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The effects of transcranial direct current stimulation on upper-limb function post-stroke: a meta-analysis of multiple-session studies

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HIGHLIGHTS

- Chronic stroke patients, in comparison to (sub)acute patients, benefitted most from adjuvant tDCS.
- Application of anodal, cathodal, or bihemispheric tDCS during conventional therapy led to greater improvements than application before conventional therapy.
- Higher charge density, current density and stimulation duration led to greater improvements, while increasing the number of sessions did not.

ABSTRACT

Objective: To systematically review how patient characteristics and/or transcranial direct current stimulation (tDCS) parameters influence tDCS effectiveness in respect to upper limb function post-stroke.

Methods Three electronic databases were searched for sham-controlled randomised trials using the Fugl-Meyer Assessment for upper extremity as outcome measure. A meta-analysis and nine subgroup-analyses were performed to identify which tDCS parameters yielded the greatest impact on upper limb function recovery in stroke patients.

Results Eighteen high-quality studies (507 patients) were included. tDCS applied in a chronic stage yields greater results than tDCS applied in a (sub)acute stage. Additionally, patients with low baseline upper limb impairments seem to benefit more from tDCS than those with high baseline impairments. Regarding tDCS configuration, all stimulation types led to a significant improvement, but only tDCS applied during therapy, and not before therapy, yielded significant results. A positive dose-response relationship was identified for current/charge density and stimulation duration, but not for number of sessions.

Conclusion Our results demonstrate that tDCS improves upper limb function post-stroke. However, its effectiveness depends on numerous factors. Especially chronic stroke patients improved, which is promising as they are typically least amenable to recovery.

Significance The current work highlights the importance of several patient-related and protocol-related factors regarding tDCS effectiveness.

KEYWORDS: Transcranial direct current stimulation; Stroke; Upper limb; Motor recovery; Review; Meta-analysis.

1. INTRODUCTION

Stroke or cerebrovascular disease is one of the leading causes of mortality and disability worldwide (Johnson et al., 2019, Virani et al., 2020). As more and more people survive a stroke (Feigin et al., 2014), the importance of rehabilitation is ever-increasing. While an enormous range of disabilities can be present post-stroke, motor disabilities are the most common (Adamson et al., 2004, Lawrence et al., 2001). Mainly the upper limb (UL) is affected with a prevalence of approximately 77% (Lawrence et al., 2001). Moreover, thirteen hours post-stroke, mild to severe paresis of the arm and hand is present in approximately 70% of patients (Nakayama et al., 1994), and only 5 to 20% achieve complete motor recovery of the initial UL impairment (Hendricks et al., 2002, Jørgensen et al., 1995, Kwakkel and Kollen, 2013). Although conventional therapies (e.g., strength training (Eng, 2004) and constraint-induced movement therapy (Taub and Uswatte, 2000, Wolf et al., 2006)) provide good recovery, their effectiveness is limited, as complete restoration of UL function seems unachievable (Byblow et al., 2015, Hendricks et al., 2002, Kwakkel and Kollen, 2013, Verheyden et al., 2008). Indeed, even in high-functioning stroke patients, deficits in UL kinematics remain present (Thrane et al., 2018).

Non-invasive brain stimulation (NIBS) appears to be a valid candidate to further improve recovery, adjunctive to conventional therapy. Through its effect on neuroplasticity processes, NIBS is suggested to potentially improve neurorecovery post-stroke (Liew et al., 2014). From a therapeutic-research point of view, transcranial direct current stimulation (tDCS) seems to be an interesting form of NIBS. Firstly, tDCS can easily be applied simultaneously with other therapies (Alisar et al., 2020, Bolognini et al., 2011, Chew et al., 2020, Liao et al., 2020), which is crucial since a combined NIBS-therapy approach generally leads to better results (Barros Galvão et al., 2014, Marquez et al., 2015, O'Brien et al., 2018, Rubi-Fessen et al., 2015). Secondly, tDCS is cheap and safe to apply, and well-tolerated (Aparicio et al., 2016, Bikson et al., 2016, Brunoni et al., 2011, Poreisz et al., 2007, Stagg and Nitsche, 2011). Thirdly, tDCS allows for placebo-controlled double-blind studies. Several studies have shown that subjects cannot reliably discriminate between tDCS and sham tDCS (StDCS) (Gandiga et al., 2006, Ghasemian-Shirvan et al., 2020, Ney et al., 2021, Saldanha et al., 2020). In addition, tDCS has been widely used in a multitude of (clinical) applications, mostly in the domain of neurological disorders (Bai et al., 2019, Byeon, 2020, da Silva et al., 2020, Mishra and Thrasher, 2020, Pilloni et al., 2020, Viana et al., 2014). tDCS can induce (long-term) neuroplastic effects (Fritsch et al., 2010, Hattori et al., 1990, Islam et al., 1995, Liew et al., 2014, Monte-Silva et al., 2013, Nitsche et al., 2008, Nitsche et al., 2003), promote motor learning (Cuypers et al., 2013, Firouzi et al., 2020, Fritsch et al., 2010, Márquez-Ruiz et al., 2012, Masoudian et al., 2020, Takeuchi and Izumi, 2012), and influence regional cerebral blood flow (Peruzzotti-Jametti et al., 2013, Wachter et al., 2011, Workman et al., 2020, Zheng et al., 2011). In a standard paradigm, a low continuous current of 1mA – 2mA is provided from two 20 – 35cm² area

surface electrodes: an anode and a cathode (Arul-Anandam et al., 2009, Liew et al., 2014, Nitsche et al., 2008). This results in the modulation of the underlying brain regions (Liew et al., 2014, Nitsche and Paulus, 2000, 2001). In general, the anode has been suggested to increase cortical excitability, whereas the cathode has been suggested to decrease cortical excitability (Nitsche and Paulus, 2000, 2001). This hypothesis, however, seems to be an oversimplification, as factors such as stimulation intensity and stimulation duration can diminish or even reverse the effects of anodal and cathodal tDCS (Agboada et al., 2019, Batsikadze et al., 2013, Hassanzahraee et al., 2020, Jamil et al., 2017, Mosayebi Samani et al., 2019, Vignaud et al., 2018).

In stroke patients, tDCS is generally applied in the context of the interhemispheric competition model. This model states that post-stroke, the overactive unaffected hemisphere yields an inhibitory influence over the underactive affected hemisphere (Bütefisch et al., 2008, Di Pino et al., 2014, Hummel and Cohen, 2006, Murase et al., 2004, Nowak et al., 2009, Rehme et al., 2012, Schjetnan et al., 2013, Schlaug and Renga, 2008). This leads to the ipsilesional hemisphere not only being disabled due to the stroke-induced tissue damage but also due to excessive interhemispheric inhibition (Bütefisch et al., 2008, Di Pino et al., 2014, Murase et al., 2004). On this basis, tDCS can serve as a means to either increase ipsilesional cortical excitability through anodal stimulation, to decrease contralesional cortical excitability through cathodal stimulation, or to do both through a bihemispheric electrode montage (Bai et al., 2019, Hummel and Cohen, 2006, Schjetnan et al., 2013, Schlaug and Renga, 2008). However, the interhemispheric competition model has fallen into dispute, as evidence suggests that both M1 excitability in the unaffected hemisphere and interhemispheric inhibition were similar in healthy controls and both acute, and chronic stroke patients (McDonnell and Stinear, 2017, Stinear et al., 2015). The more recent bimodal balance recovery model (Di Pino et al., 2014) postulates that applicability of the interhemispheric competition model depends on the amount of structural reserve a patient has; more specifically, the integrity of the corticospinal tract in the affected hemisphere (Harris-Love and Harrington, 2017). This model states that in severely affected patients, functional recovery is achieved by means of substitution of the affected hemisphere by the unaffected hemisphere (Di Pino et al., 2014, Duyckaerts and Litvan, 2008, Harris-Love and Harrington, 2017, Sankarasubramanian et al., 2017, Slavin et al., 1988).

As tDCS has sparked the interest of many researchers throughout the years, it should come as no surprise that numerous researchers have assessed its effectiveness regarding UL rehabilitation post-stroke. Likewise, numerous reviews and meta-analyses of the topic exist (Bai et al., 2019, Butler et al., 2013, Chhatbar et al., 2016, Elsner et al., 2017, Lefebvre and Liew, 2017, Lüdemann-Podubecká et al., 2014, Nowak et al., 2010, Triccas et al., 2016). While some conclude that tDCS as adjunctive therapy in UL rehabilitation is promising (Butler et al., 2013, Chhatbar et al., 2016, Lüdemann-Podubecká et al.,

2014, Nowak et al., 2010), others report a non-significant effect (Elsner et al., 2017, Triccas et al., 2016). The most recently available meta-analysis was conducted by Bai et al. (2019) and summarised studies published up until 2018. Since then, numerous novel studies have appeared (Alisar et al., 2020, Beaulieu et al., 2019, Bornheim et al., 2020, Chew et al., 2020, Edwards et al., 2019, Iodice et al., 2020, Jin et al., 2019, Liao et al., 2020, Mazzoleni et al., 2019, Yao et al., 2020). Furthermore, the work of Bai et al. (2019) did not evaluate the effect of factors such as sequence of stimulation, charge density and baseline impairment. However, these factors are known to influence tDCS efficacy (Chhatbar et al., 2016, Jin et al., 2019, Lefebvre and Liew, 2017, Marquez et al., 2015, Sriraman et al., 2014). The review of Lefebvre and Liew (2017) provides a compelling overview of numerous parameters [i.e., patient characteristics (biological factors, time after stroke, location and nature of lesion, and baseline impairment); therapy content; electrode placement; tDCS montage] that can influence the effect of tDCS.

The current work aims to identify if tDCS improves post-stroke UL function. Moreover, it intends to unravel whether and how the effectiveness of tDCS relates to patient characteristics (stroke stage and baseline impairment), tDCS configuration (stimulation type, stimulation sequence and target region), and/or dose-related parameters (current density, charge density, stimulation duration, and the number of sessions). Although there is evidence that all of these factors influence tDCS effectiveness, consensus is lacking (Bai et al., 2019, Chhatbar et al., 2016, Lefebvre and Liew, 2017, Marquez et al., 2015). Only high-quality sham-controlled randomised trials will be included in the current analysis to maximise the value and interpretability of the results Furthermore, only studies using the Fugl-Meyer Assessment for upper extremity (FMA-UE) (Fugl-Meyer et al., 1975) as outcome measure will be analysed. Not only is the FMA-UE the most used outcome measure post-stroke and considered the gold standard for measuring post-stroke UL function, the inclusion of solely one outcome measure will benefit the interpretability of the current work (Baker et al., 2011, Chhatbar et al., 2016, Kwakkel et al., 2017, Santisteban et al., 2016).

2. METHODS

2.1. Search methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2009). Three electronic databases (Embase, PubMed and Web of Science) were consulted to answer the following question: “Does tDCS improve UL function post-stroke, measured by the FMA-UE, in comparison to sham treatment”. Search terms were modified for each database and are displayed in Table 1. The last search was undertaken on October 30th, 2020. All duplicate studies were removed. Three researchers (EB, LV and SVH), conducted

the literature search independently. All studies were screened based on title and abstract. Subsequently, the full-texts of the remaining articles were retrieved and screened for eligibility (cf., 2.2. Eligibility criteria). Disagreements between the researchers were resolved via a consensus-based discussion.

2.2. Eligibility criteria

Studies included in this systematic review had to meet the following inclusion criteria: (i) the study was a randomised controlled trial, in which the control group received sham therapy; (ii) the applied intervention consisted of solely tDCS or tDCS in combination with an additional intervention (e.g., constraint-induced movement therapy, strength training); (iii) the included population had suffered a stroke and presented with UL impairment; (iv) the FMA-UE was reported as an outcome measure; (v) studies were written in English. Studies were excluded if: (i) other forms of NIBS were applied in combination with tDCS; (ii) the study was a cross-over study; (iii) full-text or essential information, such as p-values, baseline and post-intervention FMA-UE score and standard deviation (SD), was missing and could not be retrieved after contacting the corresponding author.

2.3. Data extraction

Data were extracted by three researchers (EB, LV and SVH), using a standardised data extraction form (Nancy, 2010). Information regarding study design, number of participants, patient characteristics (stroke stage and baseline impairment), tDCS configuration (stimulation type, stimulation sequence and target region), dose-related parameters (current density, charge density, stimulation duration and number of sessions), and results (FMA-UE outcome and significance) were documented. For further statistical analysis of the FMA-UE score, the mean difference (MD) and SD between pre- and post-intervention for each group (i.e., tDCS and StDCS) were extracted from each study. When the MD and SD were not reported, available data was used to calculate them.

2.4. Quality assessment

The methodological quality of each included study was assessed by three independent researchers (EB, LV and SVH), using two different assessment tools. (i) The PEDro scale (Blobaum, 2006) assessed the internal validity of studies (Maher et al., 2003). Consisting of 11 items, this scale awards one point when a criterion is fulfilled. Since the first item is not included in the total result, a study can maximally score 10/10, which indicates high methodological quality. Studies were excluded when scoring ≤ 6/10. (ii) The Cochrane Collaboration's tool for assessing the risk of bias evaluated the risk of bias across the studies included in the review (Higgins et al., 2011). The tool consists of seven items, each evaluating a subtype of bias. The total risk of bias per item can be either 'Low', 'Unclear' or 'High'. Studies were excluded if 'High' was scored on ≥ 2 items.

2.5. Data analysis

The effectiveness of tDCS vs StDCS was evaluated using the MD and SD of each group per study (cf., 2.3. Data extraction). Data was analysed with R 4.0.2. (R Foundation for Statistical Computing, Vienna, Austria) and RStudio (RStudio Team, PBC, Boston), using the *dmetar* (version 0.0.9000) (Harrer et al., 2019a) and *meta* (version 4.15-1) (Balduzzi, 2019) packages. A Random-Effects Model was applied to enable the generalisation of the results beyond the included studies (Borenstein et al., 2011, Cuijpers, 2016, Harrer et al., 2019b, Hedges and Vevea, 1998). The effect size was expressed as the standardised MD (SMD), calculated in the Hedges' g format (Hedges, 1981). This format was chosen as it controls for bias in small studies and is commonly used in meta-analyses (Borenstein et al., 2011, Chhatbar et al., 2016, Harrer et al., 2019b). Hedge's g values of respectively < 0.2 – 0.5, 0.5 – 0.8 and > 0.8, were considered to be mild, moderate, and strong effects (Chhatbar et al., 2016; Cohen, 1988). A 95% confidence interval (CI) was calculated. Prediction intervals were calculated as well using formula 12 of Higgins et al. (2009). This was done because CI's do not incorporate a measure of the extent of heterogeneity, although this is important to correctly estimate effects in future patients (Higgins et al., 2009, IntHout et al., 2016). Nine factors, bundled into three clusters (Fig. 1), were analysed using a Mixed-Effects-Model subgroup-analysis (Borenstein et al., 2011, Cuijpers, 2016, Harrer et al., 2019b, Hedges and Vevea, 1998). The first cluster, patient characteristics, consisted of two factors; stroke stage and baseline impairment. Factors in this cluster were divided into subgroups based on previous literature (Bernhardt et al., 2017, Woytowicz et al., 2017). The second cluster, tDCS configuration, consisted of three factors; stimulation type, stimulation sequence and target region. Factors in this cluster were divided into subgroups based on clear, demarcated differences. The third cluster, dose-related parameters, consisted of four factors; current density, charge density, stimulation duration and number of sessions. As it was impossible to divide the factors in the third cluster into subgroups on the basis of previous literature or clear, demarcated differences, arbitrary ranges were used.

Between-study heterogeneity was estimated using Cochran's Q and I^2 (Harrer et al., 2019b, Higgins and Thompson, 2002). I^2 values of respectively ~0.25, ~0.50 and ~0.75 were considered to indicate low, moderate and substantial heterogeneity (Higgins et al., 2003). In the general Random-Effects Model, studies inducing a large degree of heterogeneity were identified using three statistical procedures; (i) outlier detection (i.e., studies of which the 95% CI bound was lower/higher than the pooled 95% CI upper/lower bound) (Harrer et al., 2019b); (ii) a Baujat plot (i.e., plot displaying each individual study's contribution to overall heterogeneity plotted against its contribution to the overall pooled result) (Baujat et al., 2002) and (iii) a graphical display of study heterogeneity (GOSH) (i.e., scatterplot displaying summary estimates of the SMD and I^2 for one million randomly selected meta-analyses (subsets), enabling investigation of heterogeneity and identification of influential studies) (Olkin et al.,

2012). Identified studies were marked as outliers and were removed. The general Random-Effects model was reconducted to assess the robustness of the current findings (Higgins, 2008). Regarding subgroup analyses, the outlier-studies were retained as there was no clear way to evaluate if these effect sizes were attributable to coincidence or not and their removal could result in data manipulation (Higgins, 2008). Publication bias was assessed through a Contour-enhanced Funnel Plot (Peters et al., 2008). In this plot, the effect size of each study is plotted against the standard error of the study (with larger studies having a smaller standard error) (Harrer et al., 2019b). If no publication bias is present, the plot resembles a symmetrical funnel shape (J. Light and B. Pillemer, 1986). The colours of the funnel plot aid interpretation as they signify in which significance level the effect sizes of each study fall (Peters et al., 2008). The Egger test was performed as a quantitative assessment of the funnel plot (a)symmetry (Egger et al., 1997). For all analyses, α was set to 0.05.

3. RESULTS

3.1. Study selection and quality

The complete study selection procedure is displayed in Figure 2. Across the three electronic databases, 632 results were retrieved. A total of 243 duplicate studies were removed, resulting in 389 studies that were screened for inclusion based on title and abstract. Out of those studies, 327 studies were excluded. The remaining 62 studies were assessed for eligibility based on the full-text and study quality, as evaluated by the PEDro scale and Cochrane Collaboration's tool for assessing risk of bias. Finally, 18 high-quality, randomised sham-controlled studies were included in this meta-analysis, involving 507 stroke patients. Table 2 displays the characteristics of all included studies. Four studies were divided into sub-studies. These studies consisted of two experimental groups (with the groups differing regarding patient characteristics or tDCS protocols), and reported the FMA-UE score for each subgroup separately (Jin et al., 2019, Kim et al., 2010, Rocha et al., 2016, Triccas et al., 2015). Each sub-study was included separately in the meta-analysis (Table 2). On average, studies scored 8.56 ± 0.76 (mean ± SD) on the PEDro scale, indicating high internal validity (Table 3). Regarding the Cochrane Collaboration's tool for assessing risk of bias (Fig. 3), risk of bias was either low or unclear but never high.

3.2. Drop-outs

In total, 480 out of 507 subjects completed the intervention reported in the included studies. Twenty-seven dropouts (i.e., 5.33%) were identified: 18 in the tDCS group and 9 in the StDCS group. In the tDCS group, reasons for drop-out were: death unrelated to treatment (1), refusal to continue (1), unrelated illness (4), headache (1), dizziness (1), skin reaction and pain (1), personal reasons (1) or not further specified (8). Reasons for drop-out in the sham group were: refusal to continue (2), unrelated illness (2), transfer to another hospital (2), technical failure (1) or not further specified (2).

3.3. General effectivity of tDCS

The results of the Random-Effects meta-analysis show that the applied tDCS protocols in the different studies on average yielded a moderate effect on UL function (SMD = 0.64; 95% CI = 0.29 - 0.99; $p < 0.001$; Fig. 4). Between-study heterogeneity was moderate to substantial (Cochran's Q = 66.08 ($p < 0.01$); I^2 = 68.2% [50.6% - 79.6%]). The prediction interval ranged from -0.79 to 2.07. Regarding the contour-enhanced funnel plot (Fig. 5A), some studies fell out of the shape of the funnel, with the study of Koh et al. (2017) deviating the most. Nonetheless, the studies were approximately uniformly distributed along the center line, as evaluated by the Eggers' test ($p = 0.142$), indicating that there was no publication bias. Outlier detection identified two studies as the lower limit of their 95-CI exceeded the upper limit of the pooled 95%-CI; Bornheim et al. (2020) and Koh et al. (2017). The Baujat plot (Fig. 5B) showed that these two studies (Bornheim et al., 2020, Koh et al., 2017) largely contributed to the degree of overall heterogeneity, while not influencing the overall pooled effect to a large degree. Moreover, the study of Edwards et al. (2019) was revealed to be an influential study; while it contributed to overall heterogeneity, it was also influential concerning the overall pooled effect (Baujat et al., 2002). GOSH plots (Fig. 5C – D) further confirmed that the studies of Bornheim et al. (2020) and Koh et al. (2017) were outliers. Therefore, the Random-Effects meta-analysis was reconducted without these studies (Fig. 5E). The improvement in FMA-UE remained significant in favour of the tDCS group (SMD = 0.57; 95% CI = 0.29 – 0.86; $p < 0.001$). The prediction interval ranged from -0.34 to 1.49. As expected, between-study heterogeneity decreased (Cochran's Q = 36.04 ($p = 0.01$); I^2 = 47.3% [11.2% - 68.7%]).

3.4. Cluster 1: Patient characteristics

3.4.1. Stroke stage

Three subgroups were created based on stroke stage (Bernhardt et al., 2017); (1) acute (0 – 7 days), (2) subacute (7 days – 6 months) and (3) chronic stroke (> 6 months) (Fig. 6). Three studies (Alisar et al., 2020, Straudi et al., 2016, Yao et al., 2020) were not included in this subgroup analysis as they included both subacute and chronic stroke patients, and did not report separate outcome measures for each subgroup.

Acute stroke

Two studies were included in this subgroup. No significant difference between the tDCS and StDCS group was present (SMD = 1.19; 95% CI = -7.01 – 9.40; $p = 0.065$). Moreover, substantial between-study heterogeneity was present (Cochran's Q = 5.01 ($p = 0.03$); I^2 = 80% [14% - 95%]).

Subacute stroke

Four studies were included in this subgroup. There was no significant difference between the tDCS and StDCS group (SMD = 0.14; 95% CI = -0.36 – 0.63; p = 0.444). Between-study heterogeneity was low (Cochran's Q = 2.57 (p = 0.63); I^2 = 0% [0% - 68%]).

Chronic stroke

Ten studies were included in this subgroup. tDCS led to a moderate and significant improvement in FMA-UE in comparison to StDCS (SMD = 0.68; 95% CI = 0.10 – 1.25; p = 0.009). Between-study heterogeneity was moderate to substantial (Cochran's Q = 37.34 (p < 0.01); I^2 = 71% [47% - 84%]).

3.4.2. Baseline impairment

Three subgroups were created based on initial impairment (Woytowicz et al., 2017) (Table 2); (1) mild (FMA-UE score: 43 – 66), (2) moderate (FMA-UE score: 29 – 42) and (3) severe (FMA-UE score: 0 – 28) baseline impairment (Fig. 7). The mean baseline FMA-UE score was calculated for each study using the weighted-average of both the tDCS and StDCS group baseline values.

Mild baseline impairment (mean FMA-UE score ± SD: 49.20 ± 4.78)

Six studies were included in this subgroup. A moderate, significant effect in favour of the tDCS group was noted (SMD = 0.60; 95% CI = 0.31 – 0.90; p < 0.001), and heterogeneity was low (Cochran's Q = 3.13 (p = 0.87); I^2 = 0% [0% - 27%]).

Moderate baseline impairment (mean FMA-UE score ± SD: 36.68 ± 2.53)

Eight studies were included in this subgroup. A moderate, significant effect in favour of the tDCS group was found (SMD = 0.69; 95% CI = -0.09 – 1.46; p = 0.036), and heterogeneity was moderate to substantial (Cochran's Q = 33.29 (p < 0.01); I^2 = 79% [59% - 89%]).

Severe baseline impairment (mean FMA-UE score ± SD: 24.83 ± 1.46)

Six studies were included in this subgroup. There was no significant difference between the tDCS and StDCS group (SMD = 0.62; 95% CI = 0.53 – 1.77; p = 0.167), and heterogeneity was substantial (Cochran's Q = 27.19 (p < 0.01); I^2 = 82% [61% - 91%]).

3.5. Cluster 2: tDCS configuration

3.5.1. Stimulation type

Three subgroups were identified (Table 2); (1) placing the anode over the ipsilesional hemisphere and the cathode (i.e., the reference electrode) over/above the (supra)orbital region (anodal stimulation), (2) placing the cathode over the contralesional hemisphere and the anode (i.e., the reference electrode) over/above the shoulder region (Fusco et al., 2014) or the (supra)orbital region (Kim et al., 2010, Rocha et al., 2016, Yao et al., 2020) (cathodal stimulation) and (3) placing the anode over the ipsilesional hemisphere and the cathode over the contralesional hemisphere (bihemispheric stimulation) (fig. 8). The study of Oveisgharan et al. (2018) was excluded from this analysis, as it combined bihemispheric and anodal stimulation (i.e., the tDCS group received bihemispheric

stimulation followed by anodal stimulation, the StDCS group received bihemispheric stimulation followed by sham stimulation (cf., 3.5.3. Target region)).

Anodal stimulation

Eight studies were included in this subgroup. A moderate, significant effect in favour of the tDCS group was found (SMD = 0.52; 95% CI = -0.04 – 1.07; p = 0.033), and heterogeneity was moderate to substantial (Cochran's Q = 28.33 (p < 0.01); I^2 = 72% [44% - 86%]).

Cathodal stimulation

Four studies were included in this subgroup. A moderate, significant effect in favour of the tDCS group was present (SMD = 0.64; 95% = -0.05 – 1.33; p = 0.003), and heterogeneity was low (Cochran's Q = 2.45 (p = 0.48); I^2 = 0% [0% - 81%]).

Bihemispheric stimulation

Seven studies were included in this subgroup. A strong, significant effect in favour of the tDCS group was found (SMD = 0.84; 95% CI = -0.06 – 1.74; p = 0.027), and between-study heterogeneity was substantial (Cochran's Q = 31.69 (p < 0.01); I^2 = 78% [56% - 89%]).

3.5.2. Stimulation sequence

Two subgroups were identified based on stimulation sequence (Table 2); (1) applying tDCS during therapy (i.e., concurrent tDCS), and (2) applying tDCS before therapy (i.e., consecutive tDCS) (Fig. 9). Various therapy modalities were combined with tDCS (Table 2). The study of Oveisgharan et al. (2018) was excluded from this analysis, as it did not combine tDCS with additional therapy.

Concurrent tDCS

Eleven studies were included in this subgroup. Overall, a moderate, significant effect in favour of the tDCS group relative to the StDCS group, was found (SMD = 0.79; 95% CI = 0.31 – 1.28; p < 0.001). Between-study heterogeneity was moderate to substantial (Cochran's Q = 33.13 (p < 0.01); I^2 = 64% [34% - 80%]).

Consecutive tDCS

Seven studies were included in this subgroup. There was no significant difference between the tDCS and StDCS group (SMD = 0.42; 95% CI = -0.26 – 1.09; p = 0.142). Between-study heterogeneity was substantial (Cochran's Q = 28.76 (p < 0.01); I^2 = 76% [51% - 88%]).

3.5.3. Target region

Three subgroups were identified based on target region (Table 2); (1) tDCS targeting DLPFC, (2) tDCS targeting M1, and (3) tDCS targeting the dorsal premotor cortex (PMd) and supplementary motor cortex (SMA) (Fig. 10).

DLPFC

One study was included in this subgroup. Oveisgharan et al. (2018) applied bihemispheric stimulation over left and right $M1_{hand}$ in both the tDCS and the StDCS group. Following this, anodal stimulation was applied over left DLPFC in the tDCS group, and sham stimulation was applied over left DLPFC in the StDCS group (Oveisgharan et al., 2018). There was no significant difference between the tDCS and StDCS group (SMD = 0.51; 95% CI = -0.38 – 1.41; p = 0.262).

M1

Sixteen studies were included in this subgroup. A moderate, significant effect in favour of the tDCS group was found (SMD = 0.65; 95% CI = 0.26 – 1.03; p < 0.001). Between-study heterogeneity was moderate to substantial (Cochran's Q = 66.02 (p < 0.01); I^2 = 71% [55% - 82%]).

PMd & SMA

One study was included in this subgroup. Cunningham et al. (2015) probed the effectivity of ipsilesional anodal tDCS over PMd and SMA. No significant difference between the tDCS and StDCS group was present (SMD = 0.67; 95% CI = -0.51 – 1.85; p = 0.263).

3.6. Cluster 3: Dose-related parameters

3.6.1. Current density

Three subgroups were created based on current density (Table 2); (1) low (0.029 mA/cm²), (2) moderate (0.030 – 0.060 mA/cm²) and (3) high (> 0.060 mA/cm²) current density (Fig. 11). The current and electrode size used in each study is displayed in Table 2.

Low current density

Six studies were included in this subgroup. No significant difference between the tDCS and StDCS group was present (SMD = 0.31; 95% CI = -0.11 – 0.73; p = 0.086). Between-study heterogeneity was low (Cochran's Q = 8.84 (p = 0.36); I^2 = 9% [0% - 68%]).

Moderate current density (mean current density ± SD: 0.054 mA/cm² ± 0.007)

Eight studies were included in this subgroup. A moderate, significant effect in favour of the tDCS group relative to the StDCS group was found (SMD = 0.75; 95% CI = -0.11 – 1.61; p = 0.040). Substantial between-study heterogeneity was present (Cochran's Q = 44.6 (p < 0.01); I^2 = 84% [71% - 92%]).

High current density (mean current density ± SD: 0.094 mA/cm² ± 0.017)

Four studies were included in this subgroup. A strong, significant effect in favour of the tDCS group was found (SMD = 1.02; 95% CI = 0.29 – 1.76; p < 0.001). Low between-study heterogeneity was present (Cochran's Q = 5.36 (p = 0.25); I^2 = 25% [0% - 70%]).

3.6.2. Charge density

To determine the effect of charge density, three subgroups were created (Table 2); (1) low (< 0.05 C/cm²), (2) moderate (0.05 – 0.1 C/cm²) and (3) high (> 0.1 C/cm²) charge density (Fig. 12). The electric charge and electrode size used in each study is displayed in Table 2.

Low charge density (mean charge density ± SD: 0.032 C/cm² ± 0.010)

Six studies were included in this subgroup. No significant difference between the tDCS and StDCS group was present (SMD = 0.52; 95% CI = -0.15 – 1.19; p = 0.065). Between-study heterogeneity was moderate to substantial (Cochran's Q = 21.36 (p < 0.01); I^2 = 67% [31% - 84%]).

Moderate charge density (mean charge density ± SD: 0.067 C/cm² ± 0.016)

Eight studies were included in this subgroup. A mild but significant effect in favour of tDCS was found (SMD = 0.33; 95% CI = -0.02 – 0.67; p = 0.033). Between-study heterogeneity was low to moderate (Cochran's Q = 14.14 (p = 0.12); I^2 = 36% [0% - 70%]).

High charge density (mean charge density ± SD: 0.166 C/cm² ± 0.041)

Four studies were included in this subgroup. A strong, significant effect in favour of the tDCS group was found (SMD = 1.58; 95% CI = 0.10 – 3.07; p < 0.001). Between-study heterogeneity was moderate to substantial (Cochran's Q = 9.93 (p = 0.02); I^2 = 70% [13% - 90%]).

3.6.3. Stimulation duration

Three subgroups were created based on stimulation duration per session (Table 2): (1) short (~10 minutes), (2) moderate (20 minutes) and (3) long (30 minutes) stimulation duration (Fig. 13).

Short stimulation duration (mean stimulation duration ± SD: 11.25 minutes ± 1.79)

Three studies were included in this subgroup. No significant difference between the tDCS and StDCS group was present (SMD = 0.52; 95% CI = -0.38 – 1.42; p = 0.064). Between-study heterogeneity was low (Cochran's Q = 3.01 (p = 0.39); I^2 = 0% [0% - 85%]).

Moderate stimulation duration

Eight studies were included in this subgroup. No significant difference between the tDCS and StDCS group was present (SMD = 0.44; 95% CI = -0.08 – 0.96; p = 0.058). Between-study heterogeneity was moderate to substantial (Cochran's Q = 33.03 (p < 0.01); I^2 = 73% [49% - 86%]).

Long stimulation duration

Seven studies were included in this subgroup. A strong, significant effect in favour of tDCS was found (SMD = 0.96; 95% CI = 0.17 – 1.74; p < 0.001). Between-study heterogeneity was moderate to substantial (Cochran's Q = 24.19 (p < 0.01); I^2 = 71% [40% - 86%]).

3.6.4. Number of sessions

To evaluate the effect of session amount, three subgroups were created (Table 2): (1) low (5 to 12 sessions), (2) moderate (15 – 24 sessions) and (3) high (30 – 36 sessions) session amount (Fig. 14).

Low session amount

Ten studies were included in this subgroup. A moderate, significant effect in favour of the tDCS group relative to the StDCS group was present (SMD = 0.56; 95% CI = 0.18 – 0.94; p = 0.001). Between-study heterogeneity was low to moderate (Cochran's Q = 19.14 (p = 0.09); I^2 = 37% [0% - 68%]).

Moderate session amount

Six studies were included in this subgroup. tDCS yielded a strong, significant effect on FMA-UE score in comparison to StDCS (SMD = 1.07; 95% CI = 0.17 – 1.97; p = 0.004). Between-study heterogeneity was moderate to substantial (Cochran's Q = 20.95 (p < 0.01); I^2 = 71% [38% - 87%]).

High session amount

Two studies were included in this subgroup. A mild, significant effect in favour of the StDCS group was present (SMD = -0.16; 95% CI = -0.26 – -0.06; p < 0.001). Moreover, between-study variability was low (Cochran's Q = 0 (p = 0.97); I^2 = 0%).

4. DISCUSSION

Overall, the results of the current meta-analysis indicate that the applied tDCS protocols on average yielded a positive effect on UL function. All studies consisted of multiple sessions, as it seems unlikely that one session of tDCS leads to significant improvements in the FMA-UE score (Chhatbar et al., 2016). After removal of two positive outliers, this significant effect in favour of tDCS remained present, which underscores the robustness of the current findings. Moreover, a low risk of publication bias (as evaluated by the contour-enhanced funnel plot and Egger test), high study quality (as evaluated by the PEDro scale and the Cochrane Collaboration's tool for assessing the risk of bias) and the use of the FMA-UE throughout all included studies maximise the interpretability of the current results. The prediction interval underscored the importance of the subgroup analyses: future studies should consider patient characteristics, tDCS configuration, and dose-related parameters when predicting the probability of success.

4.1. Cluster 1: Patient characteristics

The current meta-analysis indicates that tDCS yields no significant benefits in acute and subacute stroke patients. However, as only two studies were included in the acute subgroup, these results should be interpreted with caution. In contrast, UL function in chronic stroke patients significantly improved as a result of tDCS, which is in line with previous literature (Bai et al., 2019, Lüdemann-Podubecká et al., 2014, Marquez et al., 2015). Among researchers and therapists, the dogma prevails that therapy efficacy is maximal in the (sub)acute stage and diminishes in the chronic stage (Ballester et al., 2019, Kitago and Krakauer, 2013, Verheyden et al., 2008). This point-of-view might need to be readjusted, as the current results indicate that through administration of tDCS in the chronic phase, therapy efficacy can be enhanced. Although it has been argued that the stage-dependent differences

in tDCS effectiveness can be attributed to differences in corticospinal excitability (Bai et al., 2019, Buma et al., 2010, Jaillard et al., 2005, Rehme et al., 2012, Rehme et al., 2011), the exact nature of these differences and, more importantly, how this relates to tDCS remains poorly understood. Possibly, the current findings may be explained through the absence of spontaneous biological recovery in the chronic phase, as it subsides six months post-stroke (Byblow et al., 2015, Cramer, 2008, Grefkes and Fink, 2014, Langhorne et al., 2011, Li and Carmichael, 2006). Spontaneous recovery is known to involve certain biochemical and cellular mechanisms that are also influenced by tDCS, such as long-term potentiation and cortical excitability modulation (Byblow et al., 2015, Cramer, 2008, Fritsch et al., 2010, Grefkes and Fink, 2014, Langhorne et al., 2011, Liew et al., 2014, Monte-Silva et al., 2013, Nitsche and Paulus, 2000, 2001, Schjetnan et al., 2013). As the precise influence of tDCS on these mechanisms remains to be elucidated, the possibility of tDCS interfering with, or even disrupting, spontaneous recovery in the (sub)acute stage cannot be ruled out (Elsner et al., 2018, Schjetnan et al., 2013). A cautious approach to NIBS in patients in the (sub)acute stage seems warranted. Furthermore, it has been speculated that increasing cortical excitability through NIBS in perilesional brain areas might lead to an expansion of the stroke-induced lesion due to higher oxygen and glucose demands in the stroke penumbra (Picconi et al., 2006, Takeuchi and Izumi, 2012).

In line with the results of Marquez et al. (2015), subgroup analysis revealed that tDCS leads to significant improvements in mild and moderately impaired patients, but not in severely impaired patients. Regardless of baseline impairment, all included studies applied tDCS within the theoretical framework of the interhemispheric competition model (i.e., facilitation of ipsilesional hemisphere and inhibition of contralesional hemisphere) (Di Pino et al., 2014). According to the bimodal balance recovery model, however, severely impaired patients benefit more from substitution of the affected hemisphere by the unaffected hemisphere (i.e., facilitation of the contralesional hemisphere) (Di Pino et al., 2014). Although the bimodal balance recovery model remains poorly implemented in practice (e.g., none of the currently included studies applied tDCS within this theoretical framework), there is evidence that demonstrates its potential. Sankarasubramanian et al. (2017) investigated the effect of inhibitory and facilitatory repetitive transcranial magnetic stimulation over the contralesional hemisphere in both mild and severely impaired patients. Inhibitory stimulation yielded the best results in mildly affected patients, while severely affected patients benefitted most from facilitatory stimulation (Sankarasubramanian et al., 2017). On a different note, all studies in the subgroup of severely affected patients targeted M1, while evidence has indicated that more impaired patients typically have greater task-related activity in secondary motor areas (e.g., PMd) (Ward, 2011, Ward et al., 2003). Hence, in this subgroup, it might be more beneficial to target these areas (Cunningham et al., 2015, Sankarasubramanian et al., 2017).

4.2. Cluster 2: tDCS configuration

Anodal tDCS over the affected hemisphere, cathodal tDCS over the unaffected hemisphere, and bihemispheric tDCS (with anodal/cathodal stimulation over the affected/unaffected hemisphere respectively) all lead to a significant improvement in UL function. One mechanism that might explain the effectiveness of cathodal tDCS is the restoration of interhemispheric balance, which is in accordance with the interhemispheric competition model (Bai et al., 2019, Elsner et al., 2017, Lüdemann-Podubecká et al., 2014). However, it should be noted that the underlying rationale of the interhemispheric competition model has been partially debunked (cf., 1. Introduction, interhemispheric competition model) (McDonnell and Stinear, 2017, Stinear et al., 2015). This suggests that the cathodal tDCS-induced motor improvement is not per se reflective of a restored interhemispheric balance, but might be caused by other cathodal-tDCS induced effects (e.g., influence on neuroplasticity, promotion of motor learning) (Cuypers et al., 2013, Firouzi et al., 2020, Fritsch et al., 2010, Hattori et al., 1990, Islam et al., 1995, Liew et al., 2014, Márquez-Ruiz et al., 2012, Masoudian et al., 2020, Monte-Silva et al., 2013, Nitsche et al., 2008, Nitsche et al., 2003, Takeuchi and Izumi, 2012).

All studies included in the current meta-analysis but one (Oveisgharan et al., 2019) applied tDCS in combination with other therapy modalities. This was to be expected as tDCS is known to ideally occur in conjunction with other therapies to maximise long-term effects (Hummel et al., 2008, Marquez et al., 2015, Schlaug and Renga, 2008). In terms of stimulation sequence, the current findings indicate that concurrent tDCS leads to significant results while consecutive tDCS (i.e., tDCS before therapy) does not. One included study, conducted by Jin et al. (2019), directly compared concurrent vs consecutive bihemispheric tDCS during mirror therapy and also concluded that concurrent tDCS yields the best results. Moreover, other studies have reported similar findings, as applying anodal tDCS in healthy persons during training led to greater skill acquisition than anodal tDCS applied before therapy (Reis et al., 2009, Sriraman et al., 2014, Stagg et al., 2011). Applied concurrently, anodal ipsilesional tDCS and/or cathodal contralesional tDCS are hypothesised to serve a priming function through 'gating', i.e., transient disinhibition of intracortical inhibitory circuits which boosts motor learning (Jin et al., 2019, Ziemann and Siebner, 2008). However, recent evidence suggests that it is misplaced to completely disregard consecutive (Buchwald et al., 2019, Liao et al., 2020). By lowering the neuronal activity in the motor cortex prior to therapy, consecutive tDCS can decrease the threshold for induction of synaptic plasticity (Ziemann and Siebner, 2008). Moreover, it should be noted that heterogeneity for the consecutive subgroup was high, which may have masked its potential effectiveness. Furthermore, the protocols used in the studies of this subgroup differed substantially (cf., Table 2 and section 4.4.

Limitations and future directions). Therefore, a possible positive effect of tDCS in consecutive protocols should not be ruled out.

Regarding the target region, tDCS targeting ipsi- and/or contralesional M1 improved UL function significantly, whereas both tDCS over DLPFC and tDCS over PMd and SMA yielded no significant results. As the studies of Oveisgharan et al. (2018) and Cunningham et al. (2015) were both the only studies in their respective subgroup (respectively DLPFC and PMd & SMA), it seems likely that the small size of the subgroups was the reason for this lack of significant results (Burke et al., 2015, Wittes, 2009). Indeed, both Oveisgharan et al. (2018) and Cunningham et al. (2015) noted significant results in their own respective studies. Oveisgharan et al. (2018) applied bihemispheric tDCS in both the tDCS and StDCS groups before applying anodal/sham tDCS over left DLPFC in the tDCS/sham group, respectively. They noted a significant effect in the tDCS group and speculated that it might be caused by cognitive and behavioural changes (Oveisgharan et al., 2018). Cunningham et al. (2015) targeted PMd and SMA and also found significant results in favour of the tDCS group. Nevertheless, more evidence is warranted to determine if stimulation of regions other than M1 post-stroke is in fact, beneficial.

4.3. Cluster 3: Dose-related parameters

A positive dose-response relationship was present for current density, charge density and session duration. Higher current density (> 0.060 mA/cm²), higher charge density (> 0.1 C/cm²), and longer session duration (30 minutes) all led to greater improvements in UL functionality. The substantial amount of between-study heterogeneity in the > 0.1 C/cm² subgroup seems to be attributable to the study of Oveisgharan et al. (2018), who used a vastly different protocol in comparison to the other studies in this subgroup (cf., 4.2. Cluster 2: tDCS configuration). The observation of a positive dose-response relationship is in agreement with previous reviews on this topic and studies with healthy controls to extent (Bai et al., 2019, Chhatbar et al., 2016, Cuypers et al., 2013, Nitsche and Paulus, 2000). For instance, Chhatbar et al. (2016) evaluated the tDCS dose-response relationship post-stroke, and found that both current density and charge density were positively related with upper-limb improvements. Nevertheless, portraying the relationship between dose and response as linear might be problematic. Not only do higher doses pose greater safety concerns (which is of no issue if protocols adhere to safety guidelines (Antal et al., 2017, Bikson et al., 2016)), evidence has also indicated that they do not always lead to increased therapeutic (Goldsworthy and Hordacre, 2017, Hassanzahraee et al., 2020, Jamil et al., 2017). For instance, Hassanzahraee et al. (2020) revealed that anodal tDCS in healthy subjects increased corticospinal excitability when applied for 22 or 24 minutes, but decreased corticospinal excitability when applied for 26, 28 or 30 minutes. Jamil et al. (2017) reported that both anodal and cathodal stimulation at higher intensities (i.e., 1.5 and 2mA) do not yield greater after-effects then stimulation at lower intensities (i.e., 0.5 and 1mA). However, as these studies included

healthy young adults, it remains unclear to what extent their conclusions can be extrapolated to a stroke population (Hassanzahraee et al., 2020, Jamil et al., 2017). Regarding the number of sessions, no dose-response relationship was present. While tDCS protocols consisting of 5 to 24 sessions improved UL function, protocols consisting of 30 to 36 sessions did not. As only two studies were present in the 30 to 36 session subgroup, the absence of a positive dose-response relationship for this parameter should be interpreted cautiously. Nonetheless, this finding corroborates the meta-regression analysis of Chhatbar et al. (2016) displaying a negative relationship between the number of sessions and tDCS effectiveness (as measured by FMA-UE change).

4.4. Limitations and future directions

The current meta-analysis is subject to some limitations. First, some subgroups consisted of only one or two studies (e.g., acute stroke stage). Increasing the homogeneity per subgroup comes at the expense of subgroup size. Consequently, clinical trials are needed to validate the robustness of the present results, drawn from these small subgroups. Second, the influence of lesion site on tDCS effectiveness remained uninvestigated, despite evidence indicating its importance regarding NIBS (Ameli et al., 2009, Emara et al., 2009, Khaleel et al., 2010). Third and most importantly, the protocols of the included studies showed marked differences. While the conducted subgroup analyses improved homogeneity and comparability within subgroups, some subgroups were still quite heterogeneous and therefore need to be interpreted cautiously. The consecutive tDCS subgroup for example included both a study applying tDCS for 9 minutes and a study applying tDCS for 30 minutes (Jin et al., 2019, Rocha et al., 2016). Comparing studies based on one factor, whilst not addressing the discrepancies in other factors is an oversimplification of the reality. Ideally, one would be able to investigate the effect of each factor while keeping all other factors identical. Overall, the emphasis of future studies should shift to identifying which tDCS parameters yield the best results through direct comparisons. An example of this would be a study probing the effect of anodal versus cathodal versus bihemispheric tDCS in similar patients (i.e., similar stage of stroke, baseline impairment and lesion location). Another interesting direction for future work is to analyse the effectiveness of tDCS in single- vs multiple-session study designs. To do so, different outcome measures should be included, as it is unlikely that the FMA-UE will display significant changes as a result of a single session (Chhatbar et al., 2016). Furthermore, the inclusion of additional outcome measures (e.g., range of motion, force control) might provide a more extensive overview of the effect of tDCS on UL function. These different outcome measures should be analysed separately, as normalisation of different outcome measures can introduce bias (Chhatbar et al., 2016). Finally, none of the currently included studies used a high-definition tDCS (HD-tDCS) set-up (Datta et al., 2009, Minhas et al., 2010, Villamar et al., 2013). However, this set-up, which uses configurations of < 12 mm diameter centre electrodes, seems promising to use post-stroke as it

allows for specific focalised modulation of a region of interest (e.g., M1) (Datta et al., 2009, Minhas et al., 2010, Villamar et al., 2013).

5. CONCLUSION

Our review provides compelling evidence that combining conventional therapy modalities with tDCS improves UL function. However, the effectiveness of tDCS seems to depend on various factors. More specifically, tDCS yielded significant results in chronic stroke patients and, therefore, seems to be a promising tool to increase therapy effectiveness in this subgroup. Moreover, patients with mild and moderate baseline impairments benefitted from tDCS while severely affected patients did not. tDCS protocols applying anodal stimulation over the affected hemisphere, cathodal stimulation over the unaffected hemisphere, or bihemispheric stimulation all led to improvements in UL function. Timing of tDCS seemed to matter, as concurrent tDCS yielded significant results, whereas consecutive tDCS did not. Regarding target region, most studies targeted contra- and/or ipsilesional M1 and overall, targeting this region resulted in a significant improvement in UL function. Finally, a positive dose-response relationship was present for current density, charge density and stimulation duration, but not for the number of sessions. Future studies should focus on comparing certain factors directly, whilst keeping all other factors identical to identify which combinations of parameters yield the best results in each patient subgroup.

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CONFLICT OF INTEREST

None of the authors have potential conflicts of interest to be disclosed.

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FIGURE CAPTIONS

Fig. 1. The three clusters investigated in the current meta-analysis. Each cluster consisted of multiple groups. Each group consisted of multiple subgroups. FMA-UE = Fugl-Meyer Assessment for upper extremity, tDCS = transcranial direct current stimulation.

Fig. 2. Flowchart displaying the study selection process. Study exclusion due to population, intervention, outcome or design was done in accordance with the in- and exclusion criteria (see 2.2. Eligibility criteria). If essential study information was missing, the corresponding author was contacted through email. If the corresponding author did not supply the essential information, the study was excluded. One study (Chew et al., 2020) was excluded because it used the same dataset as another (included) study (Ang et al., 2015).

Fig. 3. Cochrane Collaboration's tool for assessing the risk of bias, both traffic light plots (above) and summary plots (below) are displayed. + indicates a low risk, - indicates an unclear risk. D1-7 = domain 1 to 7.

Fig. 4. Forest plot displaying the general effect of tDCS, with outliers included. Some studies appear twice in the forest plot, as indicated by 'author name (year)a' and 'author name (year)b', when they have two independent experimental groups (see 3.1. Study selection and quality). 95% CI = 95% confidence interval, I^2 = I^2 square heterogeneity statistic, SD = standard deviation, IV = weighted mean difference, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

Fig. 5. Contour-enhanced funnel plot (panel A), outlier analyses (panels B-D) and a forest plot with outliers excluded (panel E). Studies were numbered in alphabetical order. **A)** Contour-enhanced Funnel Plot displaying the standard error (y-axis) against the effect size (x-axis) for each initially included study. **B)** Baujat Plot displaying the influence of each study on the pooled effect size (y-axis, expressed as the difference between the pooled effect size with the study included vs. excluded) against the contribution of that study to the overall heterogeneity (x-axis, expressed as the study's contribution to Cochran Q-test). The size of each circle indicates the weight of the respective study. Orange circles

display outliers, green circles display influential studies. **C) & D)** Graphical display of study heterogeneity (GOSH) plots for outlier studies, I^2 values (y-axis) plotted against summary effect sizes (x-axis). Blue dots indicate subsets including potential outliers. **E)** Forest plot displaying the general effect of tDCS, without outliers (study 4 and 12). **95% CI = 95% confidence interval, I^2 = I^2 square heterogeneity statistic, SD = standard deviation, SMD = standardised mean difference, IV = weighted mean** difference, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

Fig. 6. Subgroup analysis of tDCS effect depending on stroke stage. **95% CI = 95% confidence interval, I^2 = I^2 square heterogeneity statistic, SMD = standardised mean difference**, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

Fig. 7. Subgroup analysis of tDCS effect depending on baseline FMA-UE score. **95% CI = 95% confidence interval, I^2 = I^2 square heterogeneity statistic, SMD = standardised mean difference**, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

Fig. 8. Subgroup analysis of tDCS effect depending on the type of stimulation. **95% CI = 95% confidence interval, I^2 = I^2 square heterogeneity statistic, SMD = standardised mean difference**, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

Fig. 9. Subgroup analysis of tDCS effect depending on stimulation sequence. **95% CI = 95% confidence interval, I^2 = I^2 square heterogeneity statistic, SMD = standardised mean difference**, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

Fig. 10. Subgroup analysis of tDCS effect depending on target region. **95% CI = 95% confidence interval, I^2 = I^2 square heterogeneity statistic, SMD = standardised mean difference**, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

Fig. 11. Subgroup analysis of tDCS effect depending on current density. Within subgroups 2 and 3, studies are arranged from lowest to highest current density. **95% CI = 95% confidence interval, I^2 = I^2**

square heterogeneity statistic, SMD = standardised mean difference, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

Fig. 12. Subgroup analysis of tDCS effect depending on charge density. Within subgroups, studies are arranged from lowest to highest charge density. **95% CI = 95% confidence interval, I^2 = I^2 square heterogeneity statistic, SMD = standardised mean difference**, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

Fig. 13. Subgroup analysis of tDCS effect depending on the session duration. Within subgroup 1, studies are arranged from shortest to longest stimulation duration. **95% CI = 95% confidence interval, I^2 = I^2 square heterogeneity statistic, SMD = standardised mean difference**, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

Fig. 14. Subgroup analysis of tDCS effect depending on the number of sessions. Within subgroups, studies are arranged from least to greatest number of sessions. **95% CI = 95% confidence interval, I^2 = I^2 square heterogeneity statistic, SMD = standardised mean difference**, $\chi^2_{\text{degree of freedom}}$ = chi-square statistic.

TABLES

Table 1. Keywords in Embase, PubMed and Web of Science.

Search engine	Keywords		Hits
Embase	#1	tDCS [Title or Abstract] OR Transcranial direct current stimulation [Title or Abstract] AND 'Randomised Controlled Trial'	1759
	#2	Stroke [Title or Abstract] OR cerebrovascular accident [Title or Abstract] AND 'Randomised Controlled Trial'	26796
	#3	#1 AND #2	342
PubMed	#1	tDCS [MeSH] OR Transcranial direct current stimulation [MeSH]	2810
	#2	Stroke [MeSH]	137261
	#3	#1 AND #2	212
	#4	#3 AND Randomised Controlled Trial [Filter]	82
Web of Science	#1	tDCS [Topic] OR Transcranial direct current stimulation [Topic]	7288
	#2	Stroke [Topic]	359650
	#3	#1 AND #2	1034

Table 2. Characteristics of the included studies.

Author	N	Patient characteristics			tDCS configuration			Dose-related parameters			
		Age (years) (mean ± SD)	Stage	Baseline FMA-UE score *Subgroup*	Type	Stimulation sequence Additional therapy	Target	Current density (mA/cm^2) *Subgroup*	Charge density (C/cm^2) (subgroup)	Duration (min) (subgroup)	Sessions (subgroup)
Alisar et al. (2020)	32	E: 63.56 ± 10.19 S: 63.50 ± 12.60	II & III	31.6 *Moderate*	B	Concurrent PT and/or OT	M1	0.091 ($2mA/22cm^2$) *High*	0.164 ($3.6C/22cm^2$) *High*	30 *Long*	15 *Moderate*
Ang et al. (2015)	19	E: 52.1 ± 11.7 S: 56.3 ± 9.5	III	34.3 *Moderate*	B	Consecutive MI + BCI	M1	0.029 ($1mA/35cm^2$) *Low*	0.034 ($1.2C/35cm^2$) *Low*	20 *Moderate*	10 *Low*
Beaulieu et al. (2019b)	14	E: 71 ± 12.5 S: 66.7 ± 7.1	III	59.5 *Mild*	B	Concurrent Resistance training	M1	0.057 ($2mA/35cm^2$) *Moderate*	0.069 ($2.4C/35cm^2$) *Moderate*	20 *Moderate*	12 *Low*
Bornheim et al. (2020)	50	E: 62.5 ± 11.9 S: 63.5 ± 12.9	I	36.8 *Moderate*	A	Consecutive PT and/or OT	M1	0.040 ($1mA/25cm^2$) *Moderate*	0.048 ($1.2C/25cm^2$) *Low*	20 *Moderate*	20 *Moderate*
Cunningham et al. (2015)	12	E: 63.7 ± 7.6 S: 58.8 ± 9.6	III	44.5 *Mild*	A	Concurrent CIMT	PMd & SMA	0.029 ($1mA/35cm^2$) *Low*	0.051 ($1.8C/35cm^2$) *Moderate*	30 *Long*	15 *Moderate*
Edwards et al. (2019)	82	67.8	III	24.1 *Severe*	A	Consecutive RAT	M1	0.057 ($2mA/35cm^2$) *Moderate*	0.069 ($2.4C/35cm^2$) *Moderate*	20 *Moderate*	36 *High*
Fusco et al. (2014)	14	E: 56.4 ± 15.4 S: 60 ± 11.9	II	25.8 *Severe*	C	Consecutive PT and/or OT	M1	0.043 ($1.5mA/35cm^2$) *Moderate*	0.026 ($0.9C/35cm^2$) *Low*	10 *Short*	10 *Low*
Jin et al. (2019)a	20	E: 59.00 ± 9.80 S: 57.50 ± 7.08	III	51 *Mild*	B	Consecutive Mirror therapy	M1	0.029 ($1mA/35cm^2$) *Low*	0.051 ($1.8C/35cm^2$) *Moderate*	30 *Long*	10 *Low*
Jin et al. (2019)b	20	E: 58.70 ± 7.92 S: 57.50 ± 7.08	III	47.6 *Mild*	B	Concurrent Mirror therapy	M1	0.029 ($1mA/35cm^2$) *Low*	0.051 ($1.8C/35cm^2$) *Moderate*	30 *Long*	10 *Low*

Kim et al. (2010)a	14	E: 55.3 ± 16.4 S: 62.9 ± 9.2	II	37.2 *Moderate*	A	Concurrent PT and/or OT	M1	0.080 (2mA/25cm²) *High*	0.096 (2.4C/25cm²) *Moderate*	20 *Moderate*	10 *Low*
Kim et al. (2010)b	13	E: 53.6 ± 14.9 S: 62.9 ± 9.2	II	42.7 *Mild*	C	Concurrent PT and/or OT	M1	0.080 (2mA/25cm²) *High*	0.096 (2.4C/25cm²) *Moderate*	20 *Moderate*	10 *Low*
Koh et al. (2017)	25	E: 55.3 ± 11.4 S: 56.9 ± 13.5	III	23.7 *Severe*	B	Concurrent Sensory modulation	M1	0.060 (1.5mA/25cm²) *Moderate*	0.108 (2.7C/25cm²) *High*	30 *Long*	24 *Moderate*
Lindenberg et al. (2010)	20	E: 61.7 ± 14.7 S: 55.8 ± 12.9	III	39 *Moderate*	B	Concurrent PT and/or OT	M1	0.092 (1.5mA/16cm²) *High*	0.166 (2.7C/16m²) *High*	30 *Long*	5 *Low*
Mazzoleni et al. (2019)	40	E: 67.5 ± 16.3 S: 68.7 ± 15.8	II	37.6 *Moderate*	A	Concurrent RAT	M1	0.057 (2mA/35cm²) *Moderate*	0.069 (2.4C/35cm²) *Moderate*	20 *Moderate*	30 *High*
Oveisgharan et al. (2018)	20	E: 52.1 ± 12.8 S: 65.3 ± 16.5	I	49.3 *Mild*	A	No other therapy	DLPFC	0.125 (2mA/16cm²) *High*	0.225 (3.6C/16cm²) *High*	30 *Long*	10 *Low*
Rocha et al. (2016)a	14	E: 58.3 S: 58.5	III	47.8 *Mild*	A	Consecutive modified CIMT	M1	0.029 (1mA/35cm²) *Low*	0.022 (0.8C/35cm²) *Low*	13 *Short*	12 *Low*
Rocha et al. (2016)b	14	E: 58.5 S: 58.5	III	51.3 *Mild*	C	Consecutive modified CIMT	M1	0.029 (1mA/35cm²) *Low*	0.015 (0.5C/35cm²) *Low*	9 *Short*	12 *Low*
Straudi et al. (2016)	23	E: 52.7 ± 16.0 S: 64.3 ± 9.7	II & III	23 *Severe*	B	Concurrent RAT	M1	0.029 (1mA/35cm²) *Low*	0.051 (1.8C/35cm²) *Moderate*	30 *Long*	10 *Low*
Triccas et al. (2015)a	17	E: 64.3 ± 10.4 S: 62.5 ± 13.6	II	36.7 *Moderate*	A	Concurrent RAT	M1	0.029 (1mA/35cm²) *Low*	0.034 (1.2C/35cm²) *Low*	20 *Moderate*	18 *Moderate*
Triccas et al. (2015)b	17	E: 64.2 ± 8.6 S: 62.5 ± 13.6	III	27.4 *Severe*	A	Concurrent RAT	M1	0.029 (1mA/35cm²) *Low*	0.034 (1.2C/35cm²) *Low*	20 *Moderate*	18 *Moderate*
Viana et al. (2014)	20	E: 56.0 ± 10.2 S: 55.0 ± 12.2	III	40.3 *Moderate*	A	Consecutive VR therapy	M1	0.057 (2mA/35cm²) *Moderate*	0.045 (1.6C/35cm²) *Low*	13 *Short*	15 *Moderate*

Yao et al. (2020)	42	E: 63.0 ± 7.5 S: 66.2 ± 6.2	II & III	25.2 *Severe*	C	Concurrent VR therapy	M1	0.057 (2mA/35cm²) *Moderate*	0.069 (2.4C/35cm²) *Moderate*	20 *Moderate*	10 *Low*

I = acute stroke, II = subacute stroke, III = chronic stroke, A = Anodal tDCS, B = bihemispheric tDCS, BCI = brain-computer interface, C = Cathodal tDCS, CIMT = constraint-induced movement therapy, DLPFC = dorsolateral prefrontal cortex, E = experimental group, FMA-UE = Fugl-Meyer Assessment for upper extremity, M1 = primary motor cortex, MI = motor imagery, NA = not available, OT = occupational therapy, PMd = dorsal premotor cortex, PT = physiotherapy, RAT = robot-assisted therapy, S = sham/control group, SD = standard deviation, SMA = supplementary motor cortex, tDCS = transcranial direct current stimulation, VR = virtual reality.

Table 3. PEDro characteristics of each included study.

Study	PEDro items											
	1	2	3	4	5	6	7	8	9	10	11	Total
Alisar et al. (2020)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	9/10
Ang et al. (2015)	✓	✓	✗	✓	✓	✗	✗	✓	✓	✓	✓	7/10
Beaulieu et al. (2019)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	9/10
Bornheim et al. (2020)	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	9/10
Cunningham et al. (2015)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	9/10
Edwards et al. (2019)	✓	✓	✓	✓	✓	✓	✓	✗	✗	✓	✓	8/10
Fusco et al. (2014)	✓	✓	✓	✓	✓	✗	✓	✓	✗	✓	✓	8/10
Jin et al. (2019)	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓	8/10
Kim et al. (2010)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10/10
Koh et al. (2017)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	9/10
Lindenberg et al. (2010)	✓	✓	✓	✓	✓	✓	✗	✓	✗	✓	✓	8/10
Mazzoleni et al. (2019)	✓	✓	✓	✓	✓	✗	✗	✓	✗	✓	✓	7/10
Oveisgharan et al. (2018)	✓	✓	✓	✓	✓	✗	✗	✓	✓	✓	✓	8/10
Rocha et al. (2016)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	9/10
Straudi et al. (2016)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	9/10
Triccas et al. (2015)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	9/10
Viana et al. (2014)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	9/10
Yao et al. (2020)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	9/10

✓ *= fulfilled,* ✗ *= not-fulfilled, 1 = Eligibility criteria specified, 2 = Randomisation, 3 = Concealed allocation, 4 = Baseline characteristics, 5 = Blinding subjects, 6 = Blinding therapists, 7 = Blinding researchers, 8 = >85% Follow-up, 9 = Intention-to-treat analysis, 10 = between group comparisons, 11 = Point measures and variability measures*.

Fig. 1

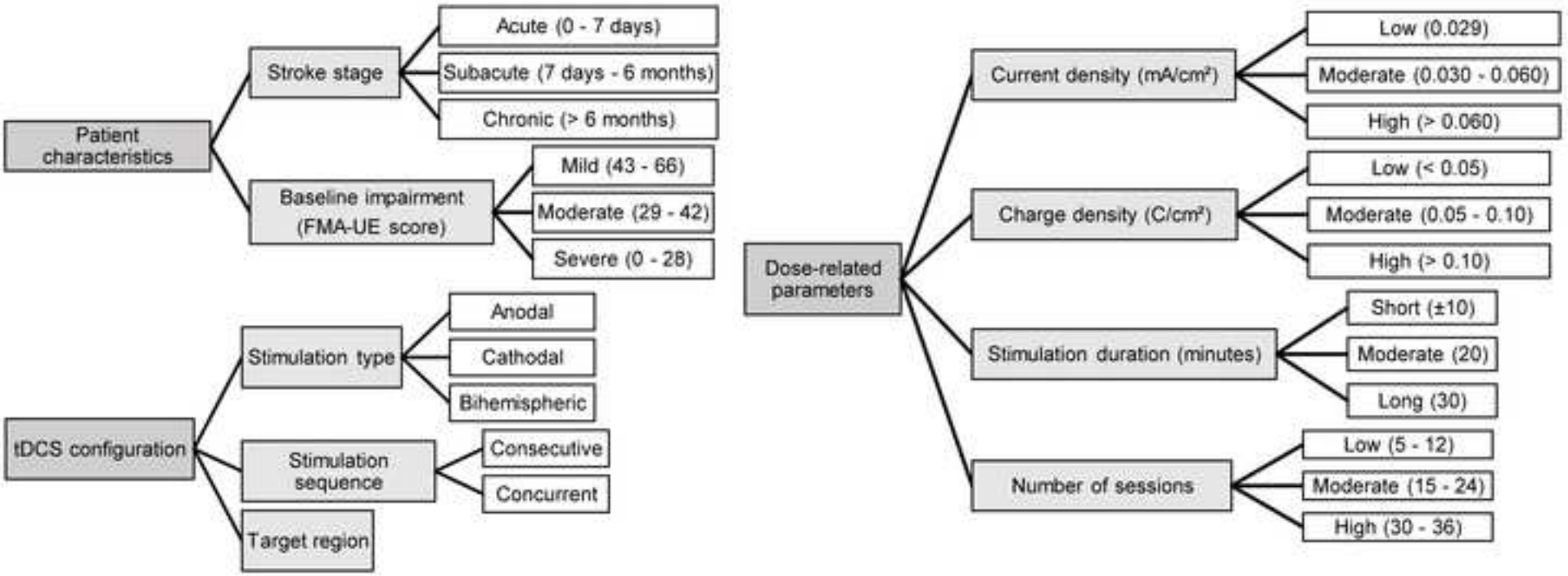


Fig. 2

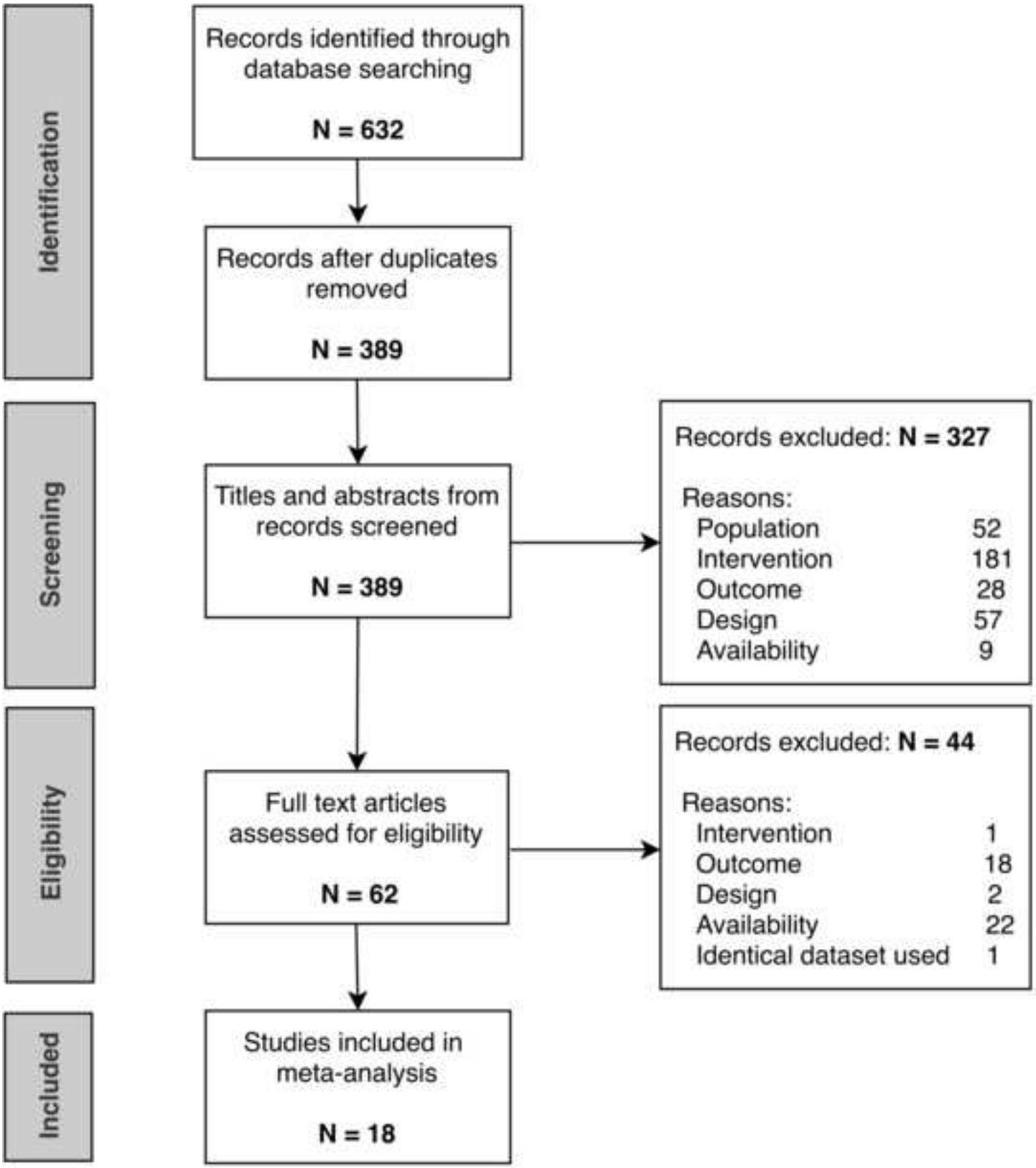


Fig. 3

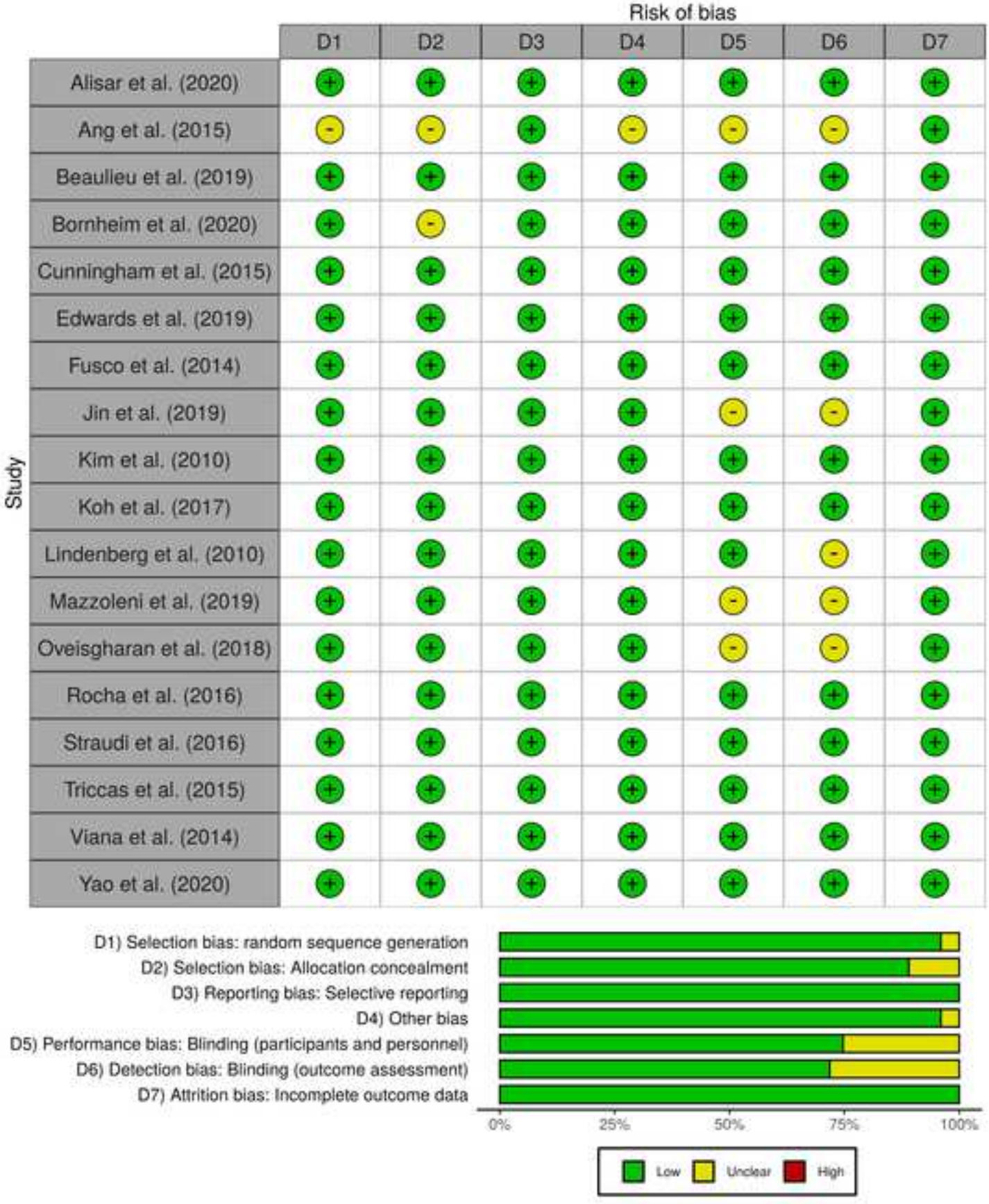


Fig. 4

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Alisar et al. (2020)	9.12	7.11	16	1.75	2.04	16	5.1%	1.37 [0.59; 2.15]
Ang et al. (2015)	0.90	3.00	10	2.80	4.00	9	4.7%	-0.52 [-1.44; 0.40]
Beaulieu et al. (2019)	5.71	4.54	7	2.71	3.20	7	4.1%	0.72 [-0.38; 1.81]
Bornheim et al. (2020)	11.80	4.71	23	5.08	2.14	23	5.4%	1.81 [1.11; 2.50]
Cunningham et al. (2015)	6.83	6.75	6	2.66	4.46	6	3.9%	0.67 [-0.51; 1.85]
Edwards et al. (2019)	7.00	4.00	37	7.70	4.90	40	6.3%	-0.15 [-0.60; 0.29]
Fusco et al. (2014)	4.00	5.00	5	4.00	7.00	6	3.8%	0.00 [-1.19; 1.19]
Jin et al. (2019)a	1.40	2.07	10	1.20	1.87	10	4.8%	0.10 [-0.78; 0.97]
Jin et al. (2019)b	3.30	3.27	10	1.20	1.87	10	4.7%	0.76 [-0.16; 1.67]
Kim et al. (2010)a	14.50	3.60	6	8.30	9.10	7	3.9%	0.81 [-0.34; 1.96]
Kim et al. (2010)b	13.80	13.10	5	8.30	9.10	7	3.9%	0.47 [-0.70; 1.64]
Koh et al. (2017)	6.00	1.50	14	1.30	1.80	11	3.9%	2.78 [1.62; 3.93]
Lindenberg et al. (2010)	6.10	3.40	10	1.20	1.00	10	4.1%	1.87 [0.78; 2.96]
Mazzoleni et al. (2019)	12.00	22.87	20	15.73	19.66	19	5.7%	-0.17 [-0.80; 0.46]
Oveisgharan et al. (2018)	14.30	10.90	10	9.90	4.10	10	4.8%	0.51 [-0.38; 1.41]
Rocha et al. (2016)a	11.10	2.70	7	3.85	6.40	7	3.8%	1.38 [0.17; 2.59]
Rocha et al. (2016)b	7.20	4.50	7	3.85	6.40	7	4.2%	0.57 [-0.51; 1.64]
Straudi et al. (2016)	5.17	4.30	12	5.50	4.97	11	5.0%	-0.07 [-0.89; 0.75]
Triccas et al. (2015)a	10.50	4.28	6	10.00	9.69	6	4.0%	0.06 [-1.07; 1.19]
Triccas et al. (2015)b	6.60	4.67	5	5.00	3.32	5	3.6%	0.36 [-0.90; 1.61]
Viana et al. (2014)	9.30	5.70	10	7.50	7.10	10	4.8%	0.27 [-0.61; 1.15]
Yao et al. (2020)	10.10	4.10	20	6.40	2.90	20	5.6%	1.02 [0.36; 1.68]
Total (95% CI)							**100.0%**	**0.64 [0.29; 0.99]**
Prediction interval								**[-0.79; 2.07]**

Heterogeneity: $\chi^2_{21} = 66.08$ ($P < 0.01$); $I^2 = 68\%$

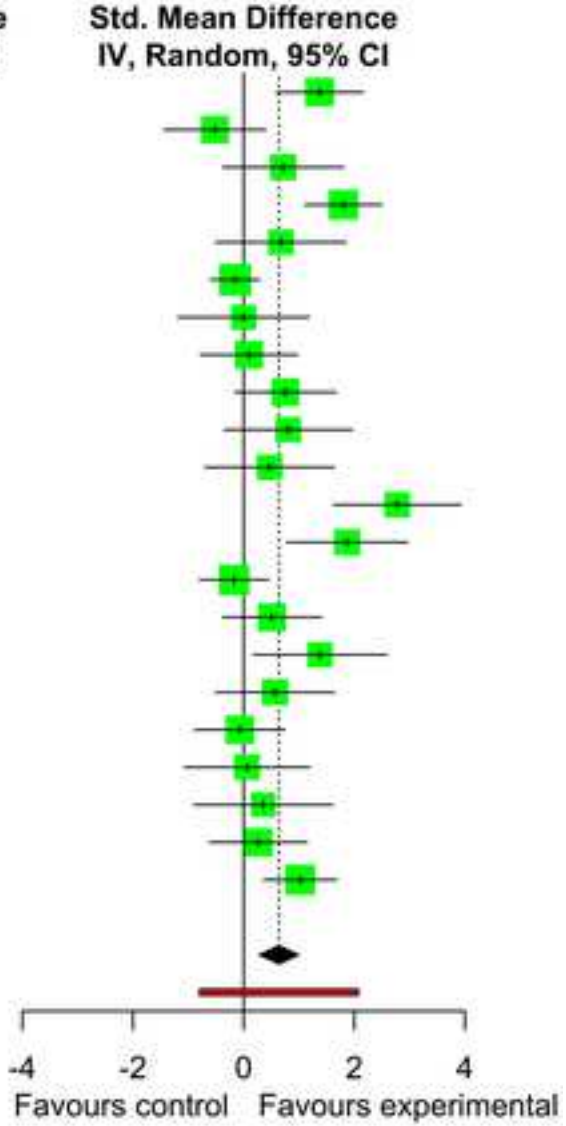
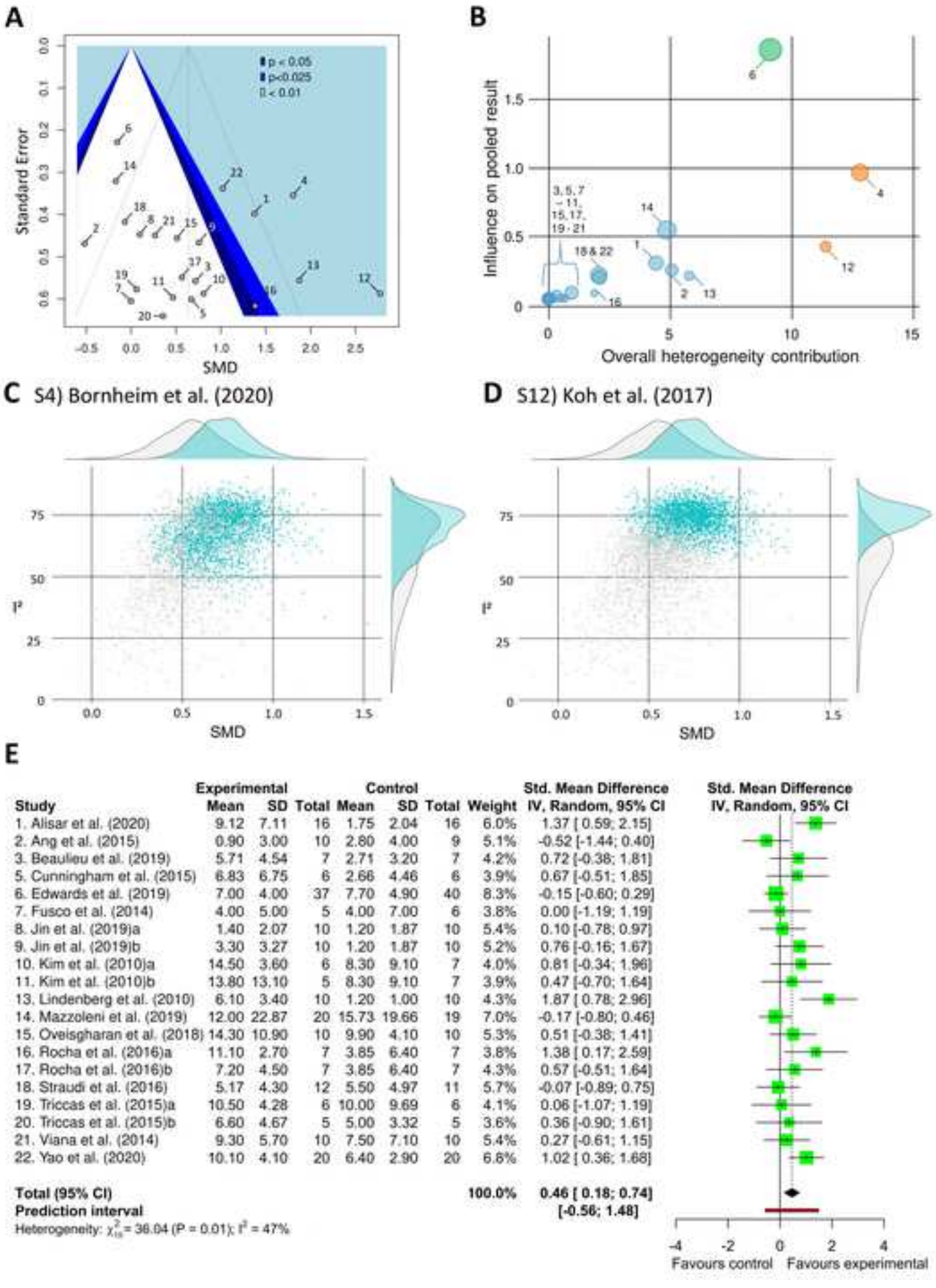


Fig. 5



E

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1. Alisar et al. (2020)	9.12	7.11	16	1.75	2.04	16	6.0%	1.37 [0.59; 2.15]
2. Ang et al. (2015)	0.90	3.00	10	2.80	4.00	9	5.1%	-0.52 [-1.44; 0.40]
3. Beaulieu et al. (2019)	5.71	4.54	7	2.71	3.20	7	4.2%	0.72 [-0.38; 1.81]
5. Cunningham et al. (2015)	6.83	6.75	6	2.66	4.46	6	3.9%	0.67 [-0.51; 1.85]
6. Edwards et al. (2019)	7.00	4.00	37	7.70	4.90	40	8.3%	-0.15 [-0.60; 0.29]
7. Fusco et al. (2014)	4.00	5.00	5	4.00	7.00	6	3.8%	0.00 [-1.19; 1.19]
8. Jin et al. (2019)a	1.40	2.07	10	1.20	1.87	10	5.4%	0.10 [-0.78; 0.97]
9. Jin et al. (2019)b	3.30	3.27	10	1.20	1.87	10	5.2%	0.76 [-0.16; 1.67]
10. Kim et al. (2010)a	14.50	3.60	6	8.30	9.10	7	4.0%	0.81 [-0.34; 1.96]
11. Kim et al. (2010)b	13.80	13.10	5	8.30	9.10	7	3.9%	0.47 [-0.70; 1.64]
13. Lindenberg et al. (2010)	6.10	3.40	10	1.20	1.00	10	4.3%	1.87 [0.78; 2.96]
14. Mazzoleni et al. (2019)	12.00	22.87	20	15.73	19.66	19	7.0%	-0.17 [-0.80; 0.46]
15. Oveisgharan et al. (2018)	14.30	10.90	10	9.90	4.10	10	5.3%	0.51 [-0.38; 1.41]
16. Rocha et al. (2016)a	11.10	2.70	7	3.85	6.40	7	3.8%	1.38 [0.17; 2.59]
17. Rocha et al. (2016)b	7.20	4.50	7	3.85	6.40	7	4.3%	0.57 [-0.51; 1.64]
18. Straudi et al. (2016)	5.17	4.30	12	5.50	4.97	11	5.7%	-0.07 [-0.89; 0.75]
19. Triccas et al. (2015)a	10.50	4.28	6	10.00	9.69	6	4.1%	0.06 [-1.07; 1.19]
20. Triccas et al. (2015)b	6.60	4.67	5	5.00	3.32	5	3.6%	0.36 [-0.90; 1.61]
21. Viana et al. (2014)	9.30	5.70	10	7.50	7.10	10	5.4%	0.27 [-0.61; 1.15]
22. Yao et al. (2020)	10.10	4.10	20	6.40	2.90	20	6.6%	1.02 [0.36; 1.68]
Total (95% CI)							**100.0%**	**0.46 [0.18; 0.74]**
Prediction interval								**[-0.56; 1.48]**

Heterogeneity: χ^2_{15} = 36.04 (P = 0.01); I^2 = 47%

Fig. 6

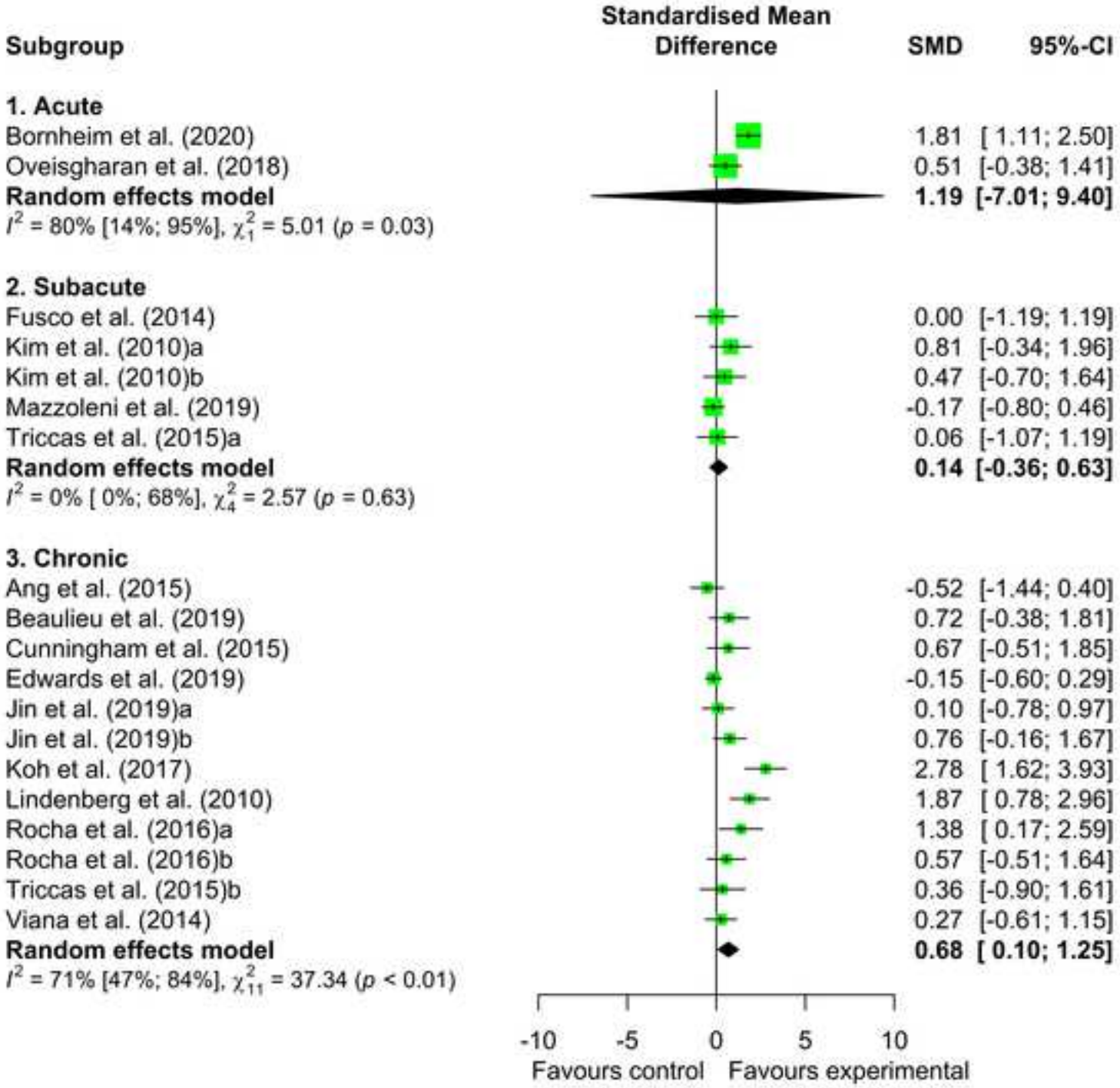


Fig. 7

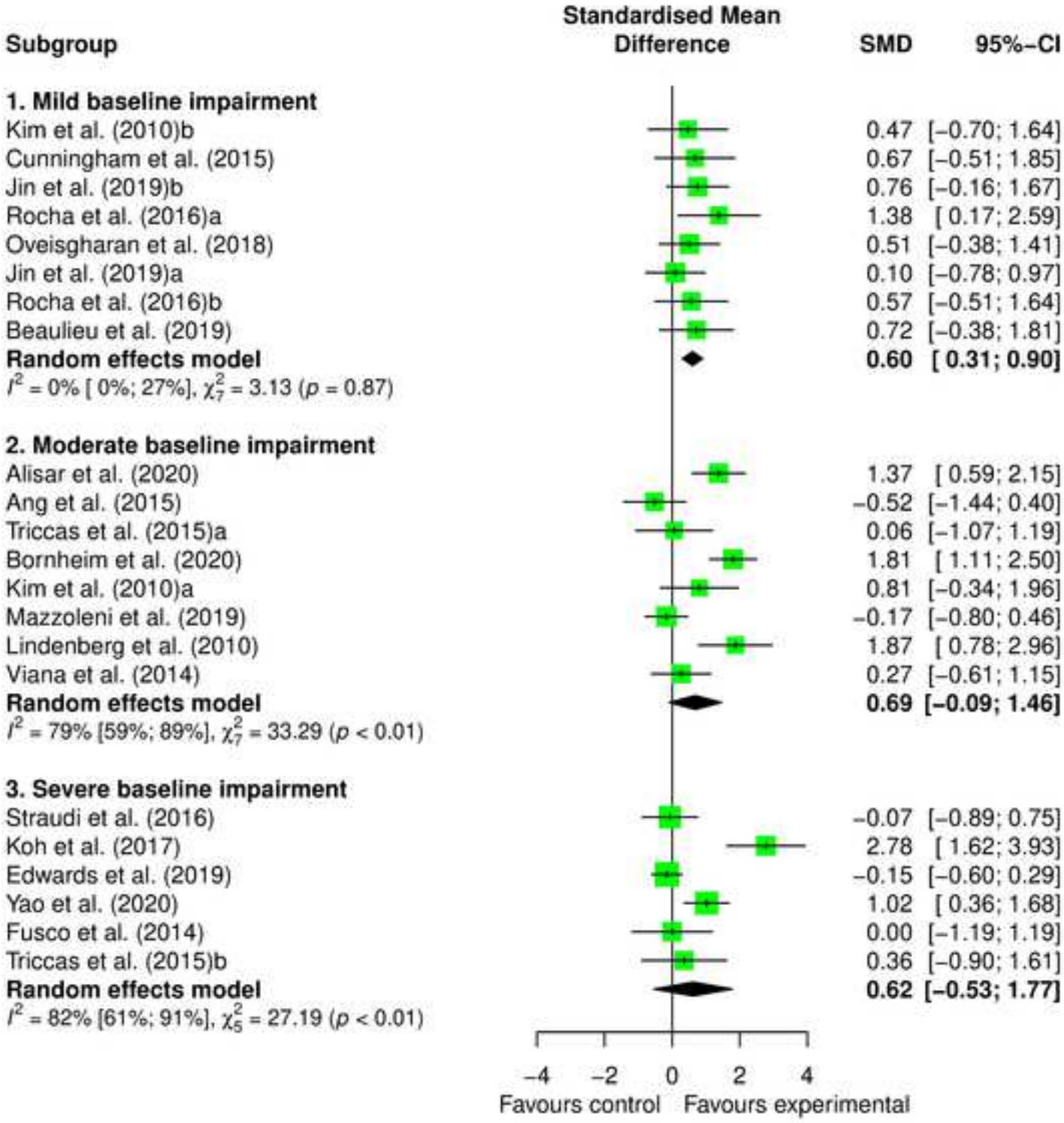


Fig. 8

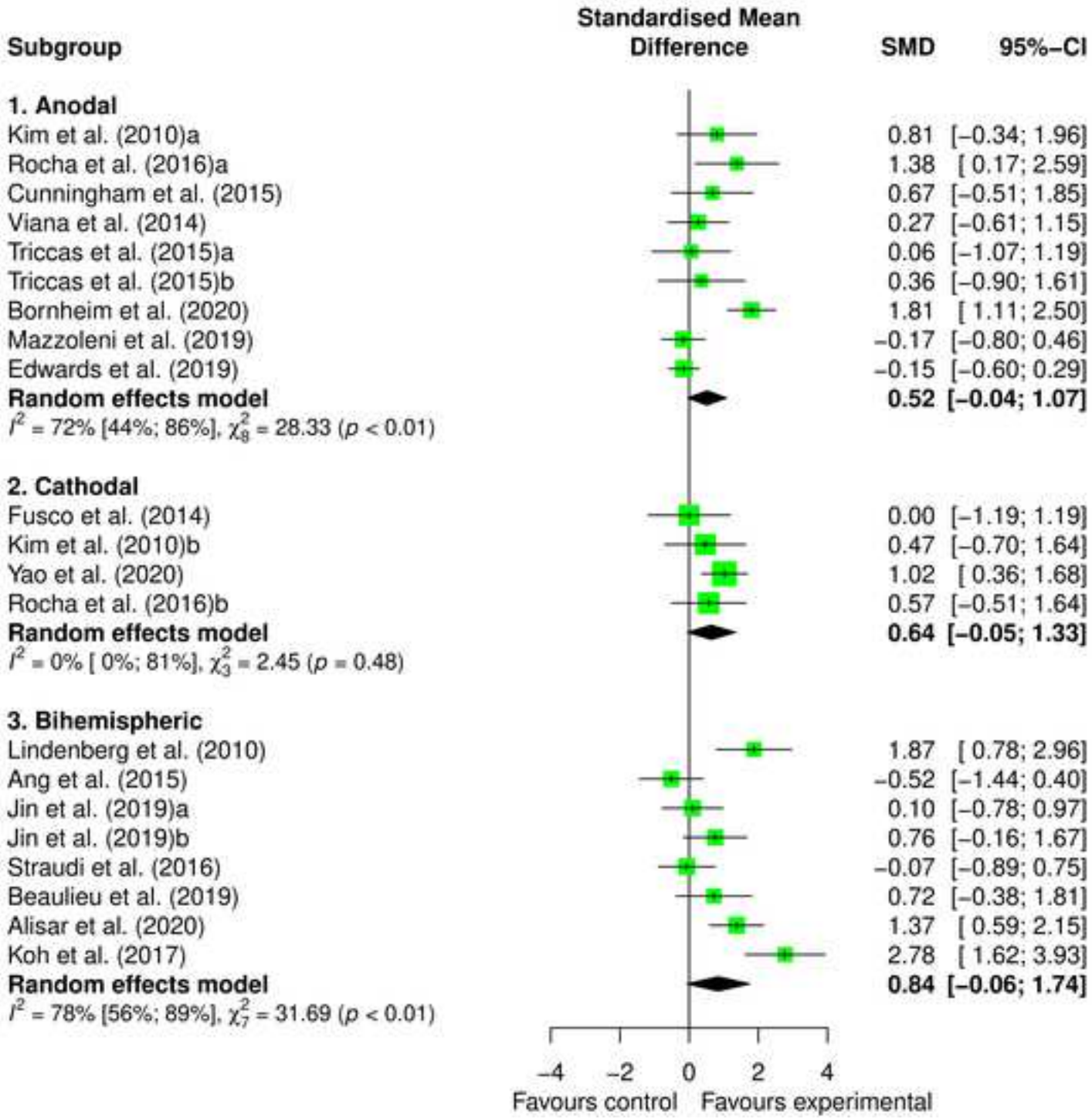


Fig. 9

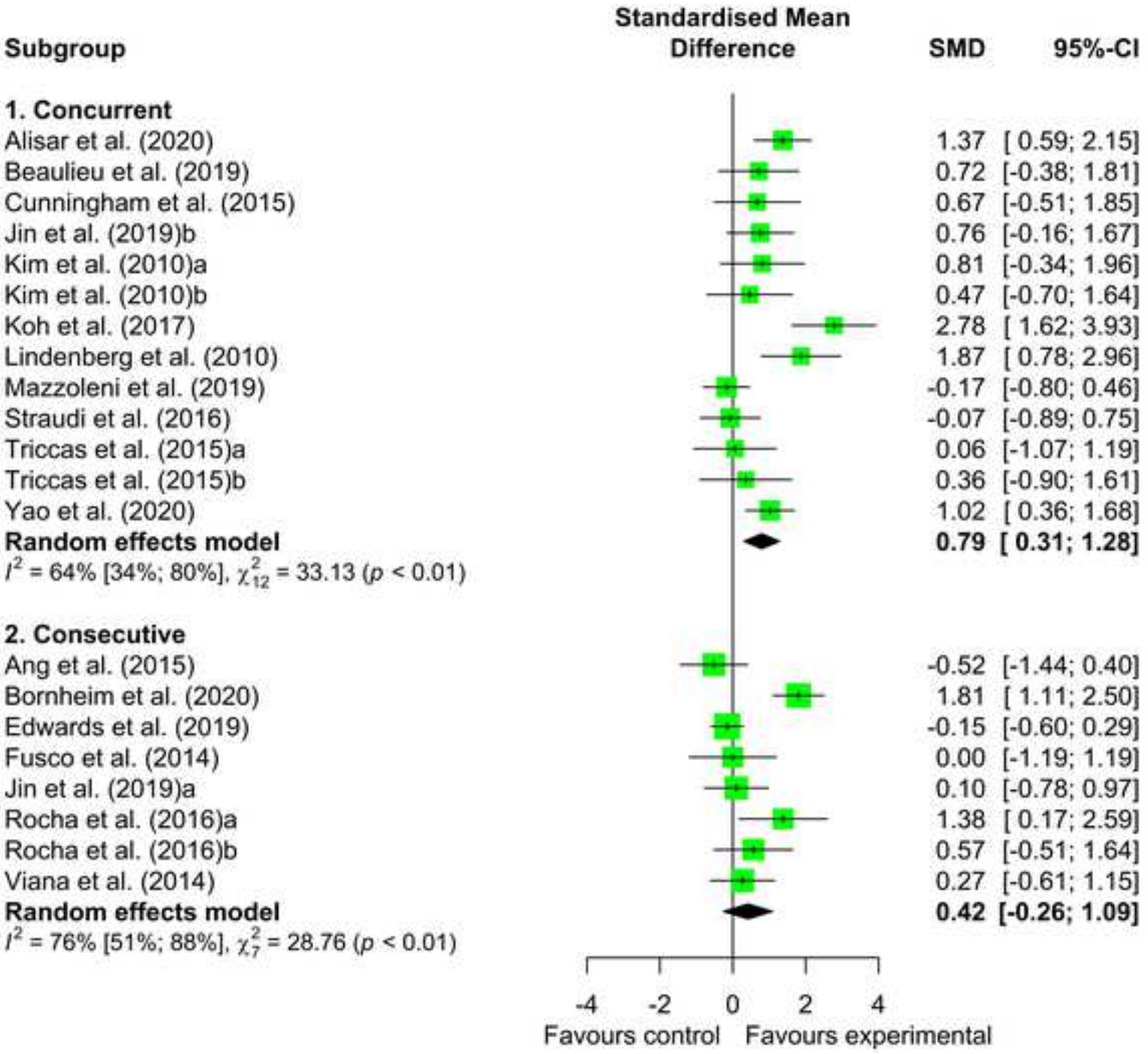


Fig. 10

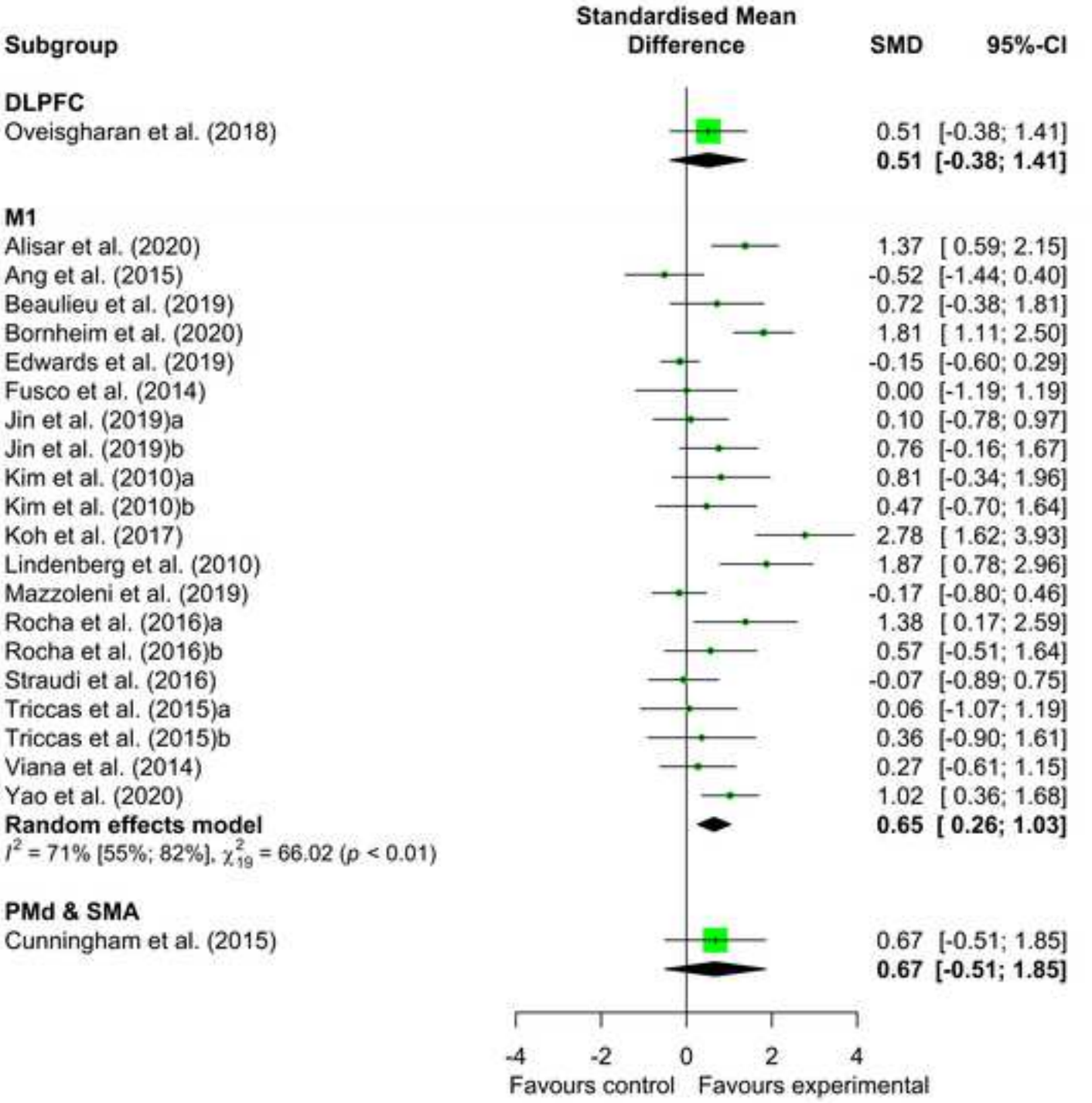


Fig. 11

Click here to access/download;Figure;Fig. 11.jpg

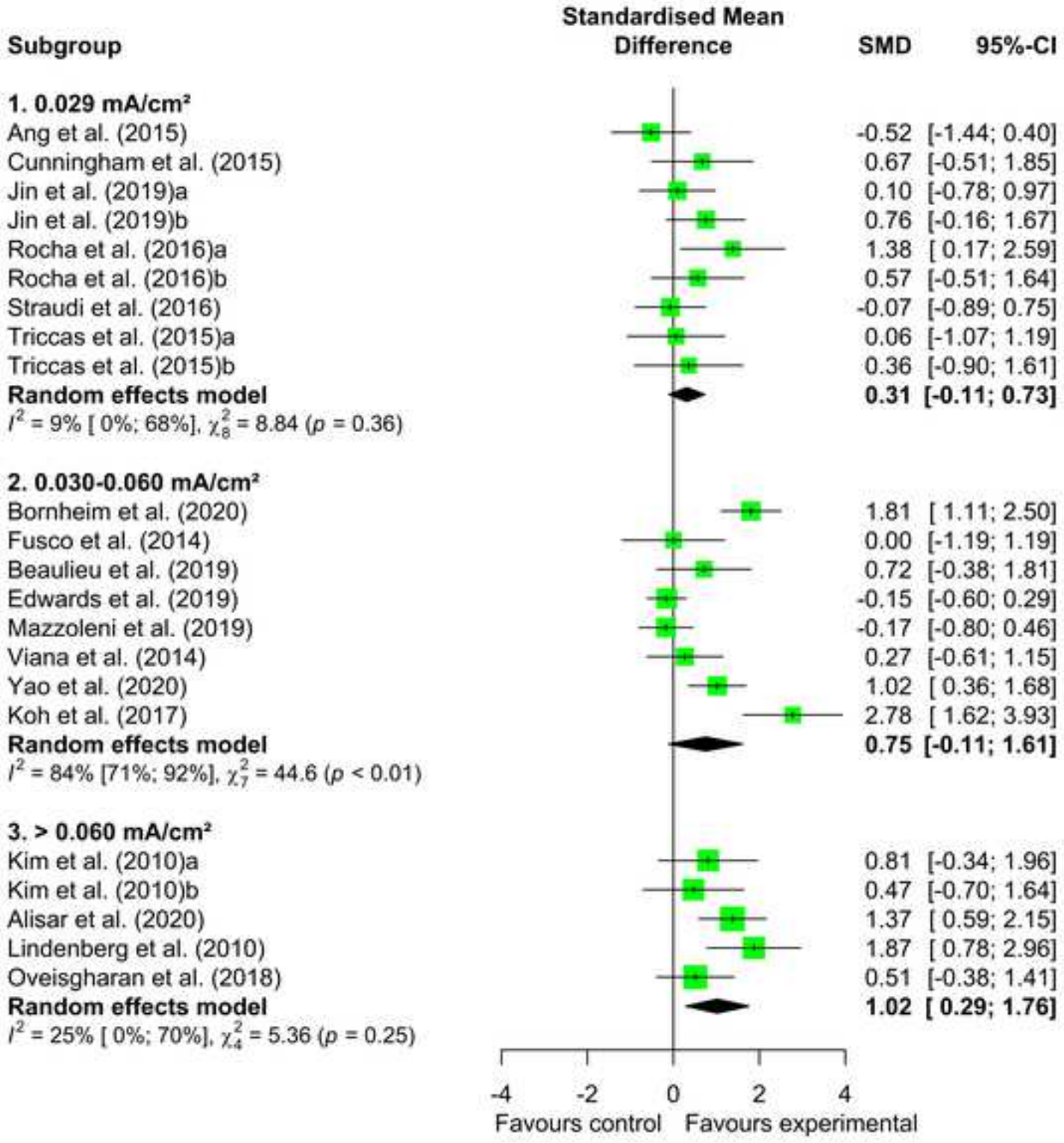


Fig. 12

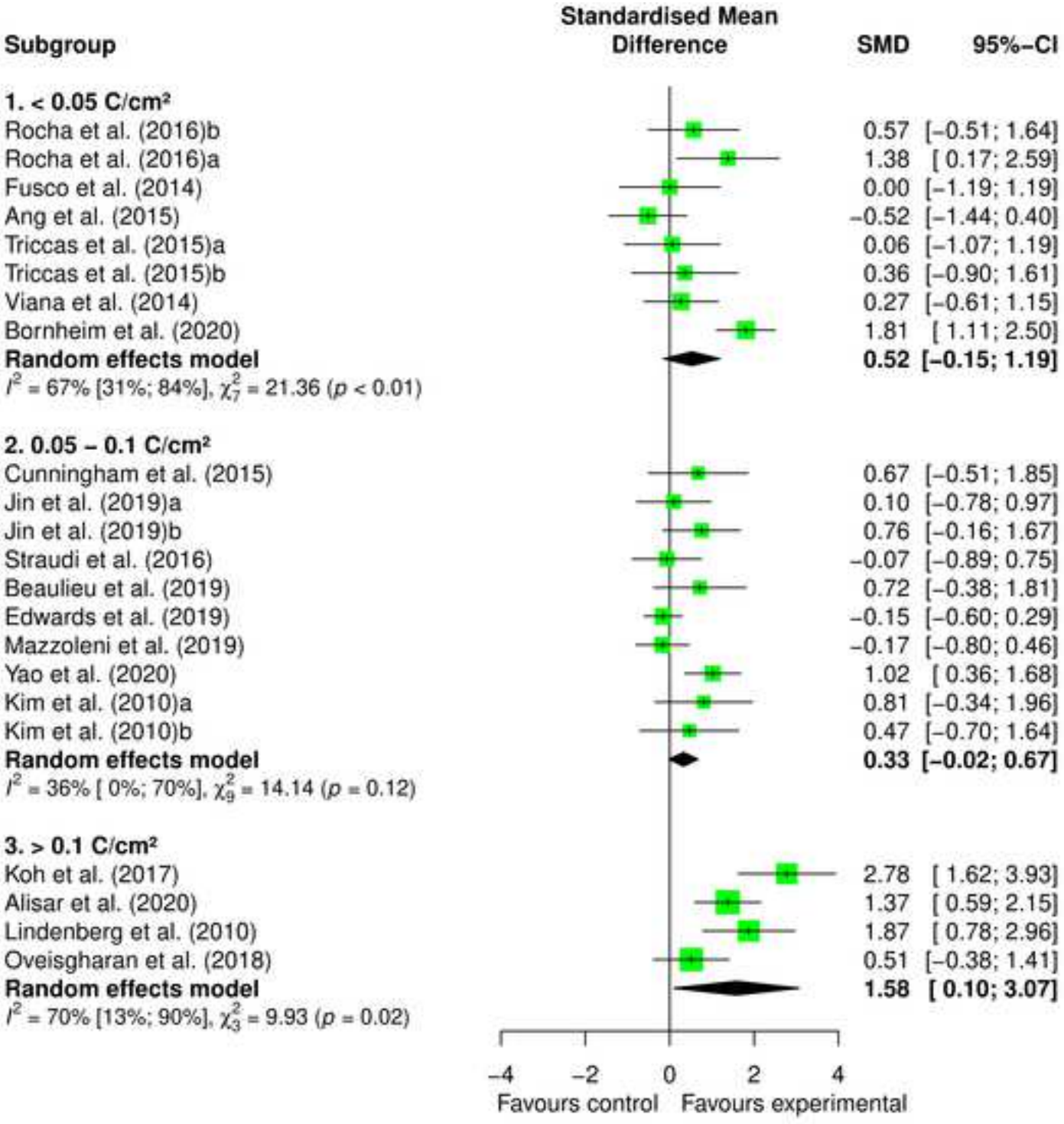


Fig. 13

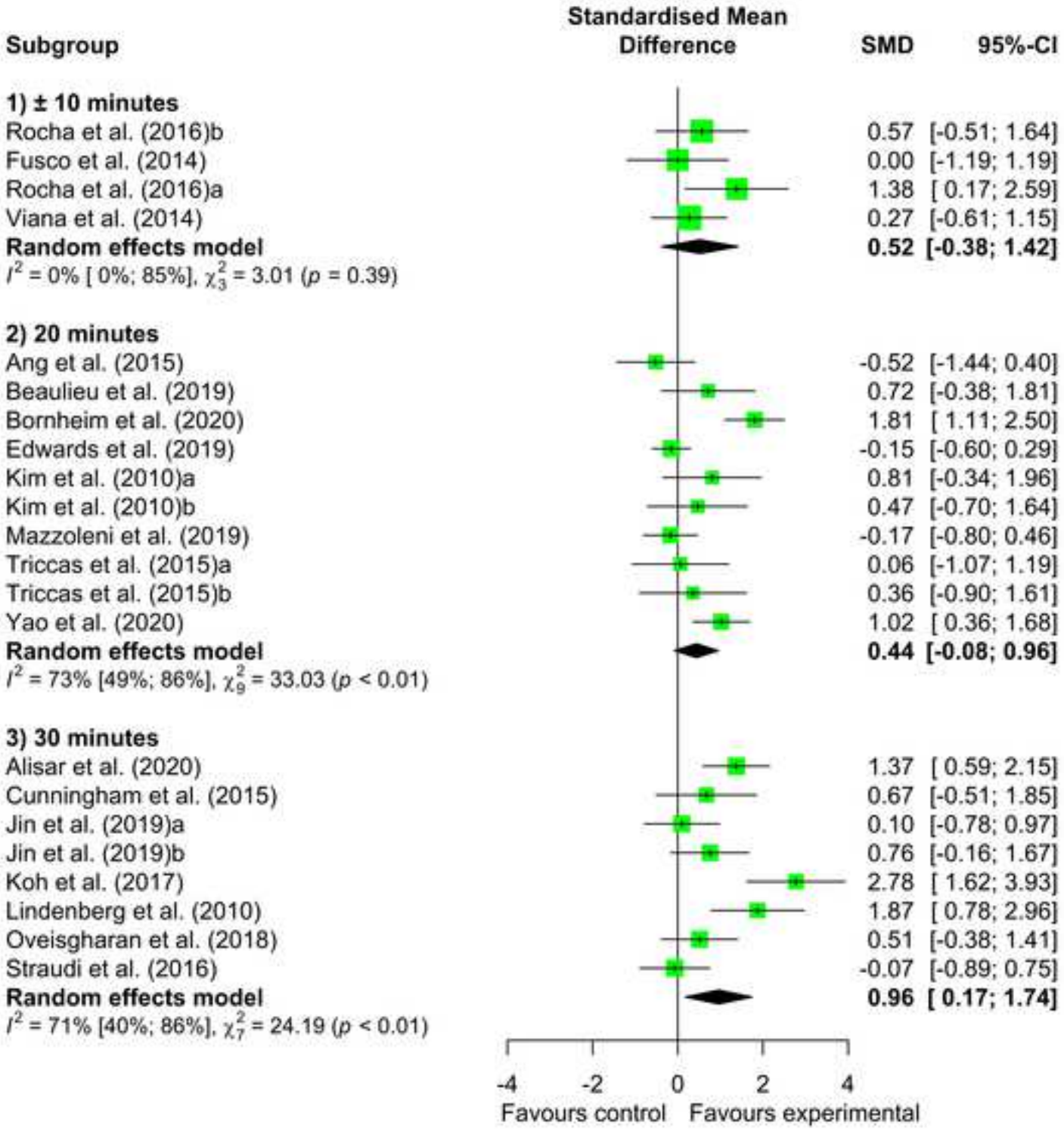


Fig. 14