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Magnetic Resonance Imaging-targeted Biopsy Versus Systematic Biopsy in the Detection of Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: Magnetic resonance imaging (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 with those by 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 randomised 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 eight RCTs, comprising a total of 14 709 men who either received both MRI-TB and systematic biopsy, or were randomised to receive one of the tests. MRI-TB detected more men with clinically significant cancer than systematic biopsy (detection ratio [DR] 1.16 [95% confidence interval {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 for 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 magnetic resonance imaging were better at detecting prostate cancer that needs to be treated and avoiding the diagnosis of disease that does not need treatment than the traditional systematic biopsy.

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1. Introduction

Multiparametric magnetic resonance imaging (mpMRI) has an increasingly important role in the diagnosis of prostate cancer [1–3]. 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 (TRUS)-guided prostate biopsy, in men with raised prostate-specific antigen (PSA), has been challenged by evidence from systematic reviews and randomised controlled trials (RCTs). There is support for an alternative pathway where men with suspicious MRI undergo biopsy of only 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 and 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-TB 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 (TPM) biopsy is becoming an increasingly used systematic biopsy technique. A comparison of MRI-TB with 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]. This 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 material, Appendix 1). We searched from inception of the databases up to 28 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 8 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 the basis of language. When multiple publications including overlapping cohorts were reported, only the most recent cohort or that which was most relevant 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 each abstract were screened independently by two reviewers from a team of 10 (V.K., A.S., J.N., F.G., M.V., Y.S., K.C., D.S., Y.P., and D.T.). Reviewers were selected from the British Urology Researchers in Surgical Training (BURST) Research collaborative [17] on the basis of expertise in MRI-TB 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]; a list of items collected is given in the Supplementary material (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 (either V.K. or J.N.).

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 material, 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 (either V.K. or J.N.).

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 of >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 DRs using the DerSimonian and Laird random-effect approach [18]. Further details on data synthesis techniques are given in the Supplementary material (Appendix 4).

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

1. Significant cancer detection rates defined as any prostate cancer with Gleason grade 3 + 4 or greater
2. Significant cancer detection rates defined as any prostate cancer with Gleason grade 4 + 3 or greater
3. 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 the assessment of publication bias and small study effects, log-transformed values of the DRs were plotted against their standard error in a contour-enhanced funnel plot.

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

1. Systematic biopsy type (TRUS or TPM biopsy)
2. Prior biopsy status (biopsy naïve, prior prostate biopsy negative for cancer, and prior biopsy positive for cancer)
3. Type of MRI-TB (cognitive registration/visual registration, software-assisted registration/fusion software, and in-bore biopsy)

We performed univariable metaregression analyses using random-effect models to statistically assess differences in DRs between subgroups.

We assessed three additional outcomes:

1. Proportion of cores positive for prostate cancer by MRI-TB compared with systematic biopsy
2. Proportion of men having MRI-TB and systematic biopsy, who had cancer upgraded or downgraded on subsequent radical prostatectomy
3. 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

Fig. 1 shows the flow of studies through the screening process. Of 7398 studies included in the screening phase, 76 were considered eligible for inclusion, of which 68 were studies with a paired design and eight were RCTs, including a total of 14 709 men who either received both MRI-TB and systematic biopsy, or were randomised to receive only one of the tests. Study characteristics for paired studies are given in Table 1 [5,19–89] and for the RCTs in Table 2 [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 the Supplementary material (Appendixes 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. The Supplementary material (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 five of the eight studies rated as having a low risk of bias across all domains and none of the studies having a domain at a high risk of bias.

3.3. Studies with paired data

3.3.1. Clinically significant cancer detection

A total of 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 1. MRI-TB detected more men with clinically significant cancer than systematic biopsy (DR 1.16 [95% confidence interval {CI} 1.09–1.24], $p < 0.0001$; Fig. 2). This effect was also evident in sensitivity analyses where the definition of clinically significant cancer was Gleason 3

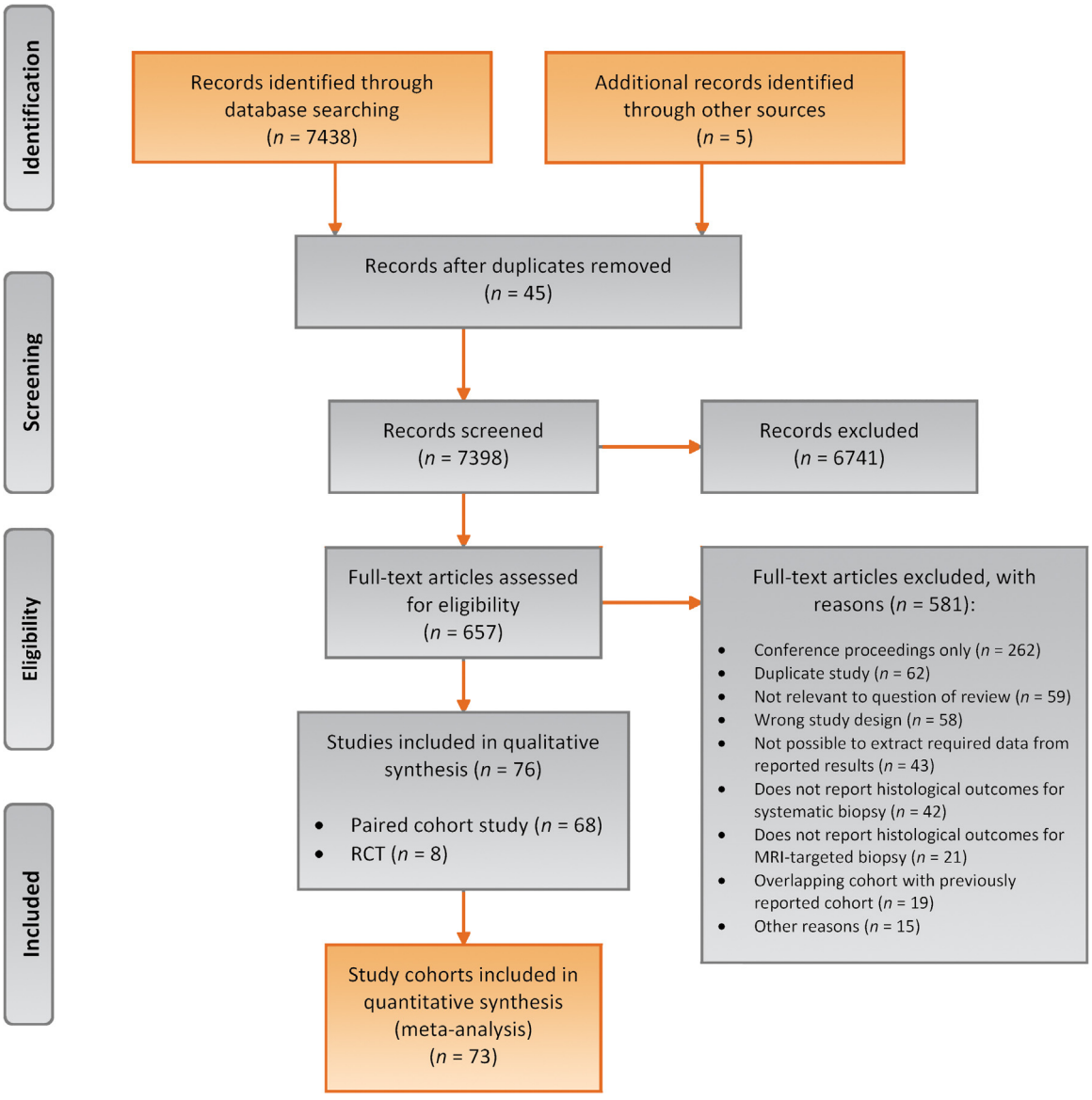

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart. MRI = magnetic resonance imaging; RCT = randomised controlled trial.

+4 or greater (DR 1.09 [95% CI 1.02–1.18], $p = 0.018$; Supplementary material, 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 material, Appendix 8). Publication bias was assessed by visual inspection of a contour-enhanced funnel plot (Supplementary material, Appendix 9). There was an indication of funnel plot asymmetry, though many studies differing in precision were in the regions of statistical nonsignificance ($5\% < p < 10\%$ and $p > 10\%$). Therefore, publication bias or small study effects may be absent. A subsequent sensitivity analysis that included only studies with >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 material, Appendix 10).

There was some evidence in the metaregression 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 3.

3.3.2. *Clinically insignificant cancer detection*

A total of 46 study cohorts including 2124 patients were included in the analysis. MRI-TB detected fewer men with

Table 1 – Characteristics of included studies with paired data

Author [Ref.]	Year	Population	No. of patients	Median age (yr)	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[a] [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[a] [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 ≥0.5 ml 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 [b])	TRUS-Bx (12)	GS >6 or 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 [b])	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 [c])	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 [c])	TRUS-Bx (12)	At least 1 core with a GS of 7 (3 + 4) or 6 with an MCCL of ≥4 mm
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 6 and MCCL ≥5 mm

Table 1 (*Continued*)

Author [Ref.]	Year	Population	No. of patients	Median age (yr)	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
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[d] [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 [b])	TRUS-Bx (12)	NR
Gunzel 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 nonsuspicious (no scoring system)	Visual-TBx (3.8 [b])	TRUS-Bx (10)	Any MRI lesions biopsied that were positive for cancer irrespective of Gleason score or any other biopsy with >5 mm 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 [c])	TRUS-Bx (12)	3 mm 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 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 [c])	TRUS-Bx (16)	GS >7 or 6 with a CCL of >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 [b])	TRUS-Bx (10)	NR
Kanthabalan et al [47]	2016	Prior biopsy positive	77	70.5	14	NR	77	1.5 T	T2, DWI, DCE	No	Likert ≥3	Visual-TBx (4.9 [b])	Transperineal template-Bx (31)	GS ≥3 + 4 and/or MCCL ≥4 mm

Table 1 (*Continued*)

Author [Ref.]	Year	Population	No. of patients	Median age (yr)	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
Kasivisvanathan et al [48]	2013	Biopsy naïve + prior negative biopsy + prior positive biopsy	182	63.3	6.7	40.6	182	1.5 T/3	T2, DWI, DCE	No	Likert ≥3	Visual-TBx (5)	Transperineal template-Bx (30)	GS ≥3 + 4 and/or 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 [c])	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 [b])	Transperineal template-Bx (32)	GS ≥7
Kuru et al [51]	2013	Prior negative biopsy	347	65.3	9.85	48.7	253	3	T2, DWI, DCE, MRSI	No	Suspicious vs nonsuspicious (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 [b])	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 [b])	Transperineal template-Bx (12)	GS ≥7 or 6 with MCCL ≥4 mm
Ma et al[d] [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% of any core positive for cancer or ≥33% of standard biopsy cores positive for cancer or GS ≥4 + 3 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 [c])	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 [b])	TRUS-Bx (10)	Gleason ≥4 + 3
Mendhiratta et al [60]	2015	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]	2015	Biopsy naïve	382	64.5	6.8	44	382	3	T2, DWI, DCE	No	Likert ≥2	Fusion-TBx (5.7 [b])	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

Table 1 (*Continued*)

Author [Ref.]	Year	Population	No. of patients	Median age (yr)	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
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 GS of 3 + 4 or 6 with MCCL ≥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[a] [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 [b])	TRUS-Bx (14.6)	GS ≥7 and/or MCCL ≥6 mm
Pepe et al [66]	2016	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]	2016	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 [c])	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)	(1) GS 3 + 3 in >2 cores or (2) GS 3 + 3 >6 mm in 1 core or (3) GS 3 + 4 >4 mm in ≥1 core or (4) 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 [b])	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 3 + 3, MCCL 50% or >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 nonsuspicious	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 ≥4 mm)

Table 1 (*Continued*)

Author [Ref.]	Year	Population	No. of patients	Median age (yr)	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
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 [b])	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 6 with MCCL ≥4 mm
Tonttila et al[a] [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 [b])	TRUS-Bx (11)	GS ≥7 and/or MCCL ≥5 mm
Valerio et al [82]	2015	Biopsy naïve + prior negative biopsy + prior positive biopsy	50	68	7.9	38	50	1.5/3	T2, DWI, DCE	No	Likert ≥3	Fusion-TBx (3)	Transperineal template-Bx (32)	GS ≥3 + 4 and/or MCCL ≥4 mm
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 nonsuspicious	Fusion-TBx (NR)	TRUS-Bx (12)	NR
Zhang et al [88]	2015	Biopsy naïve	224	69	10.05	45.5	224	3	T2, DWI, DCE	No	Likert ≥2	Fusion-TBx (3.54 [b])	Transperineal-Bx (12)	GS >6 or 6 with 50% involvement of PCa per core
Zhang et al [89]	2017	Biopsy naïve	62	68.38	10.21	34.05	62	3	T2, DWI, DCE	No	PI-RADS ≥2	Fusion-TBx (3.24 [b])	Transperineal-Bx (12)	GS of 7 (or more) or 6 with MCCL >4 mm

Bx = biopsy; CCL = cancer core length; DCE = dynamic contrast enhanced; DWI = diffusion-weighed imaging; GS = Gleason score; MCCL = maximum cancer core length; MRI = magnetic resonance imaging; MRSI = magnetic resonance spectroscopic imaging; NA = not available; NR = not reported; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; PSA = prostate-specific antigen; TBx = MRI-targeted prostate biopsy; TRUS = transrectal ultrasound.

[a] Represents paired data from an arm of a randomised controlled trial.

[b] Mean.

[c] Range.

[d] Represents a combination of cohorts by the same author.

Table 2 – Characteristics of randomised controlled trials

Author [Ref.]	Year	Population investigated	No. 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	1. No significant differences between combined biopsy approach and in-bore TBx alone Only difference is 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 T	PI-RADS ≥3	GS = 6 and MCCL ≥5 or GS ≥7	1. Overall csPCa detection rate was similar between the two groups 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 T/3T	PI-RADS ≥3	GS ≥3 + 4	The proportion of men with clinically significant cancer in the MRI arm was greater than in the TRUS-Bx arm, and the proportion of men with clinically insignificant cancer was less in the MRI arm than in the 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 3 T	PI-RADS ≥2	GS ≥3 + 4	The proportion of men with csPCa is higher among those randomised to MRI-TBx vs those randomised 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 significantly 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 T	PI-RADS ≥3	GS ≥7 or MCCL ≥5 mm	A diagnostic pathway based on MRI had higher detection rate of both PCa and csPCa compared with 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) 3 T	"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

Bx = biopsy; csPCa = clinically significant prostate cancer; DCE = dynamic contrast enhanced; DWI = diffusion-weighed imaging; GS =s Gleason score; MCCL = maximum score length; MRI = magnetic resonance imaging; NR = not reported; PCa = prostate cancer; PI-RADS = Prostate Imaging Reporting and Data System; TBx = targeted biopsy; TRUS = transrectal ultrasound; TUR = transurethral resection.

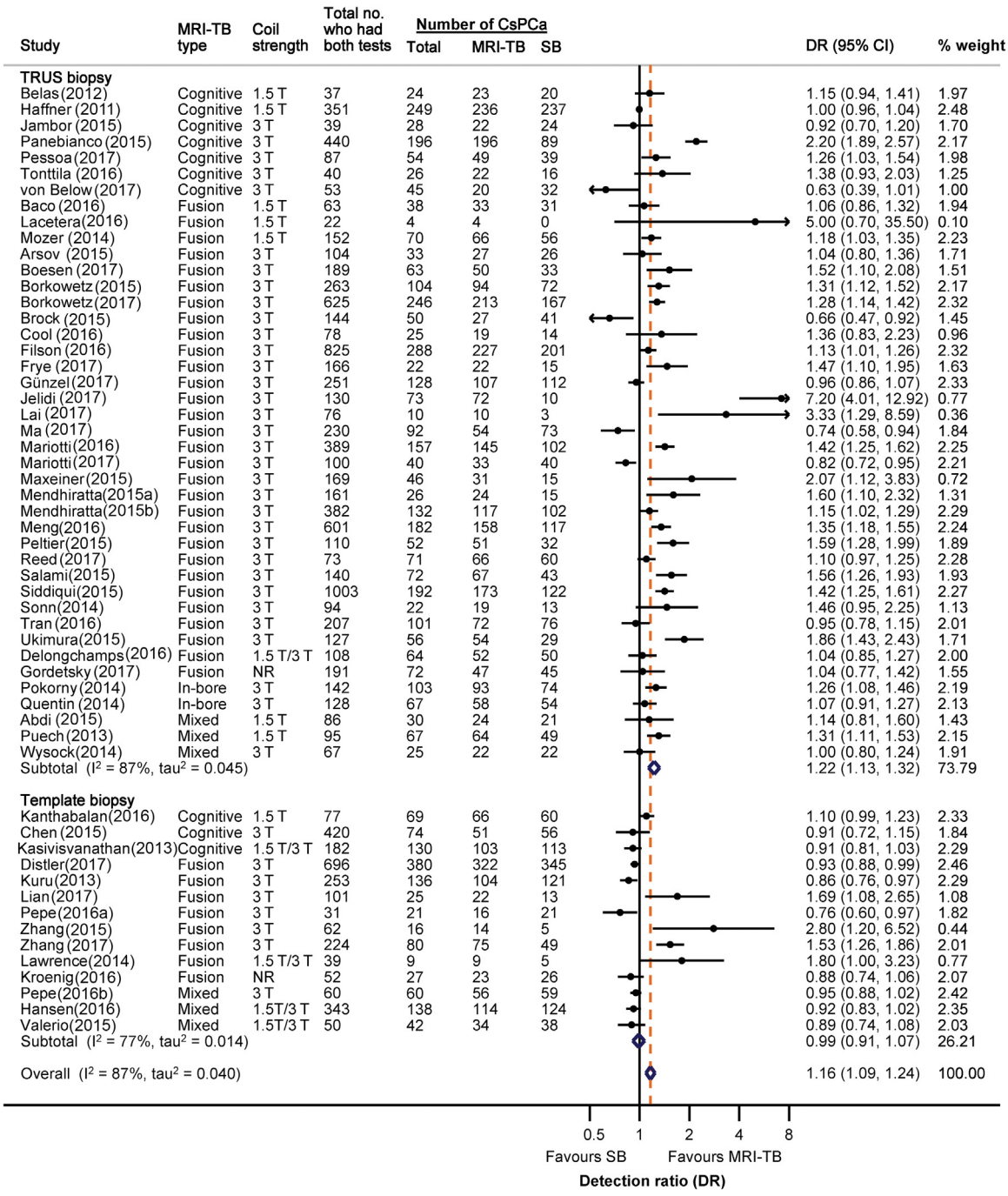

Fig. 2 – Forest plot of the detection ratio of MRI-targeted biopsy (MRI-TB) versus systematic biopsy (SB) for clinically significant prostate cancer (CsPCa). The forest plot shows 56 study cohorts. Studies are grouped by the type of comparator and sorted according to the type of MRI-TB, coil strength, and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of nonoverlapping cohorts in the same year. 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], $p < 0.0001$). CI = confidence interval; Cognitive = cognitive/visual registration; DR = detection ratio; Fusion = MRI/US image fusion; In-bore = carried out in the MRI scanner; Mixed = more than one registration method used in the study; MRI = magnetic resonance imaging; NR = not reported; Template = transperineal template prostate biopsy; TRUS = transrectal ultrasound; US = ultrasound.

clinically insignificant cancer than systematic biopsy (DR 0.66 [95% CI 0.57–0.76], $p < 0.0001$; Fig. 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 material, Appendix 11).

There was no evidence from metaregression analysis that this effect differed by systematic biopsy type (MRI-TB

Table 3 – 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 metaregression						
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		

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

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 4.

3.3.3. *Any cancer detection*

Sixty-one study cohorts including 6742 patients were included in the analysis. There was no difference in any cancer detection by MRI-TB compared with systematic biopsy (DR 1.02 [95% CI 0.96–1.08], $p = 0.49$; Supplementary material, Appendix 12).

3.4. *Randomised controlled trials*

Eight RCTs including 2635 patients (Table 2) presented results for clinically significant cancer and insignificant cancer detection. The two RCTs that most directly addressed the review objectives used MRI-TB alone as the index test when the MRI was suspicious and compared this with 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], respectively; Fig. 4A) [1,6]. However, due to heterogeneity amongst the RCTs regarding how MRI information was used to influence a decision for biopsy, regarding how that biopsy was conducted, and in the choice of index and comparator tests, we did not conduct a meta-analysis of all RCTs. We meta-analysed a subset of five RCTs that compared MRI-TB plus TRUS biopsy with 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 (Fig. 4B), the two RCTs of MRI-TB alone in MRI-suspicious men versus TRUS biopsy showed lower detection rates for MRI-TB than for TRUS biopsy [1,6]. However, after meta-analysis of the four 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 four of the eight RCTs, men with negative MRI were biopsied, and the proportions of clinically significant cancer were 0/23 (0%) [21], 0/130 (0%) [5], 1/26 (4%) [6], and 3/13 (23%) [79].

3.5. *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 35 873 (11%) for systematic biopsy. The proportion of cores positive for cancer was greater for MRI-TB than for systematic biopsy (relative risk 3.17 [95% CI 2.82–3.56], $p < 0.0001$; Supplementary material, Appendix 13).

3.6. *Proportion of men with cancer upgraded or downgraded on radical prostatectomy*

One study reported the proportions of men with both cancer upgraded and cancer downgraded by radical prostatectomy for MRI-TB and systematic biopsy [1]. In this study, four of 27 (15%) men undergoing TRUS biopsy were upgraded compared with five of 30 (17%) men undergoing MRI-TB, who were upgraded. For downgrading, four of 27 (15%) men were downgraded from TRUS biopsy to

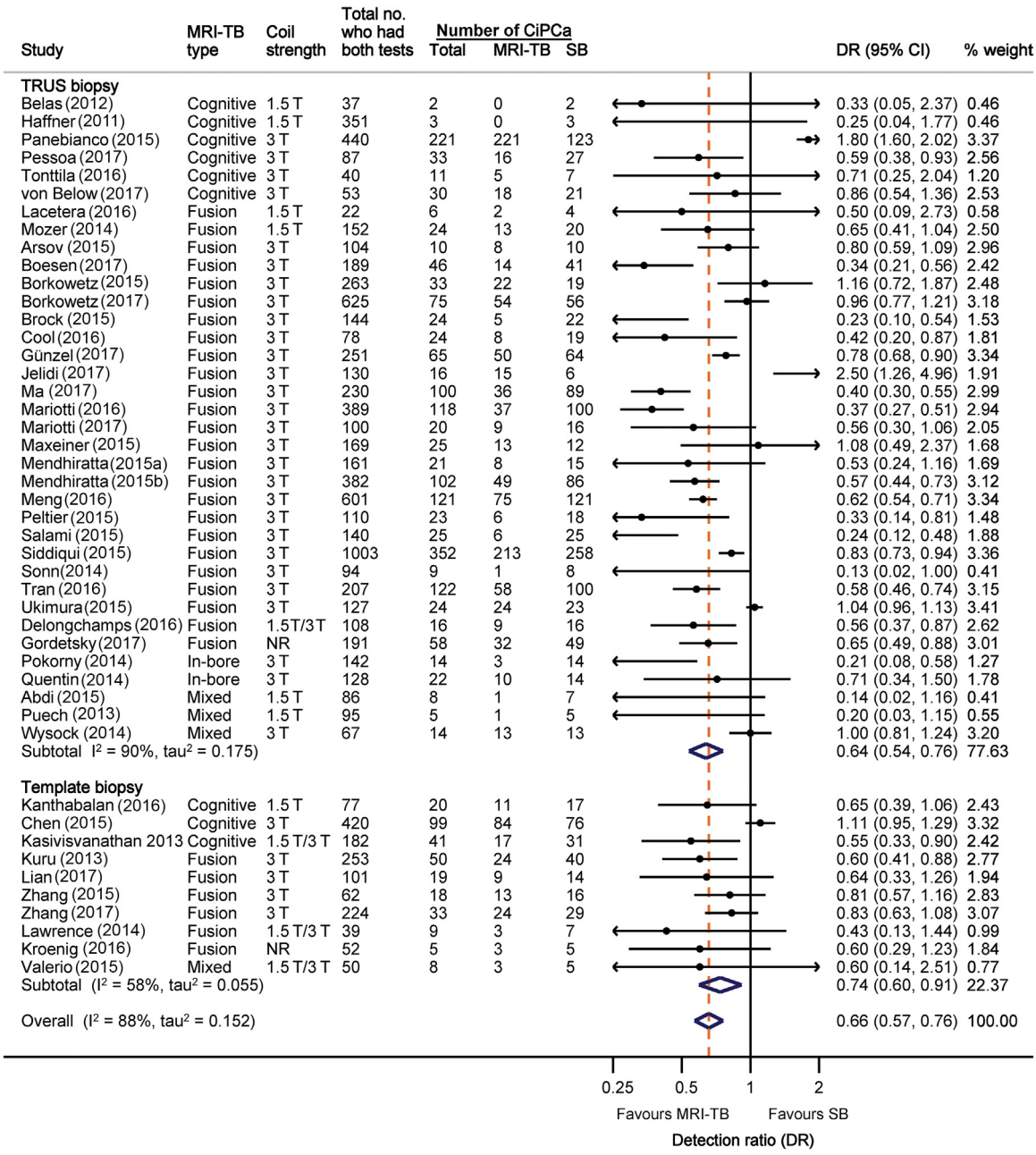

Fig. 3 – Forest plot of the detection ratio of MRI-targeted biopsy (MRI-TB) versus systematic biopsy (SB) for clinically insignificant cancer (CiPCa). The forest plot shows 46 study cohorts. Studies are grouped by the type of comparator and sorted according to the type of MRI-TB, coil strength, and study identifier. Alphabetical suffixes were used to identify studies where a first author published multiple papers of nonoverlapping 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], $p < 0.0001$. CI = confidence interval; DR = detection ratio; MRI = magnetic resonance imaging; NR = not reported; TRUS = transrectal ultrasound.

radical prostatectomy and six of 30 (20%) were downgraded from MRI-TB to radical prostatectomy.

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

Fifty-six study cohorts including 4652 patients were included in the analysis. The definition of clinically significant cancer in each study is given in Table 1. 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 material, Appendix 14).

3.8. *Discussion*

The principal findings of this systematic review are that in men with suspected clinically significant prostate cancer

Table 4 – 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 metaregression						
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		

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

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 the use of an MRI-TB strategy could identify those men who will benefit from treatment, and allow men at the 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 by whether MRI-TB was carried out with cognitive or image-fusion registration techniques. This is also consistent with the 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 biopsy, which when compared directly with 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 biopsy, 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 biopsy [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 are 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 identified RCTs that 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 four pooled RCTs that the combination of MRI-TB and 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 nonsuspicious MRI. In three of the four RCTs where clinically significant cancer was reported, this was low (0–4%) [5,6,21] but was higher in the remaining study (three of 13, 23%), albeit in a small sample [79]. Clearly, if a strategy of avoiding biopsy in men with negative MRI and a 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 negative MRI has a higher negative predictive value than a TRUS biopsy [2] and that 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 [99] 4 , M study [100], and Panebianco et al's study [3], also support the concept of incorporating MRI into the diagnostic pathway.

There are a number of limitations in this review. First, it is important to appreciate that a bias is introduced by analysing studies with a paired design, as the conclusions of such data are limited to men with MRI with suspicious findings who underwent both MRI-TB and systematic

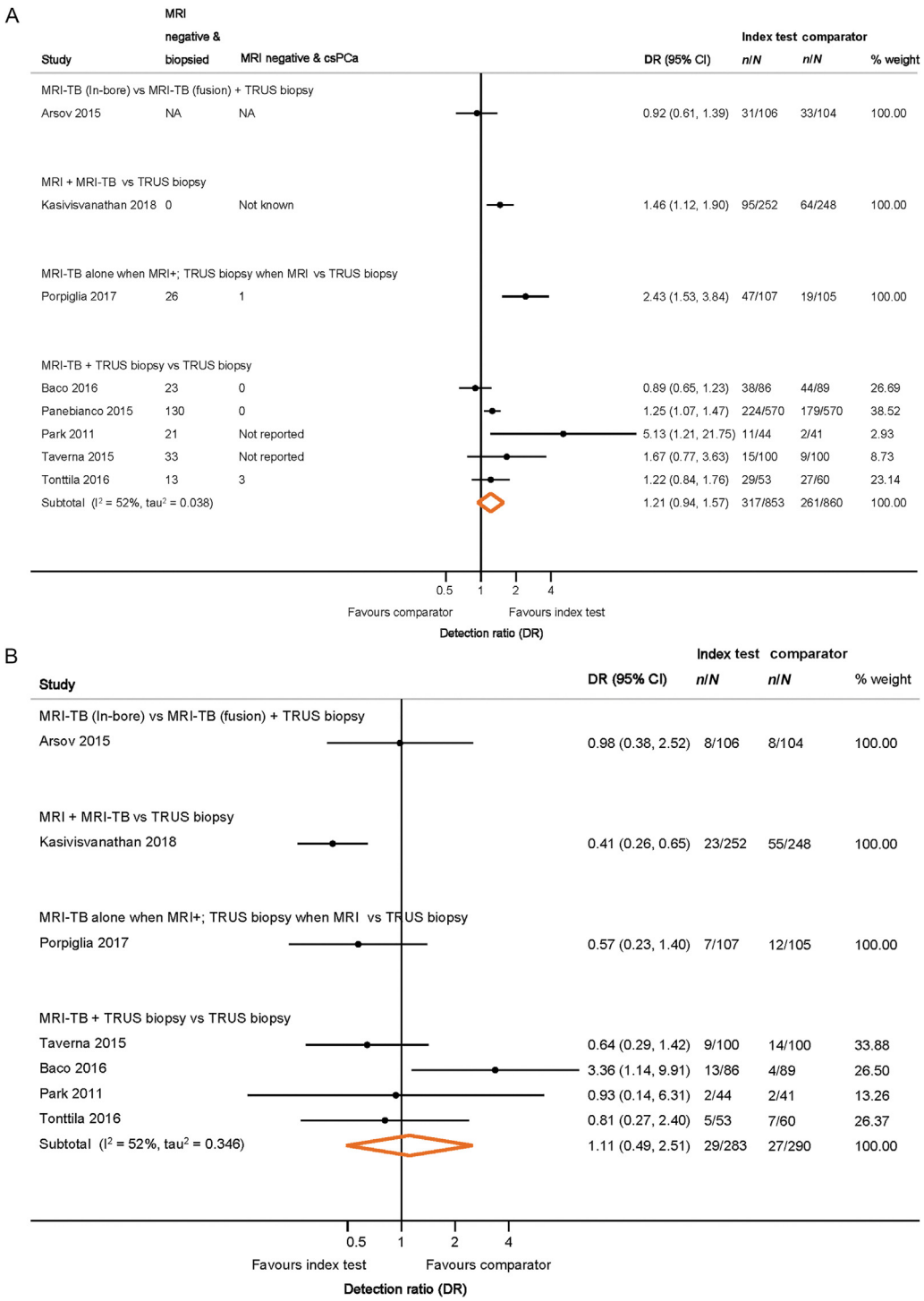

Fig. 4 – (A) Forest plot of the detection ratio for significant cancer detection (csPCa) for randomised controlled trials (RCTs) involving MRI-targeted biopsy (MRI-TB) and systematic biopsy (SB). The forest plot shows eight RCTs. Studies are grouped by study identifier and similarities in the index test (MRI-TB ± additional biopsy) and comparator arm (systematic biopsy ± additional biopsies). Where men with nonsuspicious MRI undergo systematic biopsy, the number with clinically significant prostate cancer is reported. Owing to clinical heterogeneity of the included trials, meta-analysis was carried out only for the subset of five RCTs with similar index tests and comparators. (B) Forest plot of the detection ratio for insignificant cancer detection (ciPCa) for RCTs involving MRI-TB and SB. The forest plot shows eight RCTs. Studies are grouped by study identifier and similarities in the index test (MRI-TB ± additional biopsy) and comparator arm (systematic biopsy ± additional biopsies). Owing to clinical heterogeneity of the included trials, meta-analysis was carried out only for the subset of four RCTs with similar index tests and comparators. CI = confidence interval; DR = detection ratio; MRI = magnetic resonance imaging; NA = not available; TRUS = transrectal ultrasound.

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, CIs 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 from 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. Both identifying men with clinically important disease and avoiding the overdetection of clinically unimportant disease are critical issues, and there is no certainty as to where the optimal balance lies. Previous studies suggest that efforts should be made to avoid the diagnosis of men with clinically unimportant disease who can otherwise be overtreated and experience the 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 for or an 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, the true quality of the MRI conduct, reporting, and biopsy at each centre is not known. 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 and 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]. Nonexpert 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 their own negative predictive value of MRI before considering omitting systematic biopsy.

4. Conclusions

In conclusion, this systematic review highlights that in men with a 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.

Author contributions: Veeru Kasivisvanathan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

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