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Comparison of MRI- and TRUS-informed prostate biopsy for prostate cancer diagnosis in biopsy-naïve men: a systematic review and meta-analysis

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Abstract

Purpose: Multiparametric magnetic resonance imaging (mpMRI) with informed targeted biopsies (TGBX) has changed the paradigm of prostate cancer (PCa) diagnosis. Randomized studies have demonstrated a diagnostic benefit of Clinically significant (CS) for TGBX compared to standard systematic biopsies (SBX). We aimed to evaluate whether mpMRI-informed TGBX has superior diagnosis rates of any-, CS-, high-grade (HG)-, and clinically insignificant (CI)-PCa compared to SBX in biopsy-naïve men.

Methods: Data was searched in Medline, Embase, Web of Science, and Evidence-based medicine reviews-Cochrane Database of systematic reviews from database inception until 2019. Studies were selected by two authors independently, with disagreements resolved by consensus with a third author. Overall 1951 unique references were identified, and 100 manuscripts underwent full-text review. Data were pooled using random-effects models. The meta-analysis is reported according to the PRISMA statement. The study protocol is registered with PROSPERO (CRD42019128468).

Results: Overall 29 studies (13,845 patients) were analyzed. Compared to SBX, use of mpMRI-informed TGBX was associated with a 15% higher rate of any PCa diagnosis (95% CI 10-20%, p<0.00001). This relationship was not affected by the study methodology (p=0.11). Diagnosis of CS and HG PCa were more common in the mpMRI-informed TGBX group (risk difference of 11%, 95% CI 0-20%, p=0.05, and 2%, 95% CI 1-4%; p=0.005, respectively) while there was no difference in diagnosis of CI PCa (risk difference of 0, 95% CI -3-3%, p=0.96). Notably, the exclusion of SBX in the mpMRI-informed TGBX arm significantly modified the association between a mpMRI strategy and lower rates of CI PCa diagnosis (p=0.01) without affecting the diagnosis rates of CS- or HG-PCa.

Conclusions: In comparison to SBX, a mpMRI-informed TGBX strategy results in a significantly higher diagnosis rate of any-, CS-, and HG-PCa. Excluding SBX from

mpMRI-informed TGBX was associated with decreased rates of CI-PCa diagnosis without affecting diagnosis of CS- or HG-PCa.

1. Introduction

Prostate cancer (PCa) diagnosis by systematic random histologic sampling of the prostate has, until recently, been the standard of care[1]. Transrectal ultrasound (TRUS)-guided 12-core template systematic biopsy (SBX) has been widely recommended for men at risk for PCa[2] _ENREF_2. However, SBX templates are limited by inherent random and systematic errors. Specific regions of the prostate are consistently underesampled, including the anterior region and apex[3], and, unless hypoechoic lesions are seen on TRUS, sampling occurs by chance. Thus, SBX can miss up to 20% of CS PCa, resulting in underdiagnosis[4]. Additionally, SBX detects a relatively high percentage of clinically insignificant (CI) PCa (Gleason grade group [GGG] 1), which may result in overtreatment[2], if proper use of active surveillance (AS) is not practiced.

With the introduction of multiparametric prostate magnetic resonance imaging (mpMRI), the pathways for PCa diagnosis have changed. MpMRI is unique in that it can both risk-stratify men for prostate biopsy (PB) and allow anatomic guidance for biopsy. The spatial information provided by mpMRI allows for precise mpMRI-informed targeted biopsy (TGBX), where clinically significant (CS) PCa (≥GGG 2[5]) is detected with fewer biopsy cores[6], and diagnosis of CI PCa decreases[7]. There are randomized studies demonstrating the superior diagnosis rate of TGBX in diagnosing CS PCa in biopsy-naïve men[8, 9]. However, TGBX has limitations, missing CS PCa in 2.1-15% of cases[10-13]. Although the most recent European Association of Urology (EAU)[2] and the National institute for Health and Care Excellence (NICE)[14] guidelines recommend performing mpMRI in biopsy-naïve men with suspected PCa, these recommendations are not

widely adopted in North-America, where mpMRI is usually reserved for men with a previous negative biopsy. Furthermore, the added benefit of combining SBX with TGBX remains unclear with conflicting data supporting both TGBX alone[7, 15] and combining SBX with TGBX[16]. The combination appears to detect more CS PCa than TGBX alone[4, 7]. Both the EAU and American Association of Urology (AUA) guidelines currently recommend adding SBX in men with a suspicious mpMRI lesion undergoing TGBX[2, 17].

To synthesize the available data on these questions, we undertook a systematic review and meta-analysis of all studies comparing SBX and TGBX, either alone or in combination with SBX, to assess the detection rate of any PCa, CS PCa, high grade (HG) PCa (GGG>=4) and CI PCa in biopsy-naïve men.

2. Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[18]. The study protocol was registered with PROSPERO CRD42019128468.

2.1. Research question

Is mpMRI-informed TGBX with or without SBX associated with higher rates of any-, CI-, CS-, and HG-PCa diagnosis than SBX alone in biopsy-naïve men at risk of PCa?

2.2. Types of Studies

Randomized clinical trials and observational cohort studies were included. Other publications including editorials, commentaries, review articles, meeting abstracts and publications not subject to peer-review (ie, reports of data from vital statistics and

dissertations or theses) were excluded. Only studies with paired cohorts, with patients with a positive mpMRI receiving either TGBX alone or together with SBX were included. To prevent duplication of patients used in our analyses, we selected one study (when more than one was published on the same patient cohort), based on contemporary timing, cohort size, and granularity of data reported. Our main interest was to compare the outcomes of mpMRI-informed TGBX alone or in combination with SBX to SBX outcomes in biopsy-naïve men. Thus, studies comparing mpMRI-guided TGBX and SBX in biopsy-naïve men were included and those in men with prior negative biopsy or with prior PCa diagnosis were excluded.

2.3. Outcome measures

The primary outcome of interest was the rate of any PCa diagnosis. Secondary outcomes were rates of CS PCa (GGG ≥ 2), HG PCa (GGG ≥ 4) and CI PCa (GGG=1).

2.4. Search strategy

Medline, EMBASE, Web of Science, Scopus and EBM Reviews Cochrane Database of Systematic Reviews databases were searched using the OvidSP platform for studies indexed from database inception to February 15, 2019 by a professional medical librarian. We used both subject headings and text-word terms for “prostate cancer”, “prostate neoplasm”, “biopsy”,” no prior”, “no previous”, “naïve”, “ultrasound”, “magnetic resonance imaging”, “systematic”, “targeted”, and related and exploded terms including MeSH terms in combination with keyword searching. A full search strategy is presented in appendix 1. Only English language publications were included, and all duplicates were excluded.

2.5. Study review methodology

The study selection was conducted by two authors (A.E.A. and T.C.) independently. Disagreements were resolved by consensus with a third author (H.G.). Titles and abstracts were used to screen for initial study inclusion. Full-text review was used where abstracts were insufficient to determine if the study met inclusion criteria. A data extraction form was created and piloted prior data extraction, which was performed by a single author (A.E.A.) and subsequently verified by two additional authors (H.G. and Z.K.) independently.

2.6. Risk of bias assessment

The Cochrane Collaboration's tool for assessing risk of bias[19] and the Newcastle-Ottawa Scale (NOS) were used for risk of bias assessment in randomized clinical trials and cohort studies, respectively. The NOS assesses risk of bias in three domains[20]: (1) selection of the study groups; (2) comparability of groups; and (3) ascertainment of exposure and outcome[21]. Studies with scores >=7 were considered as having a low risk of bias, scores of 4–6 as having a moderate risk of bias, and scores <4 as having a high risk of bias.

2.7. Assessment of heterogeneity

Heterogeneity was assessed using the Q test, and estimated using the DerSimonian-Laird method, and finally quantified using I^2 values[22]. Given the identified clinical heterogeneity, we employed random effects models for each of our analyses.

2.8. Data synthesis

We expressed the outcome as the risk difference for PCa diagnosis between mpMRI-informed TGBX and SBX. This was determined as the proportion of patients diagnosed with PCa in the SBX group minus the proportion of patients diagnosed in the mpMRI-informed TGBX group. Therefore, a risk difference less than zero (negative risk difference) indicates that PCa diagnosis was more frequent in the mpMRI-informed TGBX group while a risk difference greater than zero (positive risk difference) indicates that PCa diagnosis was more frequent in the SBX group.

We used the Mantel-Haenszel method for meta-analysis of dichotomous data using the risk difference as our measure of effect. For each outcome, we first performed meta-analysis among three strata defined by study methodology (randomized controlled trials, prospective cohort studies, and retrospective cohort studies) as differences in study methodology may reasonably be expected to affect study conclusions. We tested for subgroup differences between strata for each outcome using the Chi-squared test. Where the Chi-squared test for subgroup differences was insignificant, we pooled results for each outcome across the study methodologies to provide a single pooled effect estimate. Where the Chi-squared test for subgroup differences was significant ($p<0.05$), we deemed it inappropriate to pool results and thus reported pooled results among each stratum individually.

We performed *a priori* subgroup analysis to assess whether inclusion of SBX in the mpMRI-informed TGBX arm would affect the risk difference for PCa diagnosis between mpMRI-informed TGBX and SBX for each outcome. Again, we tested for subgroup differences between strata for each outcome using the Chi-squared test to assess for effect modification due to this factor.

Meta-analysis was performed using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) software. Statistical significance was determined at $p<0.05$.

3. Results

3.1. Literature search results

We identified 1951 unique references (Figure 1). 100 manuscripts underwent full-text review and 29 studies were selected for final analyses. Reasons for exclusion are provided in Figure 1. 19 studies (65.5%) enrolled patients prospectively, however only 5 studies (17.2%) randomly assigned patients to mpMRI-informed TGBX or SBX group. Publication details of all included studies can be found in Appendix 2.

3.2. Characteristics of identified studies

Studies were conducted in 4 continents (65.5% in Europe, 20.7% in Asia, 6.9% in the US, and 6.9% in Australia), and 89.7% were conducted after 2010 (Table 1). 21 studies (72.5%) were from single centers, three studies (10.3%) analyzed two centers and five studies (17.2%) were multicenter.

Across the 29 included studies, there were 13,845 patients, of whom 1,085 (7.8%) patients were enrolled in randomized trials. Nearly all studies included men based on an elevated prostate specific antigen (PSA) and/or an abnormal digital rectal exam (DRE) (Table 1).

With respect to MRI performance and interpretation, 21 studies (72.4%) used 3 Tesla mpMRI and 8 (27.6%) used 1.5 Tesla. The Prostate Imaging Reporting and Data System (PIRADS) was employed in most studies (21 [72.4%]), while 7 studies (24.1%) used the Likert and similar 4- or 5-point scales. 14 studies (48.3%) included SBX in addition to mpMRI-informed TGBX in the mpMRI arm. Targeted biopsy was performed with an ultrasound fusion biopsy technique in 18 studies (62.1%). Cognitive fusion biopsy and in-bore fusion biopsy were used in 8 (27.6%) and 2 studies (7%), respectively. Most studies (24, 82.7%) utilized transrectal biopsy.

All studies reported on overall PCa and CS PCa detection rate, defined based on Gleason score and/or maximum PCa core length (Table 1). However, for our analysis, we considered CS PCa to be GGG>=2 alone[5].

3.3. Risk of bias assessment

All randomized controlled trials included concealed random sequence generation and were similarly at low risk of attrition and reporting bias (Supplementary Table 1). While all studies were unblinded and thus potentially at risk for performance and detection bias, it is improbable that this should influence the outcome of PCa diagnosis.

The risk of bias in the prospective and retrospective cohort studies was low in all included studies (supplementary table 2). In some studies, patients with negative mpMRI were excluded which may have potentially introduced selection bias. As the outcome of interest was overall PCa or CS PCa diagnosis rate, all studies were deemed to have adequate follow up.

3.4. Quantitative synthesis

3.4.1. Any prostate cancer diagnosis

Assessing the association between use of mpMRI-informed TGBX or SBX and rates of any PCa diagnosis, we pooled results from 29 studies representing 31 unique patient cohorts and 13,845 participants. Among randomized controlled trials (5 studies, 1,085 participants), the use of mpMRI-informed TGBX +/- SBX was associated with a 16% increased likelihood of PCa diagnosis (risk difference = -0.16, 95% CI -0.22 to -0.11; p<0.00001; I^2 = 4%) when compared to SBX alone (Figure 2a). Among 14 prospective cohort studies (5,508 participants), the use of mpMRI-informed TGBX +/- SBX was associated with a 20% increased likelihood of PCa diagnosis (risk difference = -0.20, 95% CI -0.27 to -0.12; p<0.00001; I^2 = 89%) compared to SBX alone (Figure 2a). Finally, among 10 retrospective cohort studies (7,252 participants), the use of mpMRI-informed TGBX +/- SBX was associated with a 9% increased likelihood of PCa diagnosis (risk difference = -0.09, 95% CI -0.16 to -0.01; p=0.03; I^2 = 89%) compared to SBX alone (Figure 2a). The test for subgroup differences was insignificant (chi-squared = 4.40, p=0.11; I^2 = 54.5%). Thus, we pooled results across these strata: assessing all 13,845 participants from 29 studies, the use of mpMRI-informed TGBX +/- SBX was associated with a 15% increased likelihood of PCa diagnosis (risk difference = -0.15, 95% CI -0.20 to -0.10; p<0.00001; I^2 = 89%) compared to SBX alone (Figure 2a).

We then assessed whether inclusion of SBX in the mpMRI-informed TGBX arm affected the observed association between mpMRI-informed TGBX and any PCa diagnosis. Among cohorts where data was available for patients in the mpMRI-informed TGBX arm who had targeted biopsy alone (22 studies, 75.9%), the use of mpMRI-informed TGBX was associated with a 12% increased likelihood of PCa diagnosis (risk

difference = -0.12, 95% CI -0.18 to -0.07; p<0.00001; I^2 = 89%) compared to SBX alone (Figure 3a). For cohorts where data was available for patients who received both TGBX and SBX (14 studies, 48.3%), the use of mpMRI-informed TGBX was associated with a 17% increased likelihood of PCa diagnosis (risk difference = -0.17, 95% CI -0.24 to -0.09; p<0.00001; I^2 = 91%) compared to SBX alone (Figure 3a). The test for subgroup differences was insignificant (chi-squared = 0.78, p=0.38; I^2 = 0%) suggesting that the inclusion of SBX in patients undergoing mpMRI-informed TGBX does not modify the association between mpMRI-informed TGBX and rates of any PCa diagnosis.

3.4.2. Clinically significant prostate cancer diagnosis

Twenty-seven studies (13,089 participants) provided data for meta-analysis of the outcome of CS PCa. There was an increased likelihood of CS PCa diagnosis among randomized controlled trials (risk difference = -0.11, 95% CI -0.2 to 0.00; p=0.05; I^2 = 78%), among prospective cohort studies (risk difference = -0.18, 95% CI -0.24 to -0.11; p<0.00001; I^2 = 81%) and among retrospective cohort studies (risk difference = -0.07, 95% CI -0.12 to -0.02; p=0.004; I^2 = 77%) (Figure 2b). However, the test for subgroup differences was significant (chi-squared = 6.35, p=0.04; I^2 = 68.5%). Thus, we did not pool results across strata of study methodology. We found no evidence of effect modification due to inclusion of SBX in the mpMRI-informed TGBX arm on the relationship between mpMRI-informed TGBX, and rates of CS PCa diagnosis (test for subgroup differences chi-squared = 0.18, p=0.67; I^2 = 0%) (Figure 3b).

3.4.3. Clinically insignificant prostate cancer diagnosis

Similarly, 27 studies (13,089 participants) provided data for meta-analysis of the outcome of CI PCa. The use of mpMRI-informed TGBX +/- SBX was associated with no meaningful difference in the likelihood of CI PCa diagnosis, whether assessed among randomized controlled trials (risk difference = 0.01, 95% CI -0.09 to 0.11; p=0.85; I^2 = 82%), prospective cohort studies (risk difference = 0.00, 95% CI -0.05 to 0.05; p=0.99; I^2 = 79%) or retrospective cohort studies (risk difference = -0.01, 95% CI -0.05 to 0.04; p=0.83; I^2 = 84%) (Figure 2c). The test for subgroup differences was insignificant (chi-squared = 0.08, p=0.96; I^2 = 0%). Thus, we pooled results across strata of study methodology and found no meaningful difference in the likelihood of CI PCa diagnosis (risk difference = 0.00, 95% CI -0.03 to 0.03; p=0.96; I^2 = 80%) (Figure 2c).

Interestingly, there was evidence of effect modification due to the inclusion of SBX in the mpMRI-informed TGBX arm for this outcome (test for subgroup differences chi-squared = 6.49, p=0.01; I^2 = 84.6%): while studies which included SBX in the mpMRI-informed TGBX arm demonstrated a 4% higher rate of diagnosis of CI PCa among patients who received mpMRI-informed TGBX+SBX, compared to SBX alone (risk difference = -0.04, 95% CI -0.08 to -0.00; p=0.05; I^2 = 77%), those which utilized TGBX alone demonstrated a 3% lower rate of diagnosis of CI PCa among patients who received mpMRI-informed TGBX, compared to SBX alone (risk difference = 0.03, 95% CI -0.01 to 0.06; p=0.11; I^2 = 75%) (Figure 3c).

3.4.4. High-grade prostate cancer diagnosis

A smaller subset of 19 studies (9,811 participants) provided data for meta-analysis of the outcome of HG PCa. The use of mpMRI-informed TGBX +/- SBX was associated with a significantly higher likelihood of HG PCa diagnosis among

randomized controlled trials, albeit with a small effect size (risk difference = -0.04, 95% CI -0.07 to -0.01; p=0.004; I^2 = 0%) compared to SBX alone (Figure 2d). Among prospective cohort studies (risk difference = -0.02, 95% CI -0.05 to 0.01; p=0.23; I^2 = 66%) and retrospective cohort studies (risk difference = -0.02, 95% CI -0.06 to 0.01; p=0.12; I^2 = 38%) (Figure 2d), this effect was not significant though the direction and magnitude were similar. The test for subgroup differences was insignificant (chi-squared = 1.72, p=0.42; I^2 = 0%). Thus, we pooled results across strata of study methodology and found the use of mpMRI-informed TGBX was associated with a small but significantly higher likelihood of HG PCa diagnosis (risk difference = -0.02, 95% CI -0.04 to -0.01; p=0.005; I^2 = 47%) compared to SBX alone (Figure 2d). We found no evidence of effect modification due to inclusion of SBX in the mpMRI-informed TGBX arm on the relationship between mpMRI-informed TGBX and rates of HG PCa diagnosis (test for subgroup differences chi-squared = 0.40, p=0.53; I^2 = 0%) (Figure 3d).

4. Discussion

In this meta-analysis of biopsy-naïve patients undergoing a PB, we compared rates of PCa diagnosis for patients undergoing standard SBX and mpMRI-informed TGBX. Our analyses demonstrate several findings. First, patients who underwent a mpMRI-informed TGBX +/- SBX were 15% more likely to be diagnosed with any PCa than patients who underwent standard SBX. Further, this improved diagnostic yield was not affected by whether a mpMRI-informed biopsy was performed with TGBX alone or combined with SBX. Second, patients who underwent mpMRI-informed biopsy were more likely to be diagnosed with CS PCa and HG PCa, with no difference in the

diagnosis rate of CI PCa compared to those who underwent SBX alone. Third, exclusion of SBX in the mpMRI-informed TGBX arm was associated with decreased rates of CI PCa diagnosis (p=0.01) without meaningfully affecting diagnosis rates of any-, CS-, or HG PCa.

Standard TRUS-guided SBX remains the most common technique used worldwide in biopsy-naïve patients deemed to warrant PB. While affected by characteristics of the population under study, PCa detection rates are approximately 40-45% for SBX[23]. Despite this, TRUS-SBX harbors low sensitivity and specificity in the diagnosis of PCa[12]: repeat biopsy identifies PCa in 10-25% of men with an initially negative biopsy[24]. Further, TRUS-SBX underestimates tumor grade in 36% of men when compared to radical prostatectomy (RP)[25]. With the advent of mpMRI, the sensitivity of PCa imaging has improved[26]. Previous meta-analyses have shown that mpMRI-informed TGBX detects more CS PCA, with fewer cores than utilized in TRUS-guided SBX[13].

More than 70% of studies included in this analysis used 3 tesla mpMRI and incorporated the PIRADS system for interpretation of imaging. However similar results were seen in studies using 1.5 tesla mpMRI, and other reporting systems such as the Likert scale. Included studies utilized numerous strategies for TGBX including ultrasound-, cognitive-, and in-bore-fusion biopsies, all of which have demonstrated an increased detection rate of CS PCa when compared to SBX[27-29]. Presently, there is no consensus on which strategy is superior.

We identified a higher rate of CS PCa diagnosed with mpMRI-informed biopsy compared to SBX ranging from 7 to 18%, with an 11% higher diagnostic rate among

RCTs. This is on par with results of prior meta-analyses[11-13, 30]. Uniquely, this analysis found mpMRI-informed biopsy identified higher rates of HG PCa.

More actionably, we found that exclusion of SBX in the mpMRI-informed TGBX arm significantly modified the association between mpMRI and CI PCa diagnosis (p=0.01), without meaningfully affecting diagnostic rates of CS- or HG PCa. Thus, in contrast to the common hypothesis that the combination of TGBX+SBX yields a higher diagnosis rate of any and CS PCa[31], these data suggest that SBX may be safely omitted in men undergoing mpMRI-guided biopsy. This approach would be expected to decrease the over-detection of clinically indolent PCa. Further, using TGBX only, a lower number of biopsy cores are required to reach a diagnosis, leading to less discomfort and morbidity[32, 33]. Lastly, emerging data suggest that decreased number of biopsy-cores can lead to less blood loss during RP[34].

This analysis strengthens the body of evidence supporting mpMRI as a risk-stratification tool in biopsy-naïve men, showing that a positive mpMRI can lead to a higher detection rate of CS PCa. Our manuscript adds to the current knowledge and supports other recently published meta-analyses demonstrating that TGBX has a clear benefit over SBX alone in the diagnosis of CS PCa[30, 35-37]. Over a million men in the US undergo TRUS-guided SBX each year[38], at a cost of nearly 1 billion dollars, with less than 10% of the 12 million biopsy core samples demonstrating cancer. According to the PROMIS study[39], approximately 25% of the biopsies (250,000) could be avoided in patients with a negative pre-biopsy mpMRI. But, for patients with a positive mpMRI, our study shows that they could go down from a 12-core biopsy to only a 4-core biopsy (provided there is only one mpMRI-targeted lesion), resulting in a reduction of 8 million

cores processed per year. This supports the concept of an mpMRI-first strategy in biopsy-naïve men as an effective and cost-effective approach for the diagnosis of CS PCa[40]. However, we must not forget that if an mpMRI-first strategy in biopsy-naïve men is adopted, the cost of mpMRI must be taken into consideration when analyzing the cost-effectiveness of this entire approach. Taken together, the added benefit of SBX is shown to be questionable in the setting of biopsy-naïve men suspected to have PCa, and its role must be reconsidered, possibly omitted, as recommended in men with a previous negative biopsy[2].

No difference was noted in the diagnosis rate of CI PCa between mpMRI-informed biopsy and SBX. In contrast, three prior meta-analyses have demonstrated a lower rate of CI PCa diagnosis with TGBX when compared to SBX[11, 12, 30] while Valerio et al. showed that most studies demonstrated a higher rate of CI PCa in the mpMRI-informed biopsy pathology[13]. As discussed above, this may be affected using SBX in the TGBX group. In our meta-analysis, TGBX alone or combined with SBX demonstrate an equal rate of CS PCa diagnosis rate but TGBX alone resulted in a 4% reduction in CI PCa diagnosis. The definition of CI PCa varies between studies, ranging from the Epstein criteria[41] to the combination of maximal cancer core length <6 mm with GGG 1[42]. In our analysis, we used the simplified definition of GGG=1 alone, which could explain some of the discrepancies between our analysis and others.

The strength of our analysis includes a comprehensive search strategy and actionable data due to the use of mpMRI protocols in accordance with the current recommended imaging guidelines. However, there are several limitations. First, mpMRI-informed biopsy procedure lacked standardization. There was significant variability

across the studies with regards to the interpretation of suspicious MRI lesions, the decision on when to biopsy, method of TGBX, the number of cores taken, and the different stages of the learning curve of the radiologists who interpreted the imaging. Second, there was significant heterogeneity among many of the comparisons included in this review. We used random effects models to pool these studies as a result. Third, this analysis focused on biopsy-naïve men and these results may not be applicable to those with a previous negative biopsy. Fourth, this analysis only applies to patients with a positive mpMRI. For patients with a negative mpMRI, the current role of SBX remains controversial. Notably, previous analyses have demonstrated a CS PCa diagnosis rate of 12% on systematic biopsy of men with negative mpMRI[43], making the role of SBX far from obsolete, especially with a negative mpMRI. SBX is still crucial in many settings and understanding when it is mandatory and when not is imperative. Furthermore, when considering management with focal therapy, SBX might have a critical role of ruling out additional disease outside the target lesion. Importantly, aside from the changing radiologist learning curve of interpreting mpMRI images, the ease of properly obtaining an mpMRI-targeted biopsy around the world varies due to a plethora of considerations, and thus the conclusion of this study may not be applicable worldwide. Lastly, there is a potential methodological error in assuming that one type of biopsy diagnoses more CS-PCa than another based on the results of PB alone. Deciphering which strategy is better from a diagnostic perspective, would be to analyze the RP specimens of all patients who underwent either a TGBX or SBX and compare the rate of CS PCa in the final specimen to the preoperative biopsy result. Indeed, a recently published study showed that TGBX can sample the highest grade of a dominant lesion, and perhaps even a

tertiary high-score location. This resulted in reporting a higher biopsy GGG and subsequent downgrading of the final pathologic specimen following RP[44].

5. Conclusions

Based on a comprehensive, current meta-analysis, a mpMRI-informed TGBX strategy in men undergoing their first PB resulted in a significantly higher diagnosis rate of any-, CS-, and HG-PCa, compared to SBX. Furthermore, exclusion of SBX for men undergoing mpMRI-informed TGBX was associated with decreased rates of CI PCa diagnosis without affecting diagnosis rates of CS- or HG PCa.

Author Contributions:

Design and conception: HG, CJDW

Study selection: AEA, TC, HG

Data extraction: AEA, HG, ZK, CJDW

Analysis and interpretation of data: CJDW, HG, AEA

Writing of manuscript: HG, AEA, CJDW

Editing and reviewing of manuscript: ZK, TC, NF, LK, ME, MAH, SST, NP, MDT, CJDW

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Figure legends:

Figure 1. – Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart

Figure 2. Forest plot for meta-analysis of the difference in prostate cancer diagnosis between patients assessed using systematic biopsy or mpMRI-informed biopsy, stratified by study methodology: (a) any prostate cancer diagnosis, (b) clinically-significant prostate cancer diagnosis, (c) clinically-insignificant prostate cancer diagnosis, (d) high-grade prostate cancer diagnosis.

Figure 3. Forest plot for meta-analysis of the difference in prostate cancer diagnosis between patients assessed using systematic biopsy or mpMRI-informed biopsy, stratified by inclusion of systematic biopsy in the mpMRI-informed biopsy arm: (a) any prostate cancer diagnosis, (b) clinically-significant prostate cancer diagnosis, (c) clinically-insignificant prostate cancer diagnosis, (d) high-grade prostate cancer diagnosis.

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Table 1-Characteristics of included studies

Author (yr)	Country/ Number of centers	Study interval	Inclusion Criteria	Study size (SBX/ TGBX)	PSA (ng/ml) (SBX/ TGBX)	Age (yr) (SBX / TGBX)	Biopsy approach		Biopsy technique in MRI arm	MRI machine	MRI scoring system	TGBX technique	Outcome
							SBX	TGBX					
Randomized controlled trials													
Baco (2016)	Norway/1	9/2011-6/2013	Elevated PSA (PSA 4-20ng/ml) and/or abnormal DRE	175 (89/86)	Median 7.6/Median 6.9	Median 65/Median 64	Transrectal	Transrectal	Systematic + targeted	1.5T	PIRADS v1	Software fusion	Overall PCa CS PCa
Kasivisvanathan (2018)	Multiple/25	2/2016-8/2017	Elevated PSA and/or abnormal DRE	500 (248/252)	Mean 6.5/Mean 6.75	Mean 64.5/Mean 64.4	Transrectal	Transrectal Transperineal	Targeted only	1.5T, 3T	PIRADS v2	Software fusion Cognitive fusion	CS PCa Insignificant PCa Negative mpMRI
Park (2011)	South Korea/1	7/2008-12/2009	Elevated PSA and/or abnormal DRE	85 (41/44)	Mean 5.6/Mean 6.1	Mean 61/Mean 63	Transrectal	Transrectal	Systematic+ targeted	3T	NR	Cognitive fusion	Overall PCa Positive core rate
Porpiglia (2017)	Italy/2	11/2014-3/2016	Elevated PSA (PSA <=15 ng/ml) Normal DRE	212 (105/107)	Median 6.7/Median 5.9	Median 66/ Median 64	Transrectal	Transrectal Transperineal	Targeted only	1.5T	PIRADS v1	Software fusion	Overall PCa CS PCa
Tonttila (2016)	Finland/1	4/2011-12/2014	Elevated PSA (PSA	113 (60/53)	Median 6.2/Median	Median 62/ Median 63	Transrectal	Transrectal	Systematic+	3T	4-point scale	Cognitive fusion	Overall PCa

			<20 ng/ml or free-to-total PSA ratio <=0.15 and PSA <10 ng/ml in repeated measurement)		6.1				targeted				CS PCa Positive core rate
Prospective cohort studies													
Borkowetz (2018)	Germany/2	1/2016-12/2017	Elevated PSA and/or abnormal DRE	384 (214/170)	Median 6.22	Median 63	Transrectal	Transperineal	Systematic+ targeted	3T	PIRADS v2	Software fusion	Overall PCa CS PCa Positive core rate
Castellucci (2017)	Spain/1	7/2011-7/2014	Elevated PSA and/or abnormal DRE	254 (168/86)	Mean 8.3	Mean 61.4	Transrectal	Transrectal	Systematic+ targeted	1.5T	PIRADS v1	Cognitive fusion	Overall PCa CS PCa
De Gorski (2015)	France/1	1/2010-5/2014	Elevated PSA (PSA < 10 ng/ml)	232	Mean 6.5	Mean 64	Transrectal	Transrectal	Systematic+ targeted	1.5T	Likert	Software fusion	Overall PCa CS PCa
Delongchamps (2013)	France/1	1/2011-3/2012	Elevated PSA and/or abnormal DRE	605 (391/214)	Mean 8.1/Mean 8.3/Mean 9	Mean 62.7/Mean 64.6/ Mean 64.5	Transrectal	Transperineal	Systematic+ targeted	1.5T	3-point scale	Software fusion Cognitive fusion	Overall PCa Insignificant PCa

Delongchamps (2016)	France/7	6/2014-10/2014	Elevated PSA (PSA >4ng/ml)	108	Median 7.2	Median 65	Transrectal	Transrectal	Systematic+ targeted	1.5T 3T	PIRADS v1	Software fusion	Overall PCa CS PCa
Garcia Bennett (2017)	Spain/4	10/2014-4/2016	Elevated PSA (PSA > 4 ng/mL, a PSA den-sity > 0.18 ng/mL/mL, a PSA velocity > 0.75 ng/mL/year) and/or abnormal DRE	92 (60/32)	Median 7.2	Mean 64.1	Transperineal	Transperineal	Systematic+ targeted	3T	PIRADS v1	Cognitive fusion	Overall PCa CS PCa
Mozer (2015)	France/1	1/2010-9/2013	Elevated PSA (PSA 4-10ng/ml)	152	Median 6	Median 63.7	Transrectal	Transrectal	Systematic+ targeted	1.5T	Likert	Software fusion	CS PCa
Peltier (2015)	Belgium/1	3/2012-9/2013	NR	110	Median 6.9	Median 65.8	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1	Software fusion	CS PCa
Pokorny (2014)	Australia/1	7/2012-1/2013	Elevated PSA and/or abnormal DRE	365 (223/142)	Median 5.3	Median 63	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1	Cognitive fusion	Low risk PCa Intermediate/high risk PCa
Quentin (2014)	Germany/1	11/2011-10/2013	Elevated PSA (PSA >4	128	Median 6.7	Median 67	Transrectal	Transrectal	Systematic+	3T	PIRADS v1	In-bore fusion	CS PCa

			ng/ml)						targeted				
Rouviere (2019)	France/16	7/2015-8/2016	Elevated PSA and/or abnormal DRE Family history of PCa	457 (251/206)	Median 6.5	Median 64	Transrectal	Transrectal	Systematic+ targeted	1.5T 3T	Likert	Software fusion Cognitive fusion	CS PCa Insignificant PCa
Shoji (2017)	Japan/1	10/2014-8/2016	Elevated PSA (PSA 4-20ng/ml)	250	Median 6.7	Median 68	Transrectal	Transperineal	Systematic+ targeted	NR	PIRADS v1	Software fusion	Overall PCa CS PCa
Van der Leest (2018)	Netherlands /4	2/2015-2/2018	Elevated PSA (PSA >=3 ng/ml)	626 (309/317)	Median 6.4	Median 65	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v2	In-bore fusion	CS PCa
Zhang (2017)	China/1	12/2014-2/2016	Elevated PSA and/or abnormal DRE	253	Median 69	Median 10.05	Transperineal	Transperineal	Systematic+ targeted	3T	PIRADS v1	Software fusion	Overall PCa CS PCa
Retrospective cohort studies													
Acar (2015)	Turkey/1	1/2012-2/2014	Elevated PSA and/or abnormal DRE Family history of PCa Abnormal	100 (37/63)	Mean 7.6/Mean 5.9	Mean 62.3/Mean 60.4	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1	Cognitive fusion In-bore fusion	CS PCa

			PSA adjunct tests										
Bryant (2019)	United Kingdom/1	1/2015-7/2017	NR	1789 (997/792)	Median 7.9/Median 7.6	Median 69/Median 68	Transrectal	Transrectal	Systematic+ targeted	1.5T 3T	PIRADS v2	Cognitive fusion	Overall PCa CS PCa CS PCa in patients with negative MRI
Chen (2015)	China/1	6/2008-12/2013	Elevated PSA and/or abnormal DRE	420	Median 9.73	Median 67	Transperineal	Transperineal	Systematic+ targeted	3T	5-point scale	Cognitive fusion	Overall PCa
Choi (2018)	South Korea/1	9/2013-3/2017	Elevated PSA (PSA>=2.5 ng/ml) and/or abnormal DRE	1991 (1786/223)	Median 4.62/Median 4.51	Median 64/ Median 66	Transrectal	Transperineal		3T	PIRADS v2	Software fusion Cognitive fusion	Overall PCa CS PCa
Kam (2018)	Australia/1	6/2014-8/2016	NR	121	Mean 7.44	Mean 65.5	Transrectal	Transrectal Transperineal	Systematic+ targeted	1.5T	PIRADS v2	Software fusion Cognitive fusion	CS PCa
Maxeiner (2018)	Germany/1	1/2012-12/2016	at least one suspicious lesion of the prostate according to the PI-RADS	318	Median 7.14	Median 68	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1 & v2	Software fusion	CS PCa

			classification in mpMRI defined as PI-RADS ≥3										
Mendhiratta (2015)	USA/1	6/2012-6/2015	NR	382	Mean 6.8	Mean 64.5	Transrectal	Transrectal	Systematic+ targeted	3T	Likert	Software fusion	Highest Gleason score CS PCa
Peltier (2016)	Belgium/1	mpMRI 2011-2013, TRUS 2006-2007	Elevated PSA and/or abnormal DRE	119	Median 6.98/Median 6.19	Median 65/Median 63	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v1	Software fusion	Overall PCa CS PCa
Washino (2018)	Japan/2	1/2010-4/2014	Elevated PSA (PSA <15 ng/ml)	496 (281/215)	Median 6.7/Median 6.4	Median 68/Median 68	Transperineal	Transperineal	Systematic+ targeted	1.5T 3T	3-point scale	Cognitive fusion	Overall PCa CS PCa
Yarlagadda (2018)	USA/1	2014-2016	Elevated PSA (PSA > 4ng/ml) and/or abnormal DRE	69	Mean 7.71	Mean 64.33	Transrectal	Transrectal	Systematic+ targeted	3T	PIRADS v2	Software fusion	Overall PCa

CS=clinically significant; GGG=Gleason grade group; PSA=Prostate specific antigen, NR=Not reported; MRI=magnetic resonance imaging; PIRADS=Prostate Imaging Reporting and Data System; SBX = Systematic biopsy; T=Tesla; TGBX = Targeted biopsy

Figure 1. – Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow chart

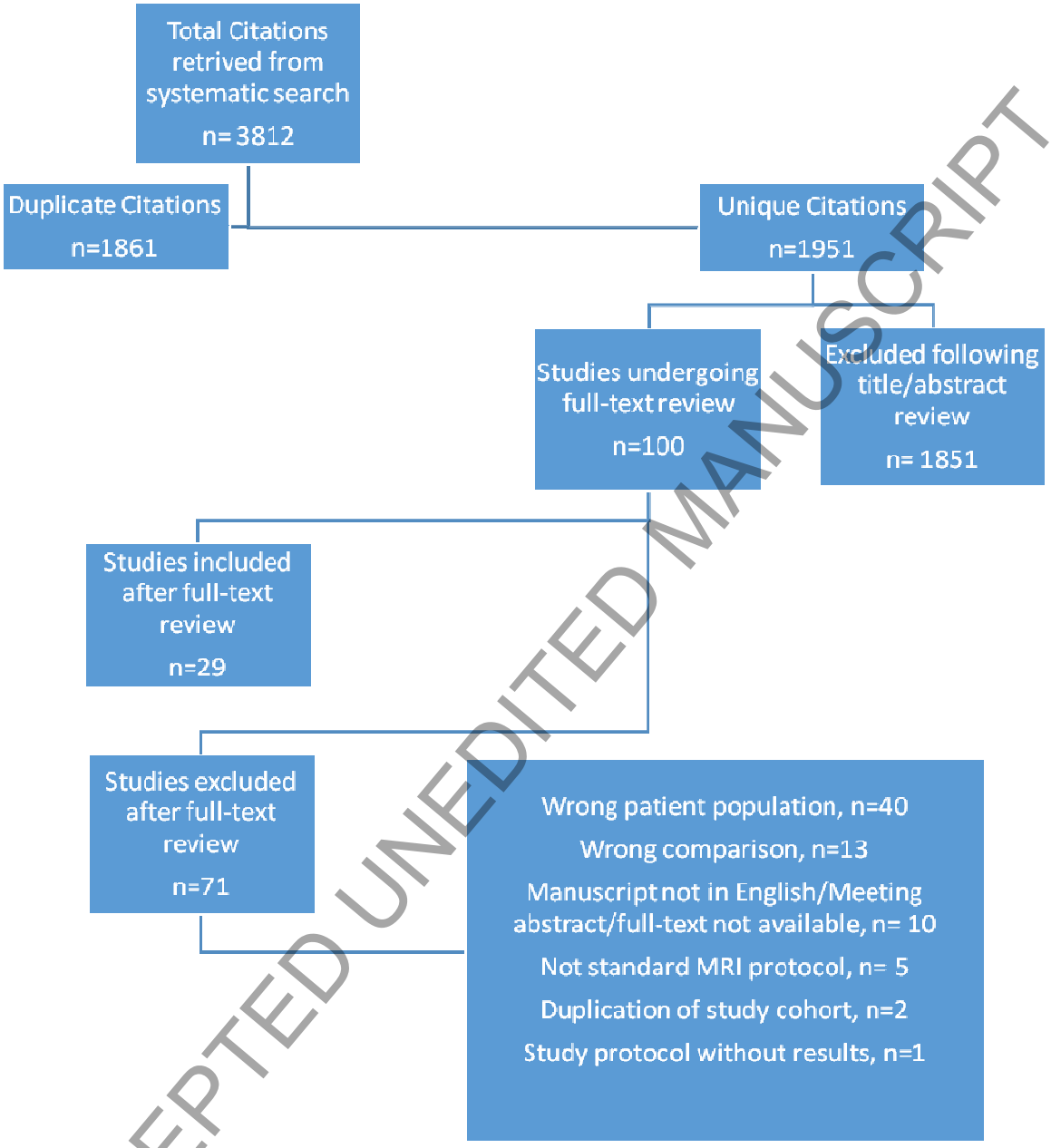
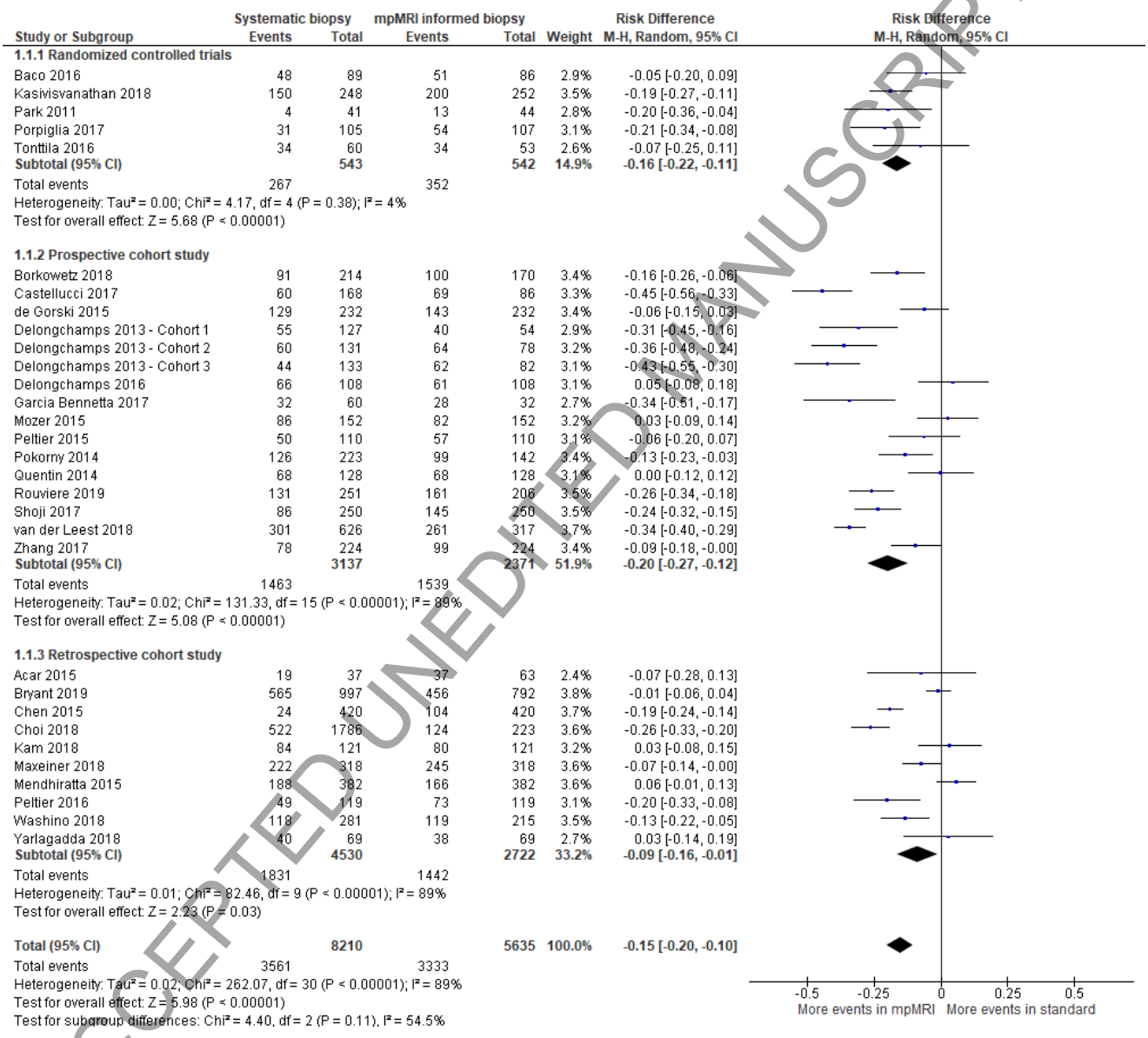
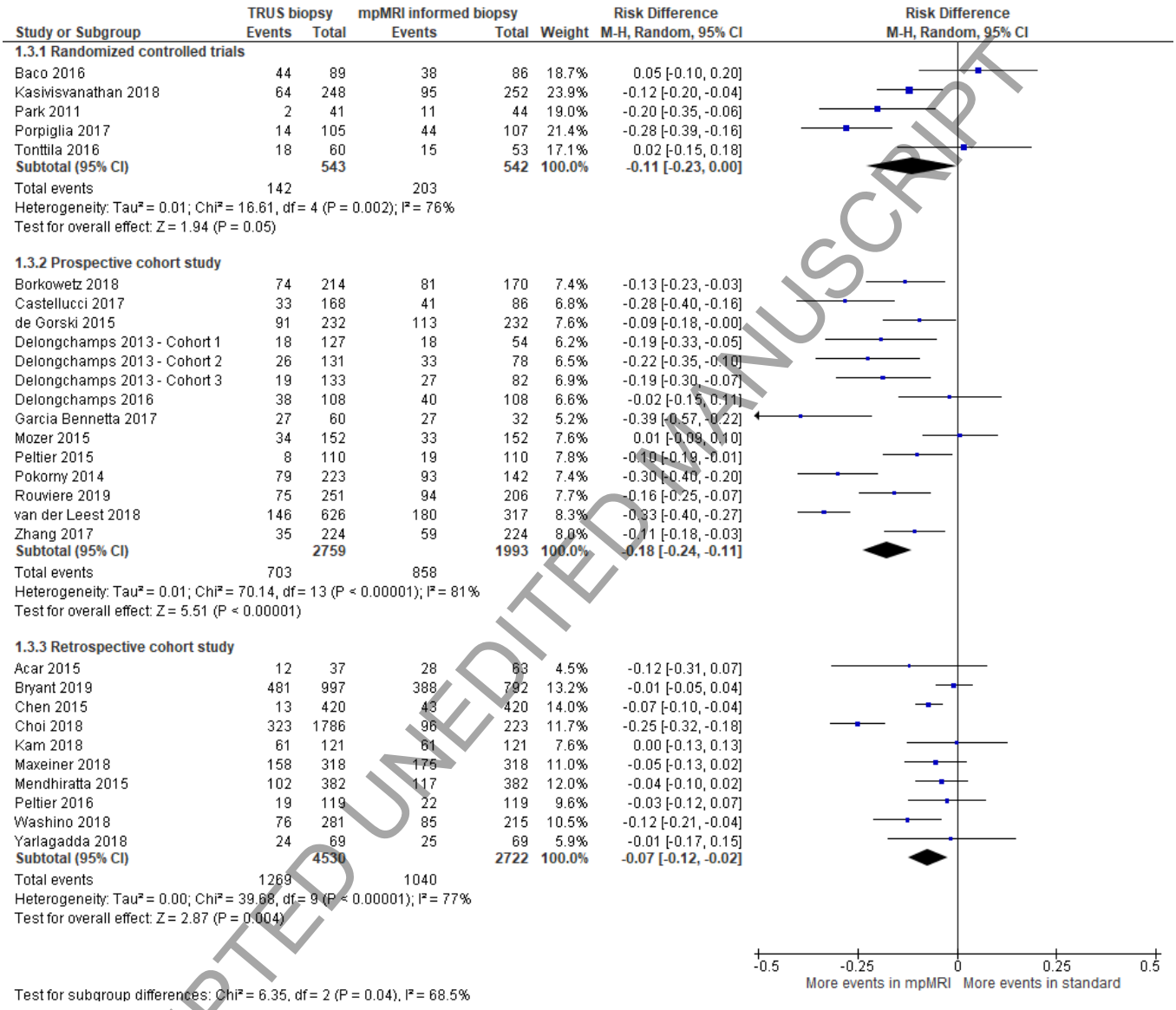


Figure 2. Forest plot for meta-analysis of the difference in prostate cancer diagnosis between patients assessed using systematic biopsy or mpMRI-informed biopsy, stratified by study methodology: (a) any prostate cancer diagnosis, (b) clinically-significant prostate cancer diagnosis, (c) clinically-insignificant prostate cancer diagnosis, (d) high-grade prostate cancer diagnosis.

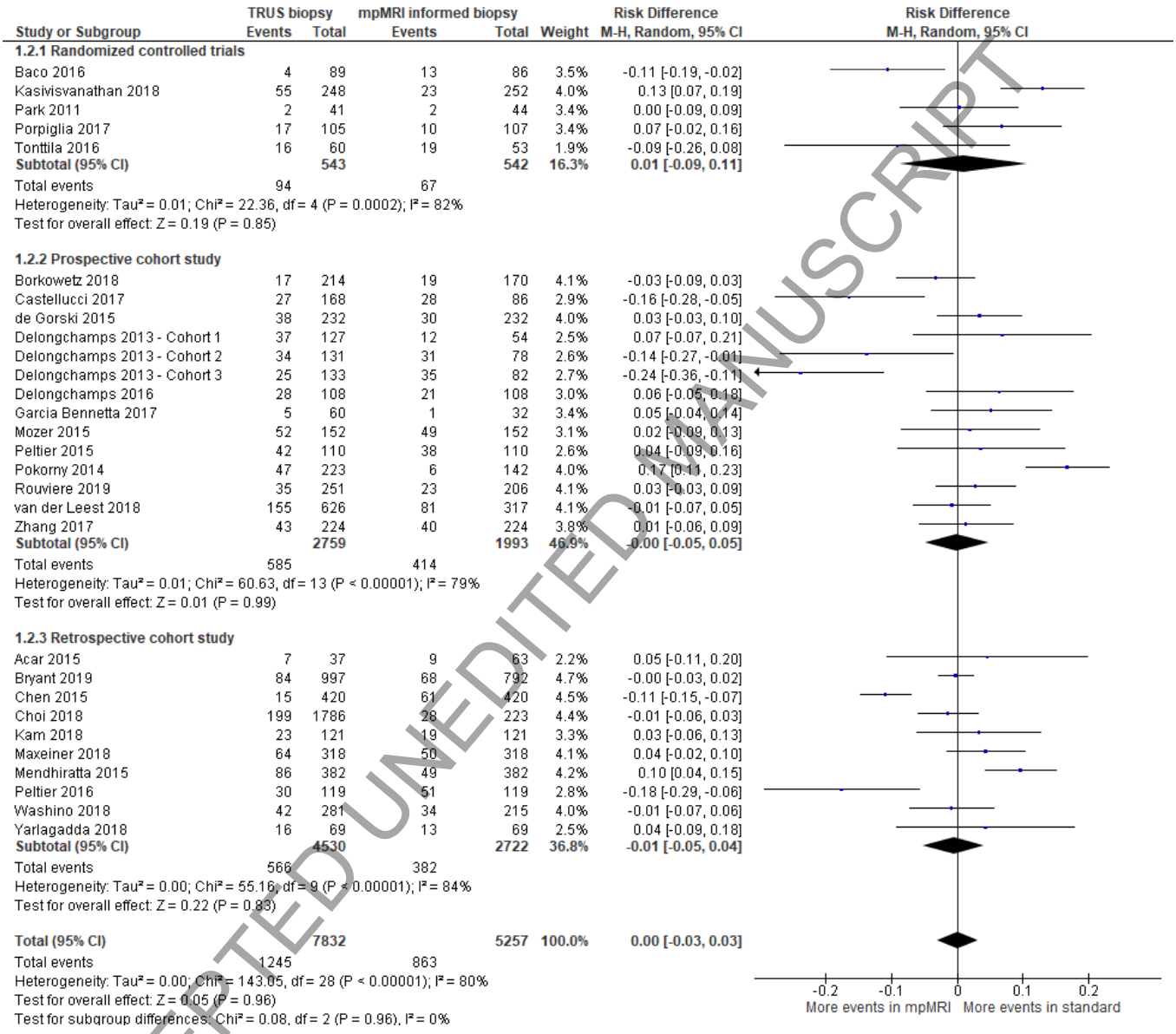
(a) any prostate cancer diagnosis



(b) clinically-significant prostate cancer diagnosis



(c) clinically-insignificant prostate cancer diagnosis



(d) high-grade prostate cancer diagnosis

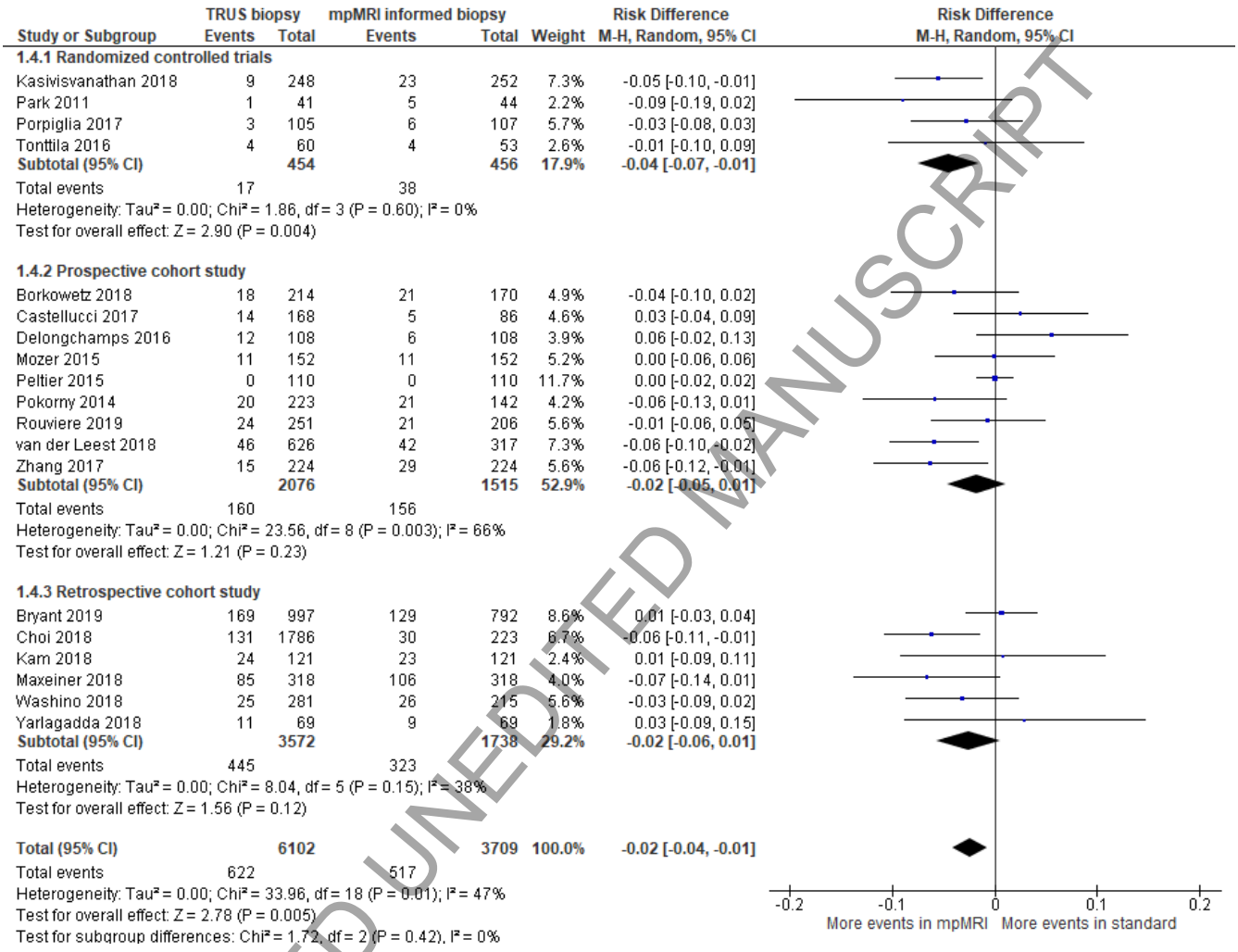
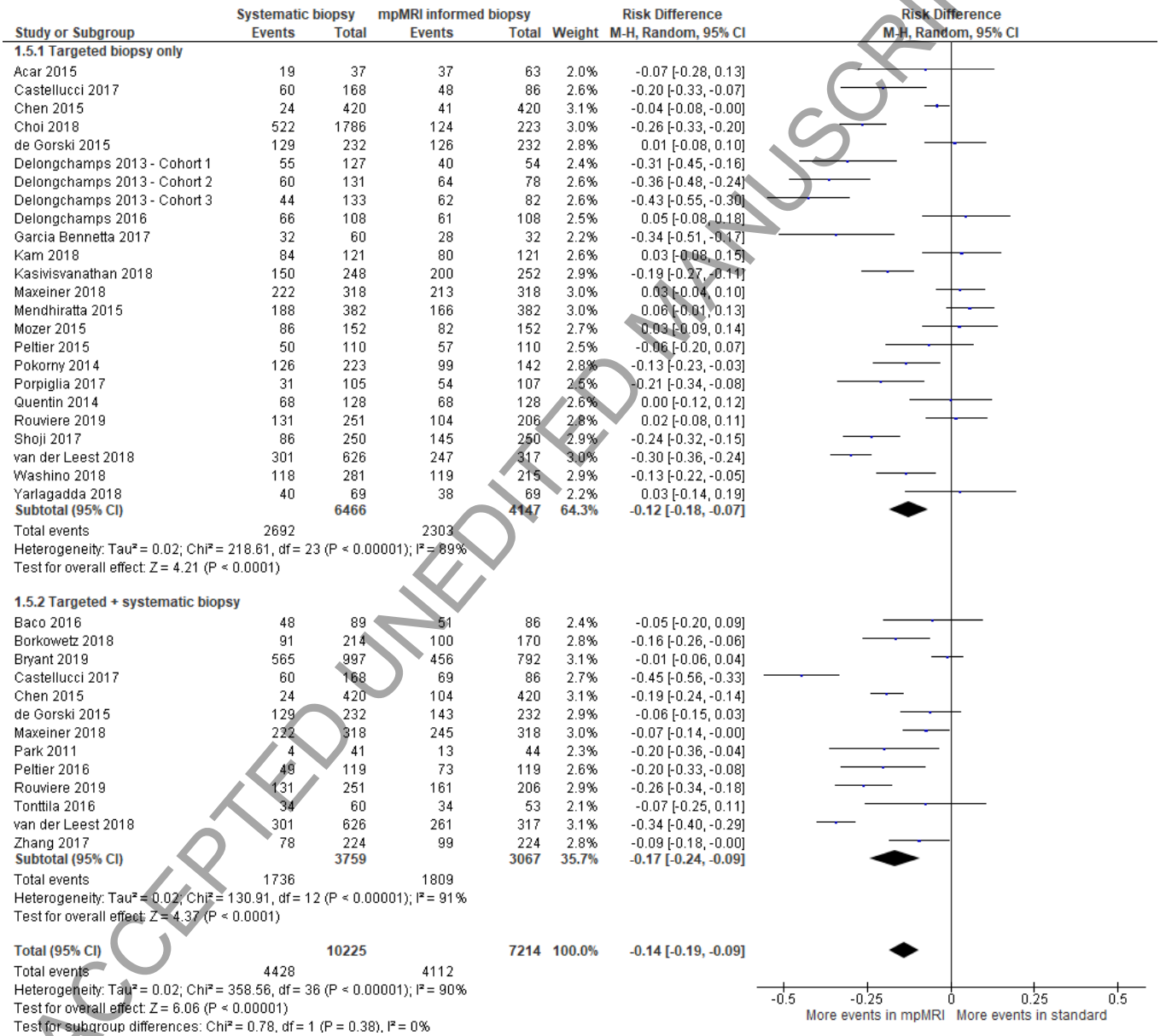
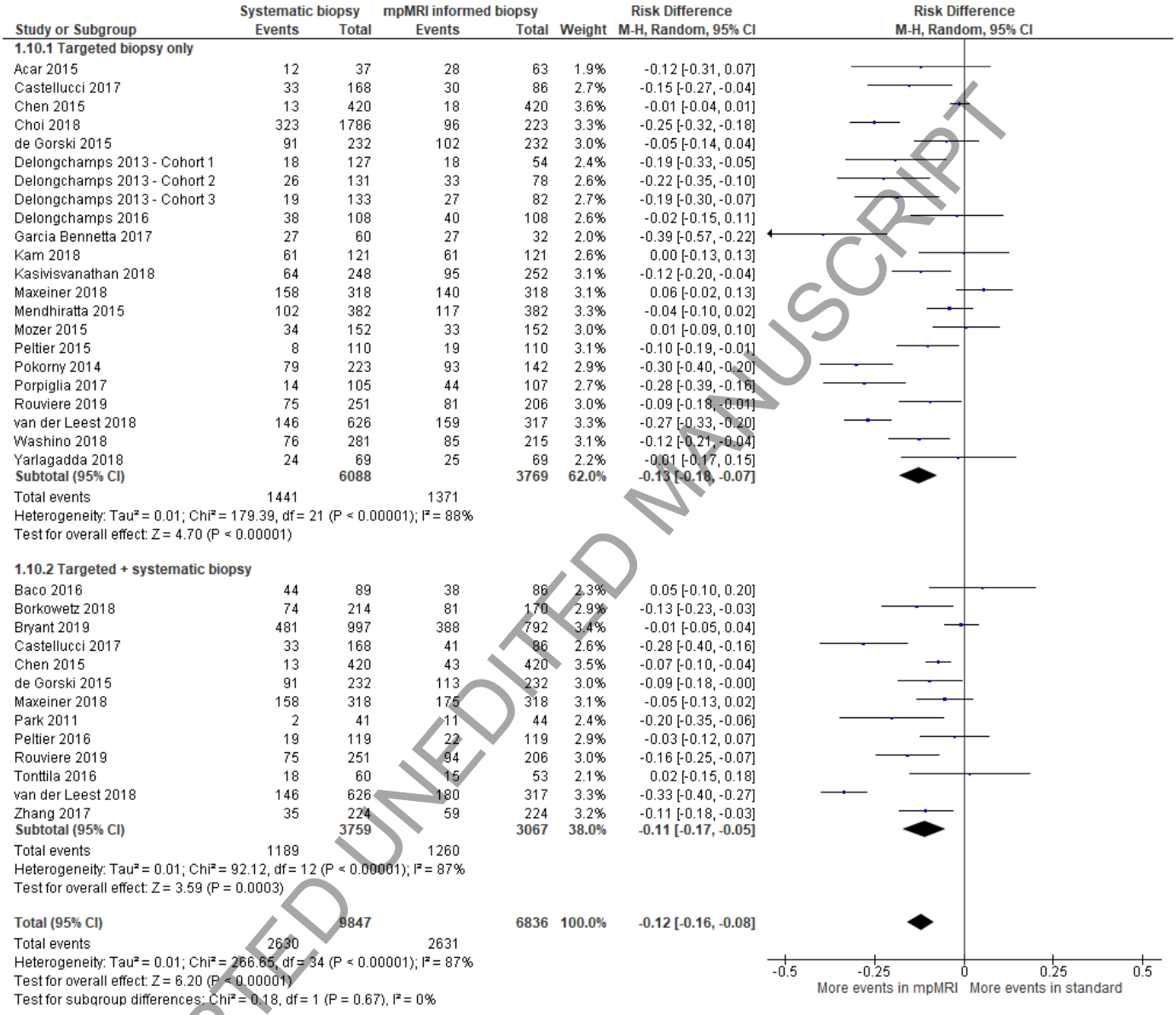


Figure 3. Forest plot for meta-analysis of the difference in prostate cancer diagnosis between patients assessed using systematic biopsy or mpMRI-informed biopsy, stratified by inclusion of systematic biopsy in the mpMRI-informed biopsy arm: (a) any prostate cancer diagnosis, (b) clinically-significant prostate cancer diagnosis, (c) clinically-insignificant prostate cancer diagnosis, (d) high-grade prostate cancer diagnosis.

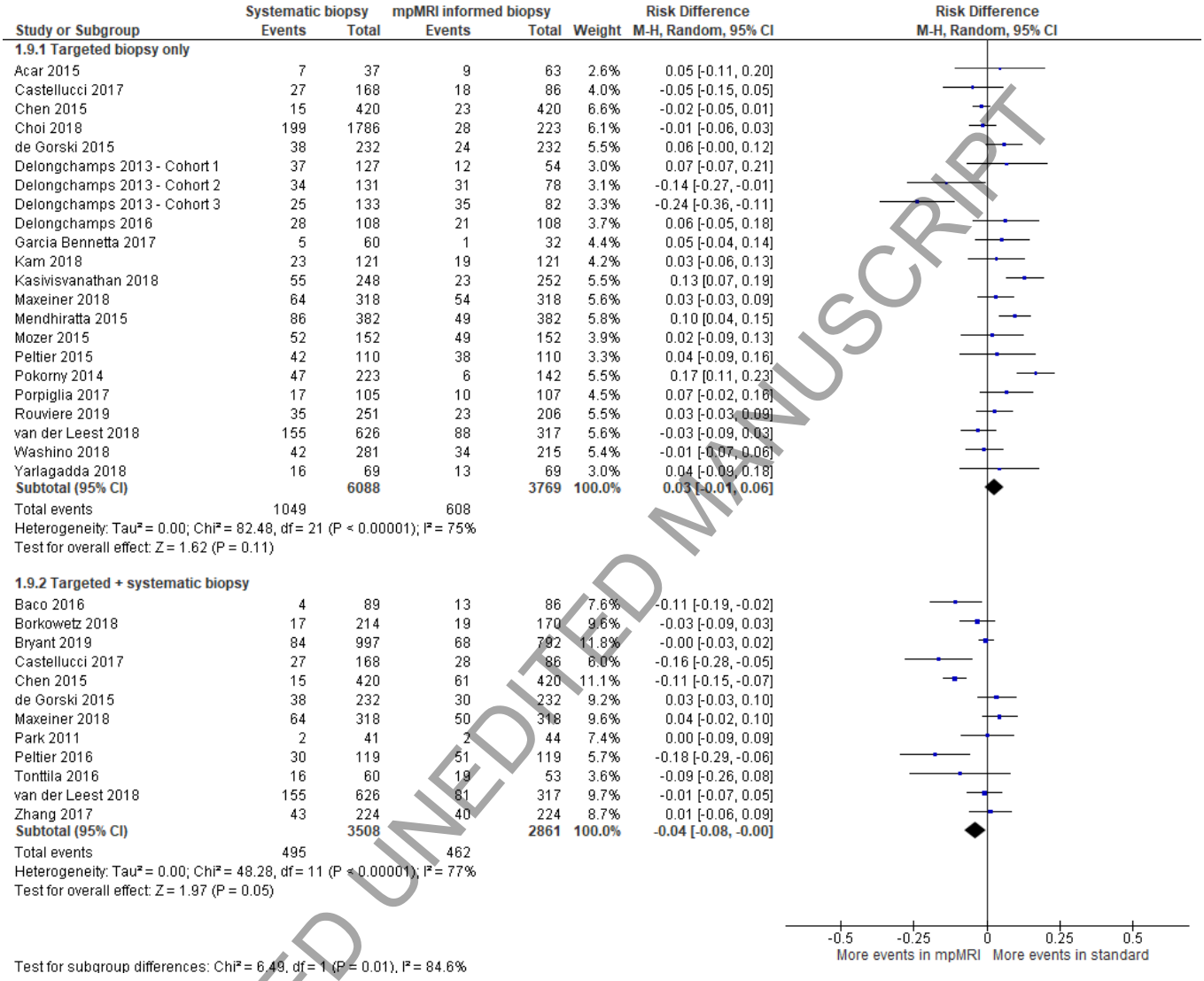
(a) any prostate cancer diagnosis



(b) clinically-significant prostate cancer diagnosis



(c) clinically-insignificant prostate cancer diagnosis



(d) high-grade prostate cancer diagnosis