number of men without prior biopsy (n)
9. Number of men with prior negative biopsy (n)
10. Number of men with prior positive biopsy (n)
11. Number of men with prior treatment to the prostate (n)
12. Average prostate volume (mls)
13. Average PSA (ng/ml)
14. MRI coil strength (1.5T, 3T, other)
15. MRI machine model (Freetext e.g. Siemens Avanto)
16. MRI sequences used (T2, T2&DWI, T2&DCE, T2&DWI&DCE, other e.g. MRS)
17. MRI Coils used (pelvic phased array only, pelvic phased array and endorectal)
18. Experience of reporting radiologist (years)
19. Scoring system used for declaring a suspicious lesion (PIRADs, Likert 1-5, other)
20. Threshold score for declaring a suspicious lesion (1, 2, 3, 4, 5, other)
21. Number of men with suspicious lesions (n)
22. Number of men who underwent MRI-targeted biopsy (n)
23. Sampling route of MRI-TB (transrectal, transperineal, other)
24. MRI-TB performed first (yes/no)
25. Order of cores taken randomized (yes/no)
26. Average number of suspicious lesions per man identified on MRI (n)
27. Type of systematic biopsy (TRUS-biopsy, transperineal biopsy, other)
28. What the reference test was (systematic & targeted biopsies together or other)
29. For MRI-targeted biopsy, the registration method used (visual registration alone, software assisted registration or in-bore MRI)
30. If software assisted, what was the software used? (Freetext e.g. Koelis urostation)
31. If software assisted used, was there a comparison of more than one method of registration (yes/no)
32. For MRI-targeted biopsy, whether the biopsy operator viewed MRI images, a prose report or diagrammatic report (MRI images viewed, prose report viewed, diagrammatic report viewed, all)
33. For MRI-targeted biopsy, modality of real-time guidance during procedure (US, MRI)
34. Anaesthesia used (LA, GA)
35. Systematic cores taken blind to location of MRI-suspicious lesions (yes/no)
36. Average number of targeted cores per patient (n)
37. Total number of targeted cores taken in whole study (n)
38. Average number of targeted cores per suspicious lesion (n)

39. Total number of systematic cores taken in whole study (n)
40. Average number of systematic cores taken per patient (n)
41. Number of men with any cancer detected by MRI-TB (n)
42. Number of men with any cancer detected by systematic biopsy (n)
43. Number of men with any cancer detected by both tests (n)
44. Threshold used to define clinically significant cancer (Freetext e.g. Gleason 7 or maximum cancer core length > 4mm)
45. Number of men with Gleason 6 cancer on MRI-targeted biopsy (n)
46. Number of men with Gleason 3+4 cancer on MRI-targeted biopsy (n)
47. Number of men with Gleason 4+3 cancer on MRI-targeted biopsy (n)
48. Number of men with Gleason 4+4 cancer on MRI-targeted biopsy (n)
49. Number of men with > Gleason 4+4 cancer on MRI-targeted biopsy (n)
50. Number of men with clinically significant cancer on MRI-targeted biopsy (n)
51. Number of men with clinically insignificant cancer on MRI-targeted biopsy (n)
52. Number of men with clinically significant cancer missed by systematic biopsy detected by MRI-TB (n)
53. Number of men with clinically insignificant cancer missed by systematic biopsy detected by MRI-TB (n)
54. Number of men with Gleason 6 cancer on systematic biopsy (n)
55. Number of men with Gleason 3+4 cancer on systematic biopsy (n)
56. Number of men with Gleason 4+3 cancer on systematic biopsy (n)
57. Number of men with Gleason 4+4 cancer on systematic biopsy (n)
58. Number of men with > Gleason 4+4 cancer on systematic biopsy (n)
59. Number of men with clinically significant cancer on systematic biopsy (n)
60. Number of men with clinically insignificant cancer on systematic biopsy (n)
61. Number of men with clinically significant cancer missed by MRI-TB detected by systematic biopsy (n)
62. Number of men with clinically insignificant cancer missed by MRI-TB detected by systematic biopsy (n)
63. Number of men with Gleason 6 cancer on reference test (n)
64. Number of men with Gleason 3+4 cancer on reference test (n)
65. Number of men with Gleason 4+3 cancer on reference test (n)
66. Number of men with Gleason 4+4 cancer on reference test (n)
67. Number of men with > Gleason 4+4 cancer on reference test (n)
68. Number of men with clinically significant cancer on reference test (n)
69. Number of men with clinically insignificant cancer on reference test (n)
70. Total number of cores positive for cancer on MRI-TB
71. Total number of cores positive for clinically significant cancer on MRI-TB
72. Total number of cores positive for clinically insignificant cancer on MRI-TB
73. Total number of cores positive for cancer on systematic biopsy
74. Total number of cores positive for clinically significant cancer on systematic biopsy
75. Total number of cores positive for clinically insignificant cancer on systematic biopsy
76. Total number of cores positive for cancer on reference test
77. Total number of cores positive for clinically significant cancer on reference test
78. Total number of cores positive for clinically insignificant cancer on reference test

Supplementary Appendix 3

The modified Quality Assessment of Diagnostic Accuracy Studies-2 checklist used for risk of bias assessment and applicability concern

Domain 1: Patient selection	
A. RISK OF BIAS: Could selection of patients have introduced bias?	
Describe the methods of patient selection briefly:	
Signalling Question (SQ)1: Was a consecutive or random sample of patients enrolled?	Yes / No / Unclear
SQ2: Was a case-control/matched cohort design avoided? If the study is a paired study (each man gets both tests) or an RCT, please answer "Yes" If the study is a matched cohort (matched cohort is when a group of men under study are compared to another group of men matched by specific factors (e.g. age, PSA). This group is usually historic. i.e. the 2 groups are not collected in the same time period / centre), please answer "No"	Yes / No / Unclear
SQ3: Did the study avoid inappropriate exclusions? Inappropriate exclusions would be exclusion of patients who are more or less likely to have disease which may influence the diagnostic accuracy of the test. Examples of inappropriate exclusions: - excluding patients with likely T3/T4 or extremely high PSA would be inappropriate - including only patients who underwent radical prostatectomy - excluding patients with prior negative biopsies (they are not including the most difficult to diagnose patients) - including only active surveillance patients (includes only patients more likely to have a positive test) Studies that avoid inappropriate exclusions are studies that have been as broad as possible in terms of the population included.	Yes / No / Unclear
SUMMARY: RISK OF BIAS FOR PATIENT SELECTION DOMAIN: High risk if 'No' for at least one SQ Low risk if 'Yes' for all SQs.	Low risk / High risk / Unclear risk

Unclear risk if “Unclear” for at least one SQ (though “No” for one SQ supersedes “Unclear” if both results present).	
B. CONCERNS FOR APPLICABILITY OF PATIENT SELECTION DOMAIN	
Describe briefly the included patients (prior testing, presentation, intended use of index test and setting):	
Are there concerns that the included patients and setting do not match the review question? This is a pragmatic review hence the inclusion criteria are wide. If the study includes patients that fulfil the criteria above, this is “Low concern”. If it does not, this is “High concern”. If insufficient data are reported to make a decision then this is “Unclear concern”	Low concern / High concern / Unclear concern

Domain 2: Index Test	
A. RISK OF BIAS: Could the conduct or interpretation of the index test have introduced bias?	
Describe briefly the nature of the MRI-targeted biopsy, how it was conducted and results interpreted:	
SQ1: Was the MRI-targeted biopsy performed without knowledge of the results of the comparator/systematic biopsy? If both biopsy tests were done in the same sitting, it is usually not possible to know the results of the systematic biopsy in which case answer “Yes”.	Yes / No / Unclear
SQ2: Was the MRI-targeted biopsy conducted independently of the conduct of the systematic biopsy? For example, if the systematic biopsy sampled a particular area in the prostate, would that influence where the MRI-targeted biopsy sampled? If yes then answer “No”	Yes / No / Unclear
SQ3: Was the MRI score / risk threshold for patients to undergo targeted biopsy pre-specified?	Yes / No / Unclear
SUMMARY: RISK OF BIAS FOR INDEX TEST: High risk if ‘No’ for at least one applicable SQ Low risk if ‘Yes’ for all applicable SQs. Unclear risk if “Unclear” for at least one applicable SQ. (Though “No” for one SQ supersedes “Unclear” if both results present).	Low risk / High risk / Unclear risk
B. CONCERNS FOR APPLICABILITY	

Are there concerns that the index test, its conduct, or interpretation differ from the review question? This is a pragmatic review hence the different types of targeted biopsy (i.e. cognitive/software fusion/in bore targeted biopsy) admissible are wide. If the study described the type of MRI-targeted biopsy in detail, this is "Low concern". If it did not, this is "High concern". In addition, if more than one type of targeted biopsy was conducted in the intervention arm and results cannot be separated for each type, then this should be categorised as "High concern". If insufficient data are reported to make a decision then this is "Unclear concern".	Low concern / High concern / Unclear concern

Domain 3: Comparator test (Systematic biopsy (TRUS-biopsy, Transperineal template biopsy, or variations of these) or Radical prostatectomy)	
A. RISK OF BIAS: Could the conduct or interpretation of the comparator test have introduced bias?	
Describe briefly the nature of the comparator test, how it was conducted and results interpreted:	
SQ1: Was the systematic /comparator biopsy performed without knowledge of the results of the MRI-targeted biopsy? If both biopsy tests were done in the same sitting, it is usually not possible to know the results of the systematic biopsy in which case answer "Yes". A radical prostatectomy (if the only comparison) would be answered "No".	Yes / No / Unclear
SQ2: Was the systematic /comparator biopsy conducted independently of the conduct of the systematic biopsy? To answer this question consider both of the following: 1. For example, if the MRI-targeted-biopsy sampled a particular area in the prostate, would that influence where the systematic biopsy sampled? If yes then answer "No". If not stated, say "Unclear" 2. Was the systematic biopsy operator blinded to the MRI report? If not, answer "No". If not stated, say "Unclear" If 1) or 2) is "No", this overrules "Unclear".	Yes / No / Unclear
SUMMARY: RISK OF BIAS FOR COMPARATOR TEST: High risk if 'No' for at least one applicable SQ Low risk if 'Yes' for all applicable SQs. Unclear risk if "Unclear" for at least one applicable SQ. (Though "No" for one SQ supersedes "Unclear" if both results present).	Low risk / High risk / Unclear risk
B. CONCERNS FOR APPLICABILITY	

Are there concerns that the comparator test, its conduct, or interpretation differ from the review question? Does the study pre-specify definition of clinically significant cancer by the comparator test? If yes, is "Low risk". If it does not, this is "High risk". If insufficient data are reported to make a decision then this is "Unclear"	Low concern / High concern / Unclear concern

Domain 4: Flow and Timing	
A. RISK OF BIAS: - Could the patient flow have introduced bias?	
Describe any patients who did not receive the index or comparator test, or who were excluded from the analysis. Describe the interval and any interventions between the index and comparator tests.	
SQ1: Was the time interval between any of the following combinations of tests less than 6 months? ● mpMRI and MRI targeted biopsy ● MRI targeted biopsy and systematic biopsy / radical prostatectomy	Yes / No / Unclear
SQ2: Did all patients receive the same comparator test? N.B. If a sub-group of patients received radical prostatectomy, this is ok, providing the whole cohort first received the same systematic biopsy technique (TRUS-biopsy OR transperineal template prostate biopsy)	Yes / No / Unclear
SQ3: Were all patients who underwent testing included in the analysis? Please look out for withdrawal numbers and lost to follow-up patients within each study arm: is the number of patients significantly different between arms? If there are imbalances between arms, please answer "No"	Yes / No / Unclear
SUMMARY: COULD THE PATIENT FLOW HAVE INTRODUCED BIAS: High risk if 'No' for at least one SQ Low risk if 'Yes' for all SQs. Unclear risk if "Unclear" for at least one SQ. (Though "No" for one SQ supersedes "Unclear" if both results present).	Low risk / High risk / Unclear risk

Supplementary Appendix 4

Further details on data synthesis methods

The table below shows the cross classification of the results of MRI-TB and systematic biopsy for the primary outcome of clinically significant cancer in a paired study.

		Systematic biopsy		
		Significant cancer	No significant cancer	Total
MRI-TB	Significant cancer	a	b	a + b
	No significant cancer	c	d	c + d
	Total	a + c	b + d	a + b + c + d

The detection ratio (DR) is the ratio of the MRI-TB detection rate divided by the systematic biopsy detection rate. Thus, using the notation in the table above, the DR was calculated as $\frac{a+b}{a+c}$. To account for the correlated data, the within-study variance of the natural log of the detection ratio, V[ln(DR)], in a study was calculated as $\frac{(b+c)}{(a+c)(a+b)}$. We then used the inverse variance weighted approach to obtain the pooled ln(DR) and its 95% confidence interval (CI). These estimates were then exponentiated to obtain the pooled DR and its 95% CI. Similar analyses were performed to obtain pooled estimates for clinically insignificant cancer and for any cancer.

For RCTs we constructed a 2x2 table by cross classifying the outcome against the randomized groups. For example, the table below represents the results of an RCT of MRI-TB versus systematic biopsy.

	MRI-TB group	**Systematic biopsy group**	**Total**
Significant cancer	a	b	a + b
No significant cancer	c	d	c + d
Total	a + c	b + d	a + b + c + d

We computed the proportion in each group, e.g. a/(a +c) for MRI-TB and b/(b + d) for systematic biopsy, and compared proportions between randomized groups to obtain the detection ratio. When there were studies that used the same index test and comparator, we performed random effects meta-analysis using the DerSimonian and Laird approach[1].

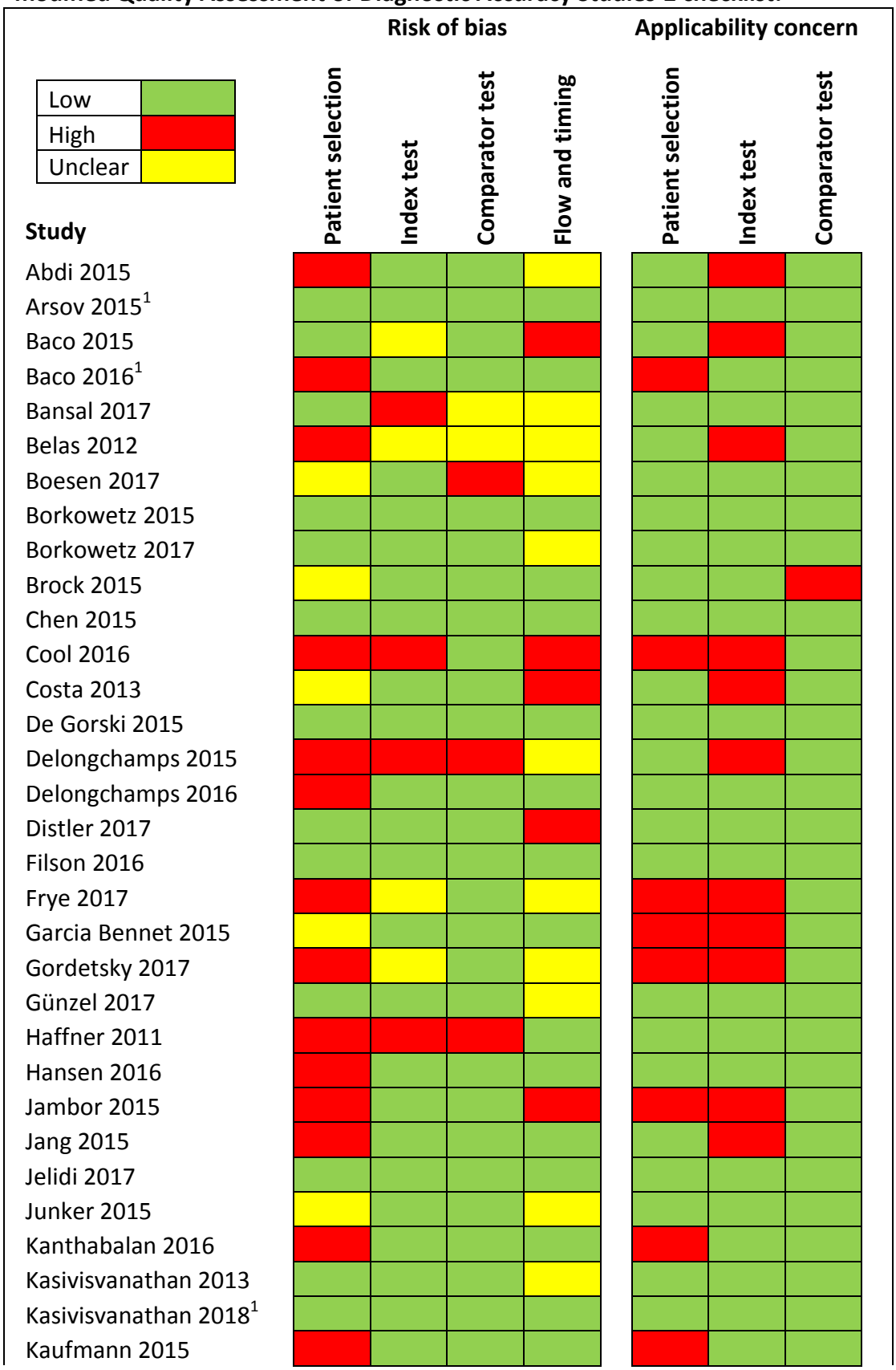
For the additional analyses, we compared the proportion of cores positive for prostate cancer by MRI-TB with that of systematic biopsy, and pooled the ratio (relative risk) in a random effects meta-analysis using the method of DerSimonian and Laird. We pooled proportions using a random effects meta-analysis with the Freeman-Tukey double arcsine transformation.

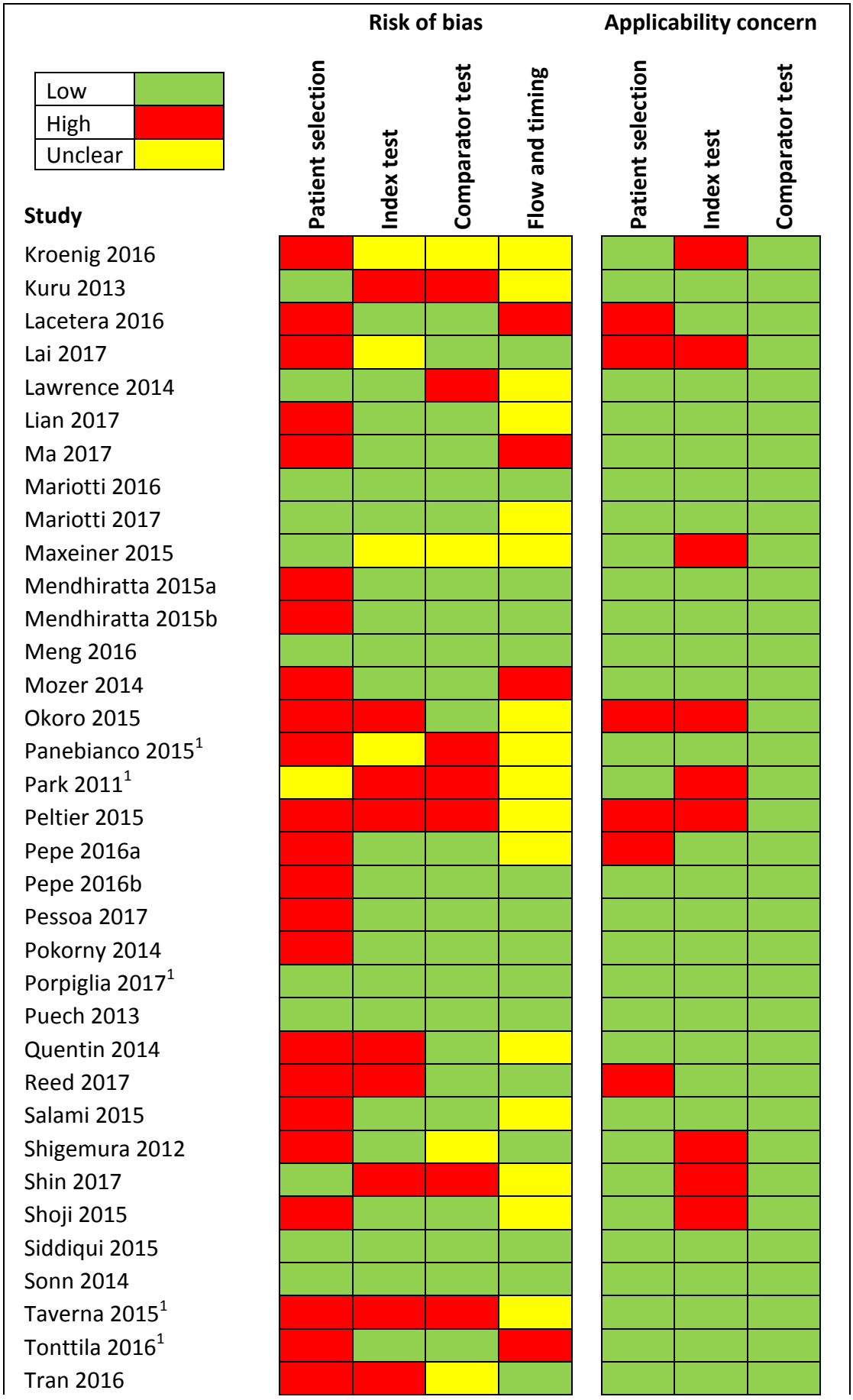
References

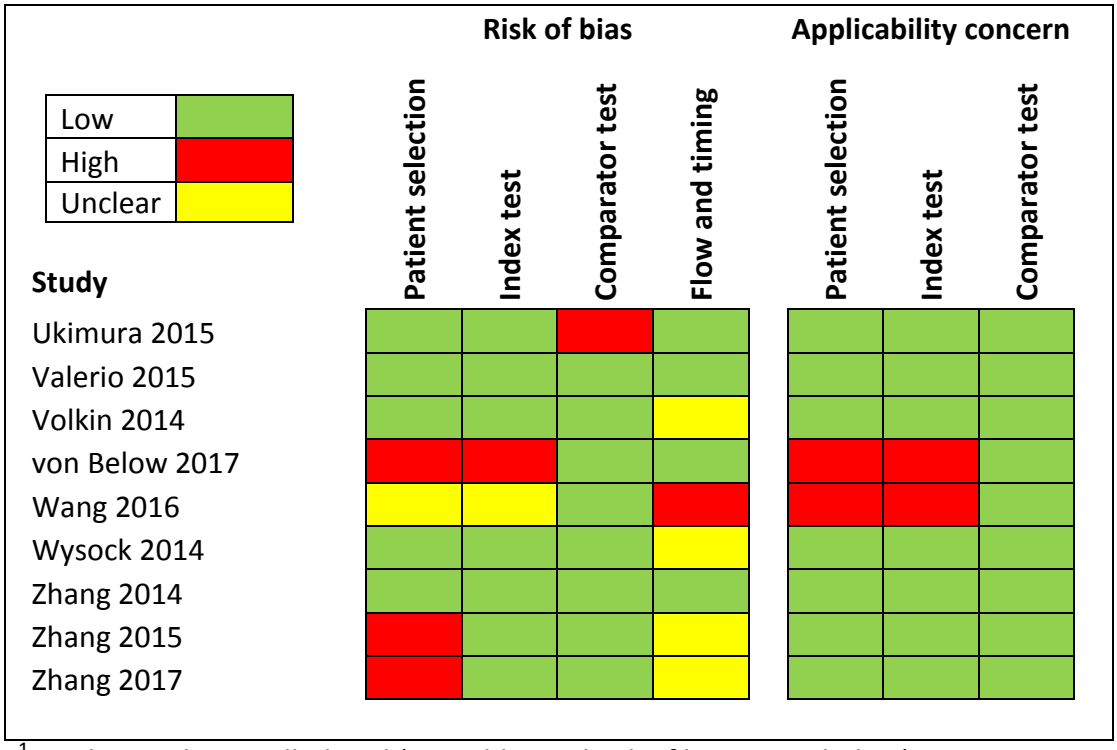
[1]DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177-88.

Supplementary Appendix 5

5a: Risk of bias assessment and applicability concern in included studies according to a modified Quality Assessment of Diagnostic Accuracy Studies-2 checklist:

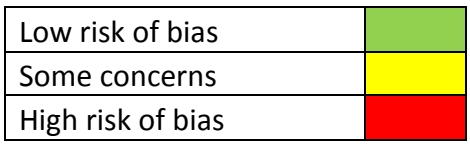


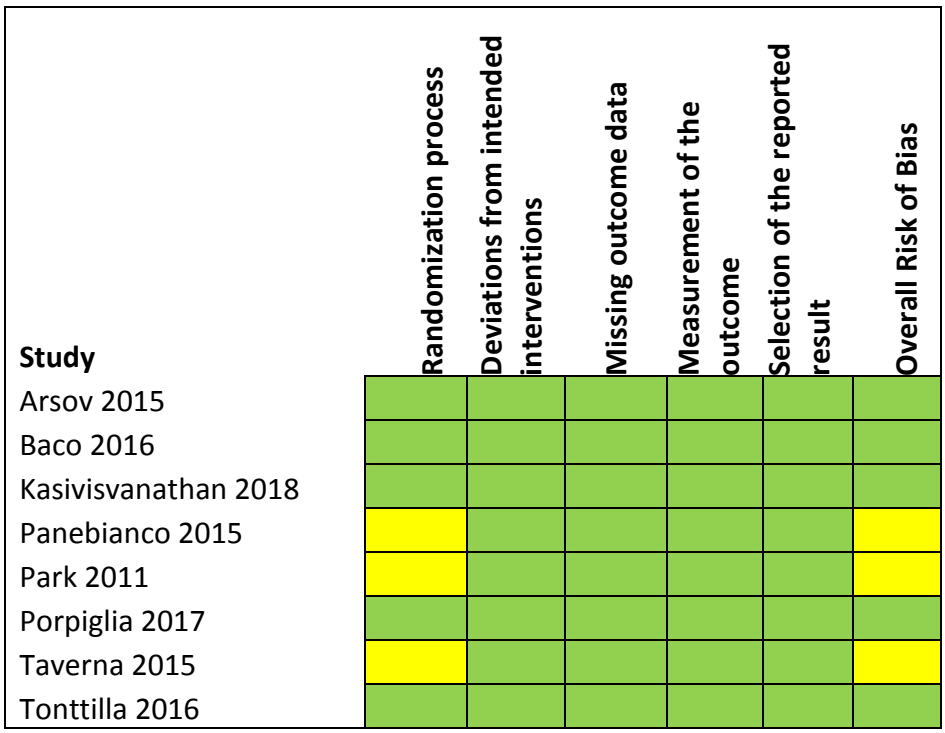

Risk of bias
Applicability concern
Low
High
Unclear
Patient selection
Index test
Comparator test
Flow and timing
Patient selection
Index test
Comparator test
Study
Kroenig 2016
Kuru 2013
Lacetera 2016
Lai 2017
Lawrence 2014
Lian 2017
Ma 2017
Mariotti 2016
Mariotti 2017
Maxeiner 2015
Mendhiratta 2015a
Mendhiratta 2015b
Meng 2016
Mozer 2014
Okoro 2015
Panebianco 2015[1]
Park 2011[1]
Peltier 2015
Pepe 2016a
Pepe 2016b
Pessoa 2017
Pokorny 2014
Porpiglia 2017[1]
Puech 2013
Quentin 2014
Reed 2017
Salami 2015
Shigemura 2012
Shin 2017
Shoji 2015
Siddiqui 2015
Sonn 2014
Taverna 2015[1]
Tonttila 2016[1]
Tran 2016



[1]Randomised controlled trial (see additional risk of bias items below)

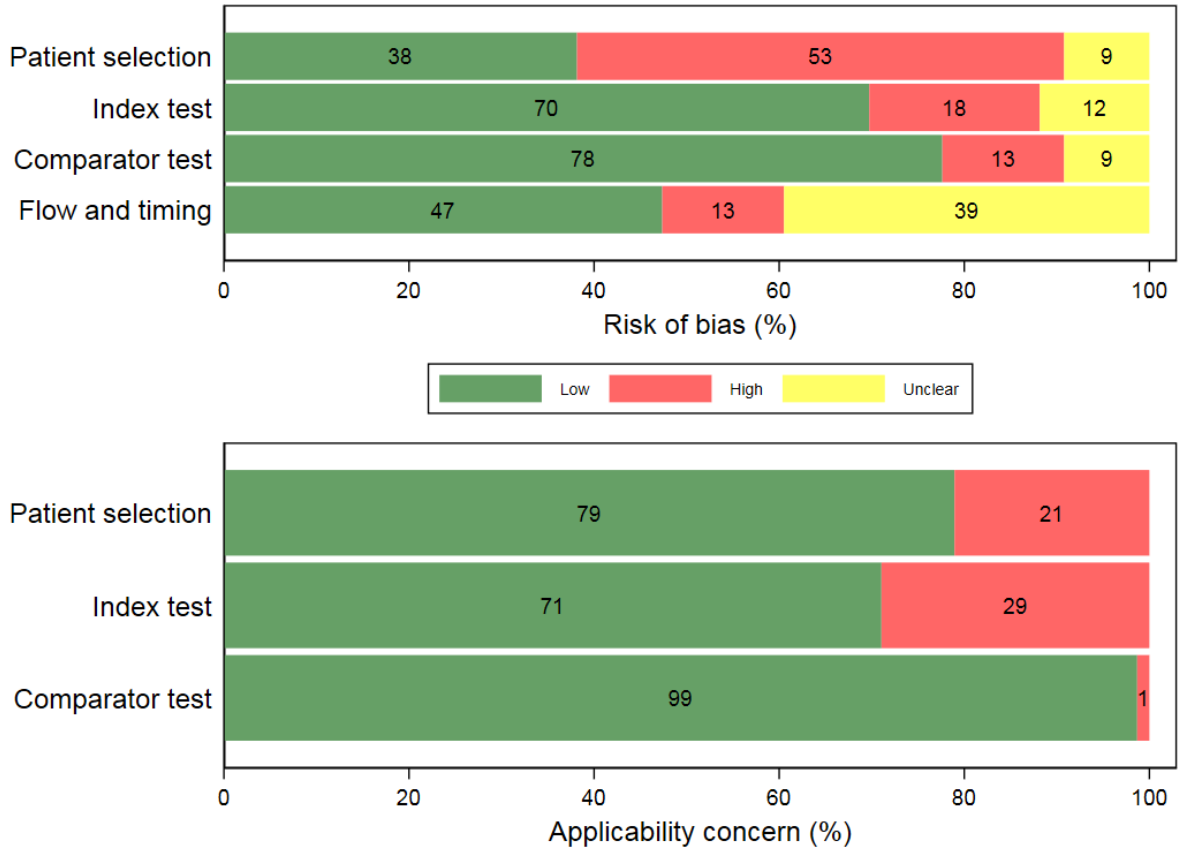
5b: Risk of bias for RCTS assessed by Cochrane risk of bias tool 2.0:





Supplementary Appendix 6

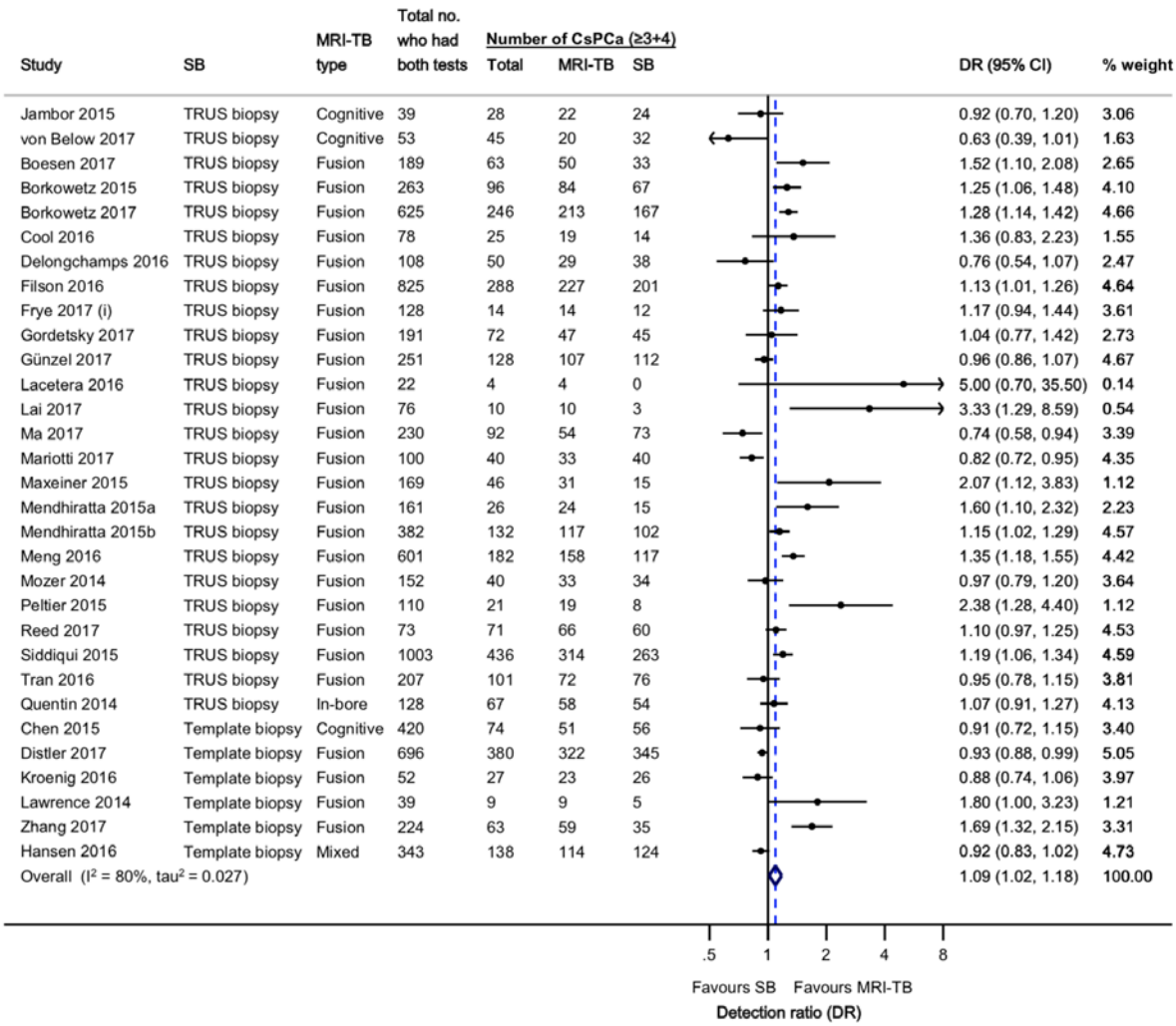
Overall summary of risk of bias and applicability concerns across studies based on a modified Quality Assessment of Diagnostic Accuracy Studies-2 checklist. The numbers shown on the bars are the percentages for each judgement.



Supplementary Appendix 7

Sensitivity analysis: forest plot of the detection ratio of MRI-targeted biopsy (MRI-TB) versus systematic biopsy (SB) for clinically significant cancer (CsPCa) using a Gleason 3+4 or greater threshold.

The forest plot shows 31 study cohorts. Studies are grouped by type of comparator and sorted according to type of MRI-TB, coil strength and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of non-overlapping cohorts in the same year. DR = detection ratio. TRUS = transrectal ultrasound guided prostate biopsy. Template = transperineal template prostate biopsy. Cognitive = cognitive / visual registration; fusion = MRI/US image fusion; In-bore = carried out in the MRI scanner; Mixed = more than one registration method used in the study. The pooled summary estimate indicated that MRI-TB detected more men with clinically significant cancer than systematic biopsy, DR 1.09 (95% CI 1.02-1.18), p = 0.018.

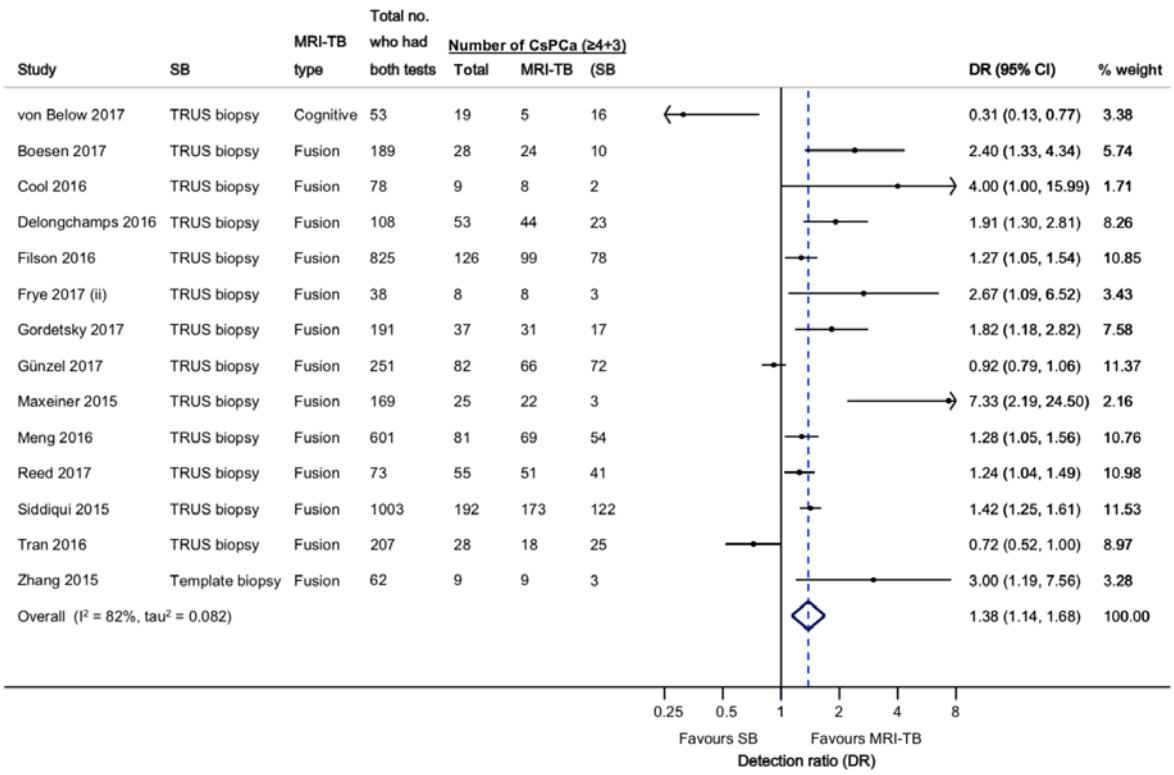


Study	SB	MRI-TB type	Total no. who had both tests	Number of CsPCa (≥3+4) Total	MRI-TB	SB	DR (95% CI)	% weight
Jambor 2015	TRUS biopsy	Cognitive	39	28	22	24	0.92 (0.70, 1.20)	3.06
von Below 2017	TRUS biopsy	Cognitive	53	45	20	32	0.63 (0.39, 1.01)	1.63
Boesen 2017	TRUS biopsy	Fusion	189	63	50	33	1.52 (1.10, 2.08)	2.65
Borkowetz 2015	TRUS biopsy	Fusion	263	96	84	67	1.25 (1.06, 1.48)	4.10
Borkowetz 2017	TRUS biopsy	Fusion	625	246	213	167	1.28 (1.14, 1.42)	4.66
Cool 2016	TRUS biopsy	Fusion	78	25	19	14	1.36 (0.83, 2.23)	1.55
Delongchamps 2016	TRUS biopsy	Fusion	108	50	29	38	0.76 (0.54, 1.07)	2.47
Filson 2016	TRUS biopsy	Fusion	825	288	227	201	1.13 (1.01, 1.26)	4.64
Frye 2017 (i)	TRUS biopsy	Fusion	128	14	14	12	1.17 (0.94, 1.44)	3.61
Gordetsky 2017	TRUS biopsy	Fusion	191	72	47	45	1.04 (0.77, 1.42)	2.73
Günzel 2017	TRUS biopsy	Fusion	251	128	107	112	0.96 (0.86, 1.07)	4.67
Lacetera 2016	TRUS biopsy	Fusion	22	4	4	0	5.00 (0.70, 35.50)	0.14
Lai 2017	TRUS biopsy	Fusion	76	10	10	3	3.33 (1.29, 8.59)	0.54
Ma 2017	TRUS biopsy	Fusion	230	92	54	73	0.74 (0.58, 0.94)	3.39
Mariotti 2017	TRUS biopsy	Fusion	100	40	33	40	0.82 (0.72, 0.95)	4.35
Maxeiner 2015	TRUS biopsy	Fusion	169	46	31	15	2.07 (1.12, 3.83)	1.12
Mendhiratta 2015a	TRUS biopsy	Fusion	161	26	24	15	1.60 (1.10, 2.32)	2.23
Mendhiratta 2015b	TRUS biopsy	Fusion	382	132	117	102	1.15 (1.02, 1.29)	4.57
Meng 2016	TRUS biopsy	Fusion	601	182	158	117	1.35 (1.18, 1.55)	4.42
Mozer 2014	TRUS biopsy	Fusion	152	40	33	34	0.97 (0.79, 1.20)	3.64
Peltier 2015	TRUS biopsy	Fusion	110	21	19	8	2.38 (1.28, 4.40)	1.12
Reed 2017	TRUS biopsy	Fusion	73	71	66	60	1.10 (0.97, 1.25)	4.53
Siddiqui 2015	TRUS biopsy	Fusion	1003	436	314	263	1.19 (1.06, 1.34)	4.59
Tran 2016	TRUS biopsy	Fusion	207	101	72	76	0.95 (0.78, 1.15)	3.81
Quentin 2014	TRUS biopsy	In-bore	128	67	58	54	1.07 (0.91, 1.27)	4.13
Chen 2015	Template biopsy	Cognitive	420	74	51	56	0.91 (0.72, 1.15)	3.40
Distler 2017	Template biopsy	Fusion	696	380	322	345	0.93 (0.88, 0.99)	5.05
Kroenig 2016	Template biopsy	Fusion	52	27	23	26	0.88 (0.74, 1.06)	3.97
Lawrence 2014	Template biopsy	Fusion	39	9	9	5	1.80 (1.00, 3.23)	1.21
Zhang 2017	Template biopsy	Fusion	224	63	59	35	1.69 (1.32, 2.15)	3.31
Hansen 2016	Template biopsy	Mixed	343	138	114	124	0.92 (0.83, 1.02)	4.73
Overall (I^2 = 80%, tau^2 = 0.027)							1.09 (1.02, 1.18)	100.00

Supplementary Appendix 8

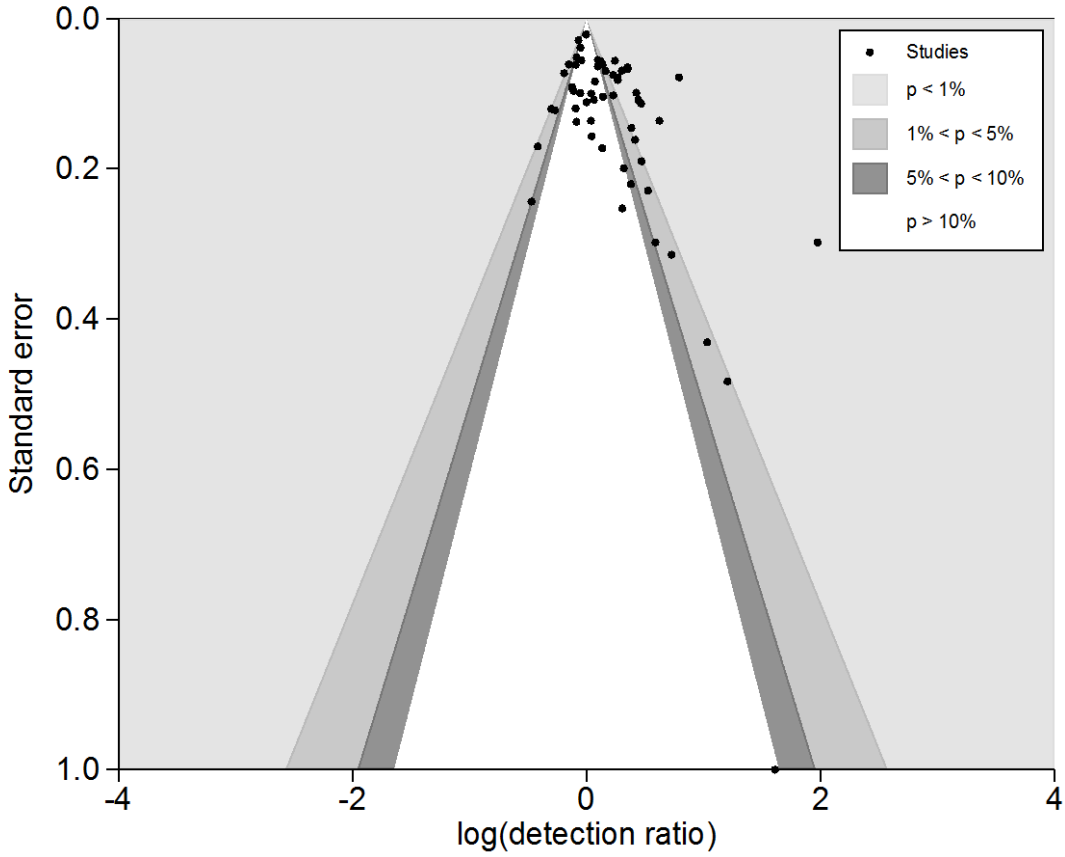
Sensitivity analysis: forest plot of the detection ratio of MRI-targeted biopsy (MRI-TB) versus systematic biopsy (SB) for clinically significant cancer (CsPCa) using a Gleason 4+3 or greater threshold.

The forest plot shows 14 study cohorts. Studies are grouped by type of comparator and sorted according to type of MRI-TB, coil strength and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of non-overlapping cohorts in the same year. DR = detection ratio. TRUS = transrectal ultrasound guided prostate biopsy. Template = transperineal template prostate biopsy. Cognitive = cognitive / visual registration; fusion = MRI/US image fusion; In-bore = carried out in the MRI scanner; Mixed = more than one registration method used in the study. The pooled summary estimate indicated that MRI-TB detected more men with clinically significant cancer than systematic biopsy, DR 1.38 (95% CI 1.14-1.68), p = 0.001.



Supplementary Appendix 9

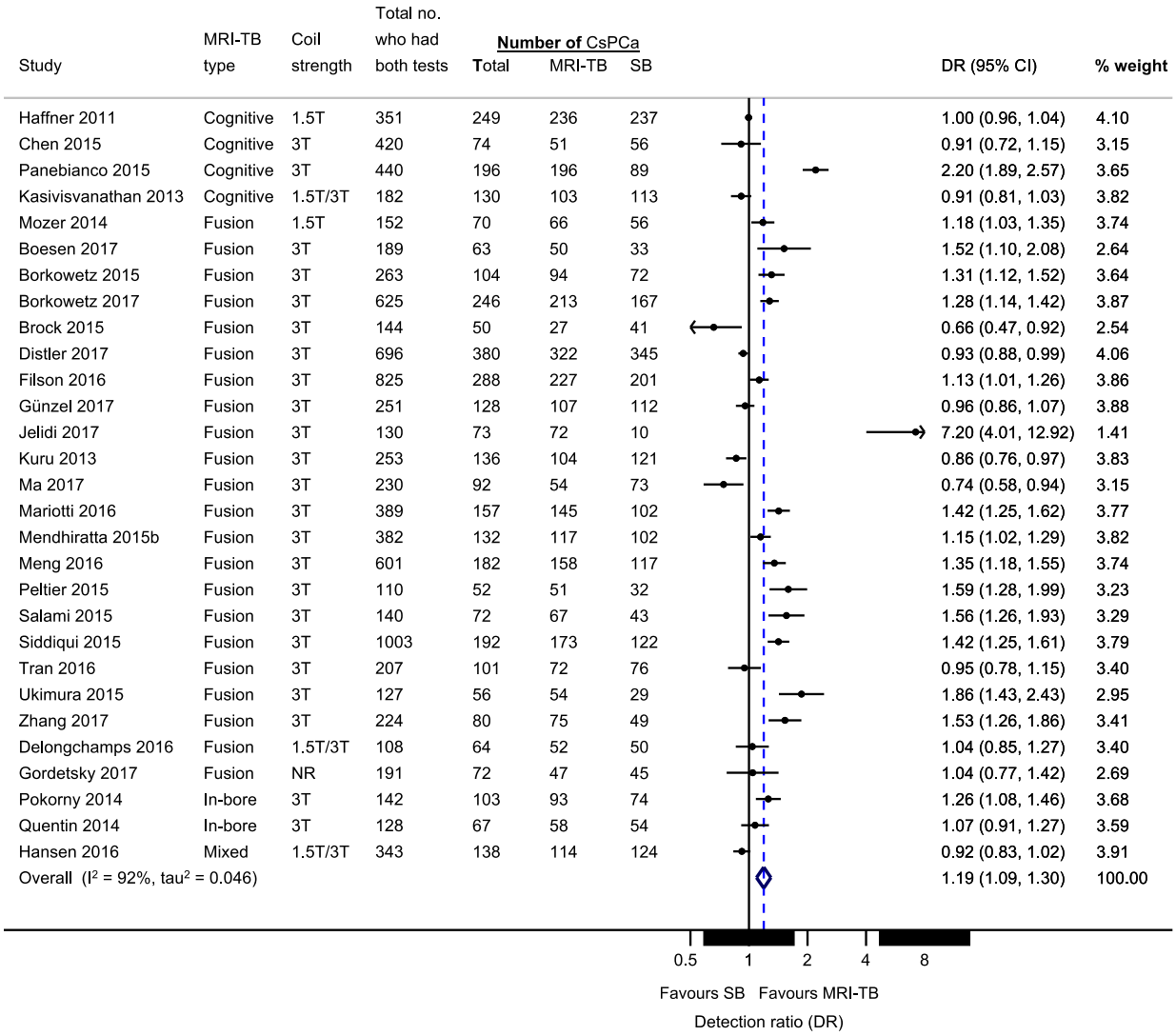
Contour enhanced funnel plot for assessment of publication bias and small study effects based on meta-analysis of detection ratios for clinically significant cancer.
The contour lines indicate levels of statistical significance corresponding to p <0.01, p <0.05 and p <0.10. As indicated by the key on the plot, the regions bounded by these lines indicate areas of statistical significance (p < 1% and 1% < p < 5%) or non-significance (5% < p < 10% and p > 10%). There was indication of funnel plot asymmetry though many studies differing in precision are in the regions of statistical non-significance. Therefore, publication bias or small study effects may be absent. A sensitivity analysis showed that exclusion of smaller studies did not change the conclusions of the main analysis. Asymmetry may be due to other factors such as heterogeneity.



Supplementary Appendix 10

Sensitivity analysis: forest plot of the detection ratio of MRI-targeted biopsy (MRI-TB) versus systematic biopsy (SB) for clinically significant cancer (CsPCa) for studies with greater than 100 patients and 50 cancer cases diagnosed.

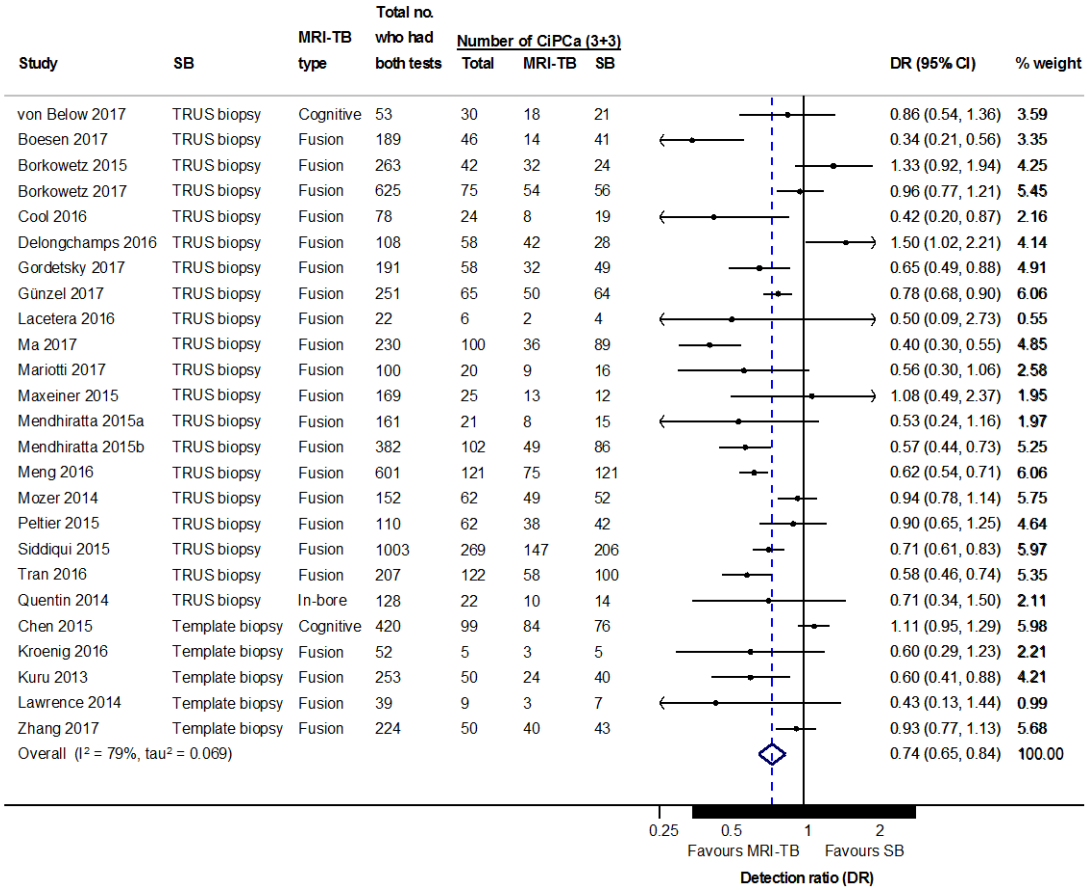
The forest plot shows 30 study cohorts. Studies are grouped by type of MRI-TB, coil strength and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of non-overlapping cohorts in the same year. DR = detection ratio. Cognitive = cognitive / visual registration; fusion = MRI/US image fusion; In-bore = carried out in the MRI scanner; Mixed = more than one registration method used in the study. The pooled summary estimate indicates that MRI-TB detects more clinically significant cancer than systematic biopsy, DR 1.19 (95% CI 1.09-1.30), p < 0.0001.



Supplementary Appendix 11

Sensitivity analysis: forest plot of the detection ratio of MRI-targeted biopsy (MRI-TB) versus systematic biopsy (SB) for clinically insignificant cancer (CiPCa) using a Gleason 3+3 definition.

The forest plot shows 25 study cohorts. Studies are grouped by type of SB, type of MRI-TB, coil strength and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of non-overlapping cohorts in the same year. DR = detection ratio. Cognitive = cognitive / visual registration; fusion = MRI/US image fusion; In-bore = carried out in the MRI scanner; Mixed = more than one registration method used in the study. The pooled summary estimate indicates that MRI-TB detected fewer men with clinically insignificant cancer than systematic biopsy (DR 0.74 (95% CI 0.65-0.84), p < 0.0001

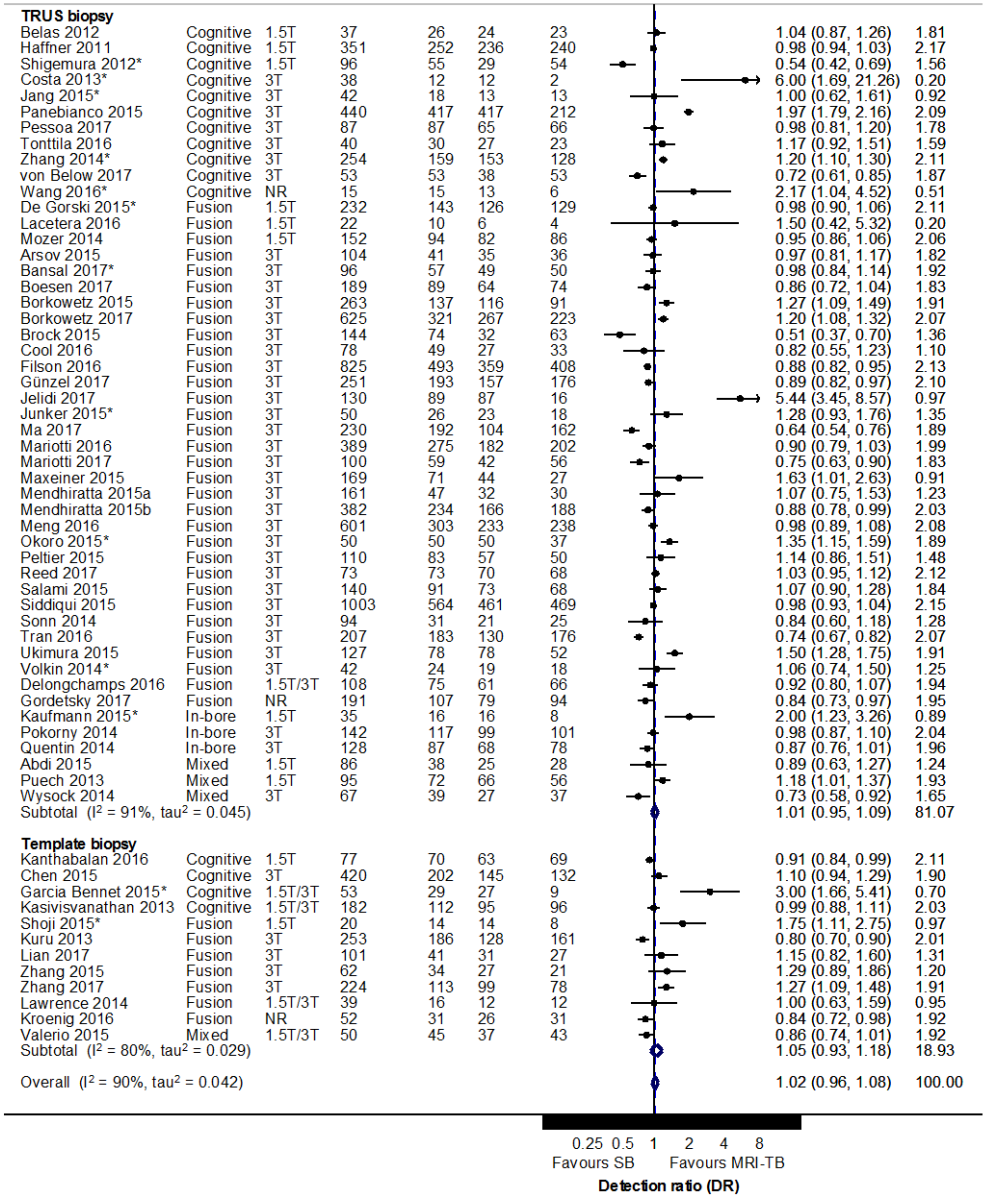


Supplementary Appendix 12

Forest plot of the detection ratio of MRI-targeted biopsy (MRI-TB) versus systematic biopsy (SB) for any cancer (PCa).

The forest plot shows 61 study cohorts. Studies are grouped by type of comparator and sorted according to type of MRI-TB, coil strength and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of non-overlapping cohorts in the same year. DR = detection ratio. TRUS = transrectal ultrasound guided prostate biopsy. Template = transperineal template prostate biopsy. Cognitive = cognitive / visual registration; fusion = MRI/US image fusion; In-bore = carried out in the MRI scanner; Mixed = more than one registration method used in the study. The pooled summary estimate indicated no difference in any cancer detection between MRI-TB and systematic biopsy, DR 1.02 (95% CI 0.96-1.08), p = 0.49.

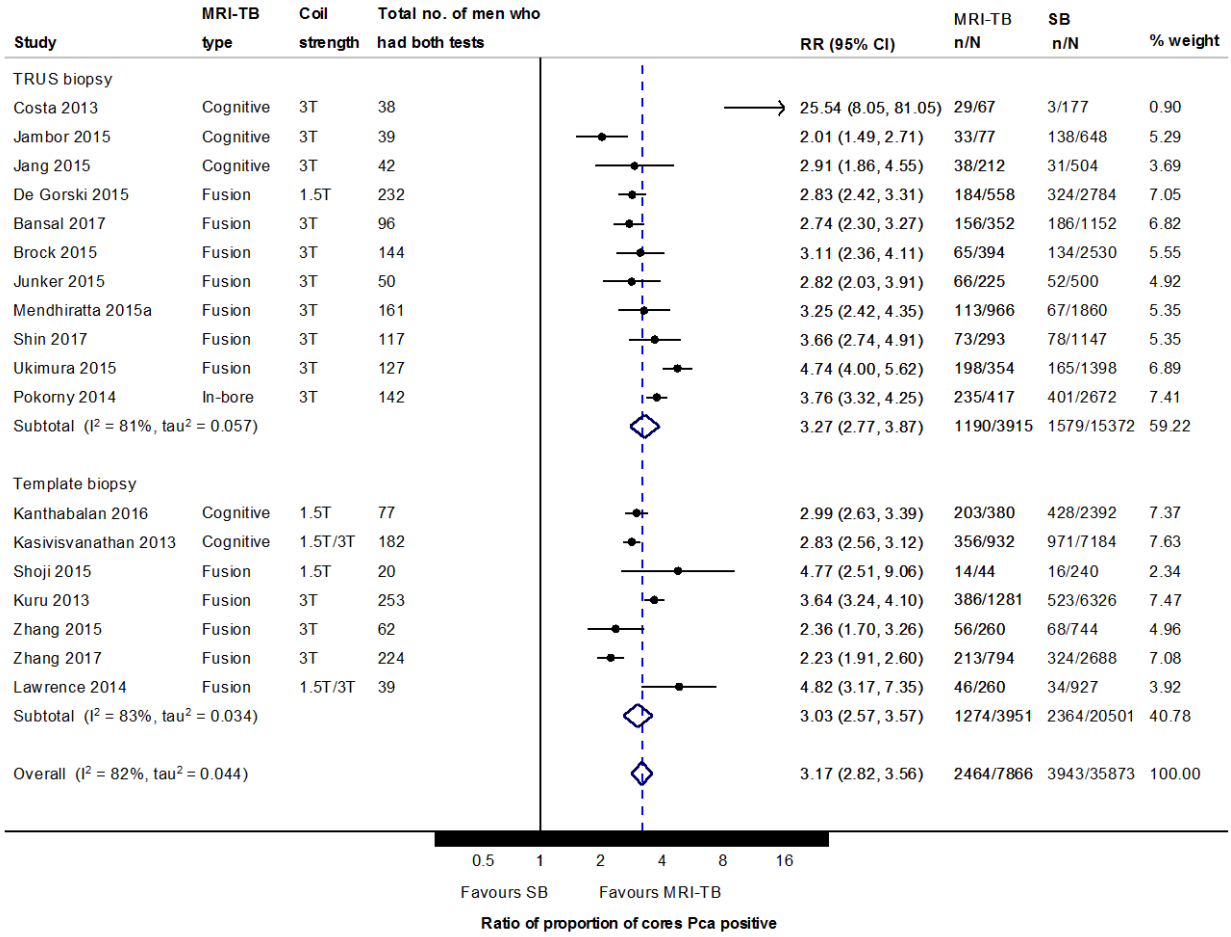
Study	MRI-TB type	Coil strength	Total no. who had both tests	Number of any PCa Total	MRI-TB	SB	DR (95% CI)	% weight
TRUS biopsy								
Belas 2012	Cognitive	1.5T	37	26	24	23	1.04 (0.87, 1.26)	1.81
Haffner 2011	Cognitive	1.5T	351	252	236	240	0.98 (0.94, 1.03)	2.17
Shigemura 2012*	Cognitive	1.5T	96	55	29	54	0.54 (0.42, 0.69)	1.56
Costa 2013*	Cognitive	3T	38	12	12	2	6.00 (1.69, 21.26)	0.20
Jang 2015*	Cognitive	3T	42	18	13	13	1.00 (0.62, 1.61)	0.92
Panebianco 2015	Cognitive	3T	440	417	417	212	1.97 (1.79, 2.16)	2.09
Pessoa 2017	Cognitive	3T	87	87	65	66	0.98 (0.81, 1.20)	1.78
Tonttila 2016	Cognitive	3T	40	30	27	23	1.17 (0.92, 1.51)	1.59
Zhang 2014*	Cognitive	3T	254	159	153	128	1.20 (1.10, 1.30)	2.11
von Below 2017	Cognitive	3T	53	53	38	53	0.72 (0.61, 0.85)	1.87
Wang 2016*	Cognitive	NR	15	15	13	6	2.17 (1.04, 4.52)	0.51
De Gorski 2015*	Fusion	1.5T	232	143	126	129	0.98 (0.90, 1.06)	2.11
Lacetera 2016	Fusion	1.5T	22	10	6	4	1.50 (0.42, 5.32)	0.20
Mozer 2014	Fusion	1.5T	152	94	82	86	0.95 (0.86, 1.06)	2.06
Arsov 2015	Fusion	3T	104	41	35	36	0.97 (0.81, 1.17)	1.82
Bansal 2017*	Fusion	3T	96	57	49	50	0.98 (0.84, 1.14)	1.92
Boesen 2017	Fusion	3T	189	89	64	74	0.86 (0.72, 1.04)	1.83
Borkowetz 2015	Fusion	3T	263	137	116	91	1.27 (1.09, 1.49)	1.91
Borkowetz 2017	Fusion	3T	625	321	267	223	1.20 (1.08, 1.32)	2.07
Brock 2015	Fusion	3T	144	74	32	63	0.51 (0.37, 0.70)	1.36
Cool 2016	Fusion	3T	78	49	27	33	0.82 (0.55, 1.23)	1.10
Filson 2016	Fusion	3T	825	493	359	408	0.88 (0.82, 0.95)	2.13
Günzel 2017	Fusion	3T	251	193	157	176	0.89 (0.82, 0.97)	2.10
Jelidi 2017	Fusion	3T	130	89	87	16	5.44 (3.45, 8.57)	0.97
Junker 2015*	Fusion	3T	50	26	23	18	1.28 (0.93, 1.76)	1.35
Ma 2017	Fusion	3T	230	192	104	162	0.64 (0.54, 0.76)	1.89
Mariotti 2016	Fusion	3T	389	275	182	202	0.90 (0.79, 1.03)	1.99
Mariotti 2017	Fusion	3T	100	59	42	56	0.75 (0.63, 0.90)	1.83
Maxeiner 2015	Fusion	3T	169	71	44	27	1.63 (1.01, 2.63)	0.91
Mendhiratta 2015a	Fusion	3T	161	47	32	30	1.07 (0.75, 1.53)	1.23
Mendhiratta 2015b	Fusion	3T	382	234	166	188	0.88 (0.78, 0.99)	2.03
Meng 2016	Fusion	3T	601	303	233	238	0.98 (0.89, 1.08)	2.08
Okoro 2015*	Fusion	3T	50	50	50	37	1.35 (1.15, 1.59)	1.89
Peltier 2015	Fusion	3T	110	83	57	50	1.14 (0.86, 1.51)	1.48
Reed 2017	Fusion	3T	73	73	70	68	1.03 (0.95, 1.12)	2.12
Salami 2015	Fusion	3T	140	91	73	68	1.07 (0.90, 1.28)	1.84
Siddiqui 2015	Fusion	3T	1003	564	461	469	0.98 (0.93, 1.04)	2.15
Sonn 2014	Fusion	3T	94	31	21	25	0.84 (0.60, 1.18)	1.28
Tran 2016	Fusion	3T	207	183	130	176	0.74 (0.67, 0.82)	2.07
Ukimura 2015	Fusion	3T	127	78	78	52	1.50 (1.28, 1.75)	1.91
Volkin 2014*	Fusion	3T	42	24	19	18	1.06 (0.74, 1.50)	1.25
Delongchamps 2016	Fusion	1.5T/3T	108	75	61	66	0.92 (0.80, 1.07)	1.94
Gordetsky 2017	Fusion	NR	191	107	79	94	0.84 (0.73, 0.97)	1.95
Kaufmann 2015*	In-bore	1.5T	35	16	16	8	2.00 (1.23, 3.26)	0.89
Pokorny 2014	In-bore	3T	142	117	99	101	0.98 (0.87, 1.10)	2.04
Quentin 2014	In-bore	3T	128	87	68	78	0.87 (0.76, 1.01)	1.96
Abdi 2015	Mixed	1.5T	86	38	25	28	0.89 (0.63, 1.27)	1.24
Puech 2013	Mixed	1.5T	95	72	66	56	1.18 (1.01, 1.37)	1.93
Wysock 2014	Mixed	3T	67	39	27	37	0.73 (0.58, 0.92)	1.65
Subtotal (I^2 = 91%, tau^2 = 0.045)							1.01 (0.95, 1.09)	81.07
Template biopsy								
Kanthabalan 2016	Cognitive	1.5T	77	70	63	69	0.91 (0.84, 0.99)	2.11
Chen 2015	Cognitive	3T	420	202	145	132	1.10 (0.94, 1.29)	1.90
Garcia Bennet 2015*	Cognitive	1.5T/3T	53	29	27	9	3.00 (1.66, 5.41)	0.70
Kasivisvanathan 2013	Cognitive	1.5T/3T	182	112	95	96	0.99 (0.88, 1.11)	2.03
Shoji 2015*	Fusion	1.5T	20	14	14	8	1.75 (1.11, 2.75)	0.97
Kuru 2013	Fusion	3T	253	186	128	161	0.80 (0.70, 0.90)	2.01
Lian 2017	Fusion	3T	101	41	31	27	1.15 (0.82, 1.60)	1.31
Zhang 2015	Fusion	3T	62	34	27	21	1.29 (0.89, 1.86)	1.20
Zhang 2017	Fusion	3T	224	113	99	78	1.27 (1.09, 1.48)	1.91
Lawrence 2014	Fusion	1.5T/3T	39	16	12	12	1.00 (0.63, 1.59)	0.95
Kroenig 2016	Fusion	NR	52	31	26	31	0.84 (0.72, 0.98)	1.92
Valerio 2015	Mixed	1.5T/3T	50	45	37	43	0.86 (0.74, 1.01)	1.92
Subtotal (I^2 = 80%, tau^2 = 0.029)							1.05 (0.93, 1.18)	18.93
Overall (I^2 = 90%, tau^2 = 0.042)							1.02 (0.96, 1.08)	100.00



Supplementary Appendix 13

Forest plot of the proportion of cores positive for prostate cancer taken by MRI-targeted biopsy compared to systematic biopsy.

The forest plot shows 18 study cohorts. Studies are grouped by type of comparator and sorted according to type of MRI-TB, coil strength and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of non-overlapping cohorts in the same year. RR = relative risk. TRUS = transrectal ultrasound guided prostate biopsy. Template = transperineal template prostate biopsy. Cognitive = cognitive / visual registration; fusion = MRI/US image fusion; In-bore = carried out in the MRI scanner; The pooled summary estimate indicated a greater proportion of cores positive for cancer for MRI-TB than systematic biopsy, RR 3.17 (95% CI 2.82-3.56), p = <0.0001.



Supplementary Appendix 14

Forest plot of the proportion of men with clinically significant cancer (csPCa) missed by MRI-TB but detected by the addition of systematic biopsy.

The forest plot shows 56 study cohorts. Studies are grouped by type of comparator and sorted according to type of MRI TB and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of non-overlapping cohorts in the same year. TRUS = transrectal ultrasound guided prostate biopsy. Template = transperineal template prostate biopsy. Cognitive = cognitive / visual registration; fusion = MRI/US image fusion; In-bore = carried out in the MRI scanner; Mixed = more than one registration method used in the study. The pooled summary estimate indicated that the proportion of men with clinically significant prostate cancer missed by MRI-TB but detected by the addition of systematic biopsy was 0.13 [95% CI 0.10-0.16], p < 0.0001.