Interventions for ADHD in Childhood and Adolescence: A Systematic Umbrella Review and Meta-Meta-Analysis

Authors: Selina Türk, M.Sc.[a],*, Ann-Kathrin Korfmacher*, M.Sc.[a], Heike Gerger, Dr.[b], Saskia van der Oord, Prof. Dr. [c], Hanna Christiansen, Prof. Dr.[a]

Affiliations:

[a] Clinical Child and Adolescent Psychology, Department of Psychology, Philipps-University Marburg, Gutenbergstraße 18, 35032 Marburg, Germany

[b] Family Medicine, Faculty of Health, Medicine and Life Sciences, Maastricht University, Universiteitssingel 60, 6229 ER Maastricht, Netherlands

[c] Clinical Psychology, KU Leuven, Tiensestraat 102, 3000 Leuven, Belgium

*corresponding authors

Philipps-University Marburg

Department of Clinical Child and Adolescent Psychology

Gutenbergstr. 18

D-35037 Marburg

Germany

E-Mail:

selina.tuerk@staff.uni-marburg.de

ann-kathrin.korfmacher@uni-marburg.de

Phone: +49(0) 6421-28-23671

Abstract

There are several meta-analyses of treatment effects for children and adolescents with attention deficit hyperactivity disorder (ADHD). The conclusions of these meta-analyses vary considerably. Our aim was to synthesize the latest evidence of the effectiveness of psychological, pharmacological treatment options and their combination in a systematic overview and meta-meta-analyses. A systematic literature search until July 2022 to identify meta-analyses investigating effects of treatments for children and adolescents with ADHD and ADHD symptom severity as primary outcome (parent and teacher rated) yielded 16 meta-analyses for quantitative analyses. Meta-meta-analyses of pre-post data showed significant effects for pharmacological treatment options for parent (SMD = 0.67, 95% CI 0.60 to 0.74) and teacher ADHD symptom ratings (SMD = 0.68, 95% CI 0.54 to 0.82) as well as for psychological interventions for parent (SMD = 0.42, 95% CI 0.33 to 0.51) and teacher rated symptoms (SMD = 0.25, 95% CI 0.12 to 0.38). We were unable to calculate effect sizes for combined treatments due to the lack of meta-analyses. Our analyses revealed that there is a lack of research on combined treatments and for therapy options for adolescents. Finally, future research efforts should adhere to scientific standards as this allows comparison of effects across meta-analyses.

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Attention deficit hyperactivity disorder (ADHD), characterized by a persistent and age-inappropriate pattern of inattentive symptoms, hyperactivity and increased impulsivity, is one of the most common neurodevelopmental disorders in childhood and adolescence (APA, 2013; Polanczyk et al., 2014). ADHD symptoms are often associated with various emotional and behavioral difficulties as well as significant impairment in aspects of the child's life such as peer relationships, school and family life (Hamed et al., 2015; Reale et al., 2017; Verkuijl et al., 2015) that often persist over the lifespan (Caye et al., 2016).

Long-term studies demonstrate that without adequate treatment, this disorder's course is associated with deficits in social development (e.g., difficult interpersonal relationships), risky behavior (e.g., traffic violations and car accidents, substance misuse) as well as a high risk of dropping out of school, low educational attainment, and the development of delinquent behavior (Pingault et al., 2011; Wilens et al., 2011). Highly effective treatments are therefore warranted to disrupt such negative developmental trajectories. A review by Arnold et al. (2015) showed that ADHD-associated outcomes improved in the long-term in people given appropriate treatment (combined psychological and pharmacological) compared to untreated individuals.

The most frequent treatment backed by the broadest evidence for school-age children to reduce ADHD symptoms is pharmacotherapy involving psychostimulants like methylphenidate (MPH) as first-line treatments (German S3-guidelines of the Working Group of Scientific Medical Societies [AMWF], 2017; guidelines of the National Institute for Health and Care Excellence [NICE], 2018). Various meta-analyses have demonstrated large short-term effects for MPH treatment, though its acceptability and tolerability as well as long-term effects remain controversial (Storebø et al., 2015). Furthermore, up to every third child with ADHD fails to benefit sufficiently from stimulant medication, or suffers adverse effects like decreased appetite, insomnia and headache (Lofthouse et al., 2012; Shim et al., 2016), and

there are parental concerns about potential negative long-term effects (Caye et al., 2019; Nafees et al., 2014; Schatz et al., 2015).

Psychological interventions are a second treatment option is focusing on alleviating deficits in functioning. Treatments such as cognitive-behavioral therapy (CBT), behavioral parent training or classroom-based treatments are regularly applied in clinical practice (Banaschewski et al., 2017; Sonuga-Barke et al., 2013). Behavioral treatments are especially recommended for pre-school age children as first-line treatment, and for mild to moderate ADHD symptoms (NICE, 2018; AWMF, 2017). Caye and colleagues (2019) claim that overall "the evidence for behavioral intervention is difficult to integrate and summarize" (p. 396); reason enough to address the efficacy of psychological and behavioral treatments in a comprehensive analysis.

The combination of stimulant medication and psychological therapy is often considered the "gold standard" in clinical practice. Theoretically, combined therapy may offer the most efficient way to treat ADHD, but research has not paid much attention to such combined treatments although individual studies reported heterogeneous results. While some studies demonstrated the superiority of combined treatment when compared to treatment alone (Arnold et al., 2015; Van der Oord et al., 2008), other long-term studies such as the Multimodal Treatment study for ADHD (MTA) failed to demonstrate superiority of combined MPH plus Behavioral Therapy treatment over each one alone in 36-month and eight-year follow-ups (Jensen et al., 2007; Molina et al., 2009). Differentiated analyses of the MTA study yielded advantages for the combined treatment for secondary outcomes such as internalizing symptoms, social skills, and school performance over the short-term (Molina et al., 2009). Few meta-analyses have reviewed the evidence on combined treatments to date, but their results have been promising (see Majewicz-Hefley & Carlson, 2007; Van der Oord et al., 2008).

Numerous meta-analyses addressed the varied ADHD treatment options for children and adolescents to synthesize knowledge and enable a deeper understanding of treatment effects. But these meta-analyses vary considerably in their methodology, quality of conduct, and reported findings (Gurevitch et al., 2018), thus hampering our ability to draw specific conclusions and reveal implications for clinical practice. In research fields in which many meta-analyses have been conducted, a promising approach to integrate the available evidence is to conduct an overview of reviews (umbrella review) to provide a systematic and comprehensive summary of related research (Bussalb et al., 2019; Fabiano et al., 2015; Riesco-Matías et al., 2019). For example, Fabiano and colleagues (2015) performed a systematic review of meta-analyses of psychosocial treatments for ADHD and figured out the diversity of inclusion criteria, types of interventions reviewed, methodological issues and effects sizes. The Cochrane Collaboration included a separate chapter in their latest handbook for systematic reviews to provide methodological guidance for implementing a high-quality standard for umbrella reviews (see Pollock et al., 2020). A quantitative approach complementing these overviews is the so-called ‘meta-meta-analysis’ or ‘second-order meta-analysis’ that synthesizes results from a number of meta-analyses addressing the same research question. To be differentiated from this are network meta-analyses, which provide information for comparisons of more than two interventions and enable ranking estimations which intervention is most effective (Kanters et al., 2016; Rouse, 2018). We explicitly have chosen the approach of meta-meta-analyses to investigate the diversity in previous meta-analyses rather than combining evidence.

The aims of the current umbrella review with meta-meta-analysis are thus to first summarize the latest meta-analytical knowledge on the efficacy of the pharmacological (e.g., stimulant or non-stimulant), psychological (e.g., behavioral therapy, school-based behavioral treatments, parent or teacher training) treatments and a combination thereof for children and adolescents with ADHD based on parents’ and teachers’ symptom ratings. We compared the

evidence narratively and if sufficient data were available, on a meta-meta-analytic level. Second, we conducted a systematic overview by identifying factors (such as characteristics of sample, study design, outcome measures) contributing to the previously observed differences in meta-analytic results and derived implications to propel ADHD treatment research forward. This is the first comprehensive overview to our knowledge that investigated qualitatively and quantitatively results from individual meta-analyses for psychological and pharmacological ADHD treatment options and their combination.

Method

Our protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) and assigned registration number CRD42015025062. Derivation from protocol can be found in supplemental material. To take the highest quality approach we followed the Cochrane Handbook guidelines (Version 6.1) for conducting "Overview of Reviews" (Higgins et al., 2019; Pollock et al., 2020) and the PRISMA-Statement (Moher et al., 2009) in reporting our meta-meta-analysis.

Criteria for selecting meta-analyses

Types of meta-analyses

We considered only meta-analyses investigating the effects of any intervention for children and adolescents with ADHD on the basis of at least two primary studies ($k \geq 2$). Meta-analyses of randomized and pseudo-randomized controlled trials, as well as meta-analyses based on between-group and within-group study designs were included that reported standardized effect sizes relying on pre-, post or follow-up data. To avoid statistical problems by integrating cross-sectional and longitudinal data, only those meta-analyses were included in further analyses that provided effect sizes calculated as standardized mean difference rather than standardized mean change (see section 10.5.2 "Meta-analysis of change scores" in

Pollock et al., 2020). We did not include cohort or case-control studies. Meta-analyses describing effect sizes only graphically were excluded.

Types of participants

Eligible meta-analyses had to include studies on children and adolescents (≤ 18 years of age) with an ADHD diagnosis based on the ICD-10 (WHO, 1992) or DSM-III, DSM-IV, or DSM-5 criteria (APA, 1980; 1994; 2013), or participants had to meet cut-off criteria on a validated ADHD diagnostic instrument (e.g., Conners 3^{TM}; Conners, 2008). We excluded meta-analyses that included studies on ADHD symptoms for other medical reasons (e.g., brain disorder, genetic disorder, epilepsy) or other disorders (e.g., autism or oppositional deviant disorder).

Types of interventions

Investigated interventions included pharmacological treatments with stimulants and non-stimulants, psychological treatments focusing on the index-patient (such as cognitive-behavioral therapy or social skills training) and psychosocial treatments (such as school-based interventions, behavioral parent or teacher training) as well as a combination of those clearly defined as "multimodal" therapy or combined treatment. We included all meta-analyses based on intervention versus control designs. Meta-analyses comparing two active interventions (both targeting ADHD, e.g., psychotherapy vs. medication) were excluded as we wanted to focus on meta-analyses of the effectiveness of only one intervention group at a time and avoid comparisons over meta-meta-analyses (see network analyses for comparing many intervention groups, Pollock et al., 2020). We listed the type of control group per meta-analysis in detail, as control groups varied in the different meta-analyses (such as waiting list, no treatment, placebo condition, semi-active intended to fail conditions). Meta-analyses of newer nonpharmacological treatment options such as neurofeedback, cognitive training or dietary interventions were searched as well, but are reviewed and analyzed in another article (Korfmacher et al., in prep).

Types of outcome measures

Our primary outcome was defined as ADHD symptom severity and refers to the difference (between active ADHD intervention and control group) on parent and/or teacher ratings or self-ratings of children and youth. We also searched for meta-analyses including outcomes of specific core components of ADHD separately (inattention, hyperactivity, impulsivity) and secondary outcomes (e.g., social functioning, academic achievement), which also appear in our literature search results, but were excluded for further analyses and will be analyzed in our project's second paper (see flowchart for further details). Relevant outcomes had to be assessed applying standardized measurement tools, such as questionnaires or clinical interviews with parents and/or teachers. Meta-analytic results based on observational unstandardized data only were excluded.

Search Strategy

We conducted a systematic literature search in PubMed, PsycINFO, Web of Science and Google Scholar initially until July 2021 to identify published meta-analyses investigating the effects of different interventions for children and adolescents with ADHD. We updated our search in January 2023 to include meta-analyses published in the meantime, but no further meta-analysis fulfilled inclusion criteria. In addition, we hand-searched reference lists of identified meta-analyses and relevant review articles. We only considered articles written in German or English as eligible. Those were searched and screened by the first authors (ST, AK). The complete search syntax for the databases is available in Appendix eTable 1.

Selection of Meta-Analyses

After removing duplicates, titles and abstracts were screened for relevance. Reviews or meta-analyses that did not meet our inclusion criteria were excluded in the first step after screening. We screened the full texts of the identified meta-analyses to ensure eligibility. Relevant data

from all remaining meta-analyses were extracted from original articles and organized in a comprehensive electronic sheet by the first authors (ST, AK) and cross-checked for accuracy. In cases of disagreement, a third rater (HC) was involved. After that, data were separately prepared according to the primary outcome of ADHD symptomology (this paper's focus) and other outcomes.

Data Extraction

Using a data collection form following the Cochrane Handbook guidelines (Chapter V: Overviews of Reviews), we extracted relevant data (se eTable 2 in Appendix) regarding characteristics of the included meta-analyses, the method of literature search, sample characteristics, treatment characteristics, and study design of included primary studies, meta-analytic methods, as well as outcome data. If data relevant for our analyses were missing in the included meta-analyses, we scrutinized the original publications of the included primary studies or contacted corresponding authors of the published meta-analysis up to three times to retrieve relevant data for analysis. If data remained unavailable, that meta-analysis was excluded. The meta-analyses included took different approaches when assessing risk of bias, methodological quality, or evidence quality. We extracted any tool used in the included meta-analyses (e.g., GRADE framework [GRADE Working Group, 2016] or Cochrane risk-of-bias tool [Higgins et al. 2011]) and we present the specific results for each meta-analysis a narratively to enable a comprehensive overview of the varied tools. We decided not to supplement any missing assessment as we aimed to review the shared features and differences of existing meta-analysis and did not aim to re-analyze data from the primary studies.

Quality of included meta-analyses

Since there is no standard for assessing the quality of meta-meta-analysis yet, and the Cochrane guidelines "cannot currently recommend one tool over another due to a lack of

empirical evidence on this topic" (section V.4.10. in Pollock et al., 2020), we utilized the PRISMA-Checklist to assess the quality of the included meta-analyses (PRISMA statement, 2009). Each item on the PRISMA-Checklist was rated for every meta-analysis independently by two authors (ST, AK) on a 3-point Likert scale coding 0 ("item not fulfilled"), 1 ("item partially fulfilled") or 2 ("item completely fulfilled"). This procedure has been applied successfully in previous meta-meta-analyses (Mingebach et al., 2018; Weber et al., 2019). The final quality score ranged between 0 and 54 and serves as a "proxy" for meta-analytic study quality. We calculated the intra-class correlation (ICC) between the two independent assessments using the Statistical Package for Social Science Version 20 (SPSS IBM Corp, 2011), which resulted in an ICC = .774 value, indicating good to excellent interrater agreement (Cicchetti, 1994; Koo & Li, 2016). To utilize the quality scores for further analysis, the mean of the total scores of both independent ratings was used.

Meta-Meta-Analytic Procedure, Data Synthesis, and Statistical Analysis

When conducting a meta-meta-analysis, statistical methods of first-order meta-analyses can be transferred to the second order (Schmidt et al., 2009). For data synthesis, we combined effect sizes from individual meta-analyses using random-effects models by weighting each effect size by its inverse variance including within study variance (v) and the estimated random effects variance (tau^2). A synthesis of meta-analytic data implies a new level of variance (second order sampling error) that we considered in using the Hunter and Schmidt estimator for tau^2 (Hunter & Schmidt, 2015; for a more detailed description see Schmidt & Oh, 2013). In our case, tau^2 represents the estimated amount of variance of mean effect sizes across meta-analyses.

Standardized mean differences (SMD) between treatment and control group on meta-meta-analytic level with 95 % confidence intervals (CI) were calculated for the group difference in order to account for heterogeneity in the measurement tools employed across

primary studies. According to Cohen (1988) a SMD of 0.2 is considered a small, 0.5 a moderate and 0.8 a large effect size. We conducted separate meta-meta-analyses for each treatment option (pharmacological, psychological and combined) and we present results for parent-rated and teacher-rated ADHD symptoms separately. This *a priori* separation is based on findings from meta-analyses demonstrating relevant discrepancies between parent and teacher ratings of ADHD symptoms (Cortese et al., 2016; Sonuga-Barke et al., 2013). The amount of between-study heterogeneity not traced to standard error of mean effect sizes but rather to systematic differences between studies was quantified using the I^2-statistic. In addition, 95 % prediction intervals of the overall SMD were estimated. All analyses were carried out using R version 4.0.0 with the packages 'meta', 'metafor' and 'dmetar' (Balduzzi et al, 2019; Harrer et al, 2019; Viechtbauer, 2010).

Primary Study Overlap

A special issue when analyzing meta-meta-analytic data is the possibility of overlapping primary studies in individual meta-analyses (see Appendix for further details). To ensure statistical independence of effect sizes, each primary study must be represented only once in the final analyses. There are several strategies to deal with primary study overlap. We created a citation matrix for every intervention and outcome separately to visualize the degree of overlap, and we calculated the corrected covered area (CCA). The CCA is a measure representing the overlap (relative coverage) of primary studies in the included meta-analyses: a CCA between 0 and 5 demonstrates slight overlap, 6 to 10 demonstrates moderate overlap, a score between 11 and 15 is considered high overlap, and greater than 15 very high overlap (Pieper et al., 2014a).

Additional Analyses

We planned to conduct sensitivity analyses to identify content-related and methodological influences on effect sizes, such as characteristics of participants or control groups. After inspecting the extracted data, we needed to adapt this initially planned procedure because of paucity of meta-analyses providing sufficient data. Instead, we now summarize all important variables narratively. Nevertheless, we performed exploratory subgroup analyses by type of intervention for pharmacological treatments: stimulants vs. non-stimulants in pharmacological treatment meta-meta-analyses.

Meta-analyses with high overlap were first included in a general l effect size estimation, and in the second step excluded for additional sensitivity analyses to examine the amount of influence on overall effects. Resulting changes in the amount of overlap and in effect sizes are reported in detail. If the number of included meta-analyses per intervention was too low (< 5) and the CCA yielded very high overlap, we decided to not aggregate data but to report each meta-analytic result narratively. Outlier analyses were conducted via the leave-one-out approach,[52] and we assessed the influence on the remaining heterogeneity of overall effects. After identifying outliers, we calculated the effect size again with those outliers removed. We continuously examined the association between meta-analyses' study-quality ratings and mean effect sizes by conducting meta-regression analyses with random-effects models.

Lastly, we conducted sensitivity analyses with meta-analyses based on between-subject design primary studies only to examine the change in effect sizes after omitting the meta-analyses with mixed designs.

Results

Results of the search

Our final literature search identified 453 relevant articles. After the screening process, 16 meta-analyses ultimately met our inclusion criteria and were included in qualitative and narrative synthesis (Figure 1). A list of excluded articles and reasons for their exclusion can be requested from the authors. One of the included 16 meta-analyses provided effect sizes for more than one intervention (Klassen et al., 1999).

In the following, each intervention's screening and selection process is described in detail: eight meta-analyses examined the effectiveness of pharmacological interventions with stimulants and non-stimulant medication. Eight meta-analyses reported relevant outcome data of parent and teacher-rated ADHD symptoms as standardized effect sizes and were subjected to meta-meta-analysis. Eight meta-analyses were on psychological interventions, specifically on (cognitive) behavioral therapy, parent training, social skills training or school-based interventions and were included in a second meta-meta-analytic synthesis. Five of these reported outcome data for parent-rated ADHD symptoms, and eight examined the overall effectiveness by relying on teacher-rated symptoms. The effectiveness of combined pharmacological and psychological interventions for ADHD symptoms was examined in only two of the 16 meta-analyses (Klassen et al., 1999; van der Oord et al., 2008).

Insert Figure 1 about here

Description of included meta-analyses

An overview of the main characteristics of included meta-analyses is presented in Figure 2. Eligible meta-analyses were published between 1999 and 2020 with a median publication year of 2015 including primary studies conducted between 1981 and 2019 with an average range of 18.8 years of evidence (SD_{range} = 9.9). On average, meta-analyses included 11 primary

studies for the outcome "parent-rated ADHD" with a range from 2 to 24 studies, and nine primary studies for "teacher-rated ADHD" with a range from 2 to 22 studies. Sample sizes ranged between 50 and 5086 participants in the included meta-analyses with an average of 1139 subjects per meta-analysis (SD_N = 1100.8). Overall, six meta-analyses (38 %) defined English or another language as a restriction for their literature search and the majority (56 %) included published and/or peer-reviewed studies only. Detailed information of data extraction and description can be found in the table in supplemental material (Appendix II).

Insert Figure 2 about here

Participants

In the meta-analyses reporting mean ages of analyzed primary studies (N = 154), the mean age ranged from 4.3 to 10.5 years. Three meta-analyses (Klassen et al., 1999; Punja et al., 2016; Storebø et al., 2019) only reported their sample's age range, ranging from 2 to 17 years. We found no meta-analysis for adolescents exclusively. The specification of mean male distribution of the sample in meta-analyses ranged from 68.8 % to 92.5 % (*M* = 79.2 %, *SD* = 6.8). Over half of the included meta-analyses (56 %) analyzed primary studies based on children and adolescents explicitly diagnosed with ADHD according to DSM or ICD, whereas six (38 %) meta-analyses (Daley et al., 2014; Richardson et al., 2015; Rimestad, et al., 2019; Sonuga-Barke et al., 2013; Storebø et al., 2019, Ward et al., 2020) also included primary studies with participants who fulfilled the cut-off score of a validated diagnostic assessment instrument such as the Conners' Parent or Teacher Rating Scale (Conners, 1997; Conners et al., 1998). One meta-analysis used standardized data but did not state which assessment they had used (Cheng et al., 2007). All of the latter investigated the effectiveness of psychological interventions. Overall, 11 of 16 (69 %) meta-analyses (Cheng et al., 2007; Daley et al., 2014; Iznardo et al., 2020; Otasowie et al., 2014; Punja et al., 2016; Richardson et al., 2015; Riera et

al., 2017; Schwartz & Correll, 2014; Storebø et al., 2015, 2019; Van der Oord et al., 2008) allowed comorbid diagnoses, and six of all eight psychological meta-analyses (Daley et al., 2014; Iznardo et al., 2020; Richardson et al., 2015; Rimestad et al., 2019; Sonuga-Barke et al., 2013; Storebø et al., 2019) allowed ADHD medication to be taken during the psychological treatment phase.

Outcome Data

Most meta-analyses (14 of 16) investigated treatment efficacy on the primary outcome, i.e., ADHD symptoms, as well as additional effects on secondary outcomes such as participants' change in social behavior, academic performance, or aggressive behavior (Cheng et al., 2007; Daley et al., 2014; Iznardo et al., 2020; Otasowie et al., 2014; Punja et al., 2016; Richardson et al., 2015; Riera et al., 2017; Rimestad et al., 2019; Schwartz & Correll, 2014; Storebø et al., 2015, 2019; Van der Oord et al., 2008; Wang et al., 2017; Ward et al., 2020). All included meta-analyses reported outcomes separately for parent and/or teacher-rated ADHD symptoms in accordance with our inclusion criteria.

Eleven meta-analyses (Cheng et al., 2007; Klassen et al., 1999; Otasowie et al., 2014; Punja et al., 2016; Richardson et al., 2015; Rimestad et al., 2019; Schwartz & Correll, 2014; Storebø et al., 2015, 2019; Van der Oord et al., 2008; Wang et al., 2017) only included primary studies that employed standardized and validated measurement instruments for assessing ADHD symptoms, and four meta-analyses (Daley et al., 2014; Iznardo et al., 2020; Sonuga-Barke et al., 2013; Ward et al., 2020) used symptom ratings based on questionnaires and standardized observations. Only four meta-analyses (Cheng et al., 2007; Punja et al., 2016; Schwartz & Correll, 2014; Wang et al., 2017) relied on ADHD-specific questionnaires (e.g., Conners 3, FBB-ADHS), whereas the majority included primary studies employing screening-instruments' subscales (e.g., CBCL subscale 'Attention Problems'). All but one meta-analysis on pharmacological interventions analyzed the number of adverse effects of

medication across primary studies. This meta-analysis (Klassen et al., 1999) investigated both the effects of medication treatment and of psychological and combination treatments. Across all 16 meta-analyses, three analyzed long-term follow-up data (i.e., assessments done three months or longer after treatment termination) (Punja et al., 2016; Rimestad et al., 2019; Storebø et al., 2019), whereas the majority originally planned to include these but needed to revise their plans as too few primary studies assessed data at follow-up.

Study Design

Overall, 14 meta-analyses included only randomized-controlled trials and two meta-analyses (Iznardo et al., 2020; Ward et al., 2020) also included non-randomized trials. All meta-analyses had a control group and standardized effect sizes were calculated based on mean difference between treatment and control group data. One meta-analysis (Iznardo et al., 2020) combined effect sizes from three studies with a between-subject design, and two with a within-subject design. We decided to include this meta-analysis study in our analyses as omitting it would have led to a loss of evidence, as relevant control-group data would have been excluded that were not summarized in other meta-analyses. We conducted sensitivity analyses excluding the last-mentioned meta-analytic effect size from our meta-meta-analyses that combined between- and within-subject analyses.

Methodological quality of included meta-analyses

Quality of included meta-analyses

The quality scores of every meta-analysis are based on the PRISMA 2009 Checklist as a "proxy" for methodological quality assessment; they ranged from 27.5 to 49.5 with a mean quality index of 38 (SD = 5.9). Nine of the included meta-analyses (56 %) (Daley et al., 2014; Otasowie et al., 2014; Punja et al., 2016; Richardson et al., 2015; Riera et al., 2017; Sonuga-Barke et al., 2013; Storebø et al., 2015, 2019; Ward et al., 2020) reported having a review

protocol prepared before starting with the literature search and meta-analytic process. Twelve meta-analyses (75 %) (Cheng et al., 2007; Daley et al., 2014; Iznardo et al., 2020; Klassen et al., 1999; Otasowie et al., 2014; Richardson et al., 2015; Schwartz & Correll, 2014; Sonuga-Barke et al., 2013; Storebø et al., 2015, 2019; Wang et al., 2017; Ward et al., 2020 included a conflict-of-interest statement. Overall, ten meta-analyses (63 %) (Daley et al., 2014; Klassen et al., 1999; Otasowie et al., 2014; Punja et al., 2016; Richardson et al., 2015; Sonuga-Barke et al., 2013; Storebø et al., 2015, 2019; Wang et al., 2017; Ward et al., 2020) were funded or authors received financial support for their work. Five of the 16 meta-analyses (Cheng et al., 2007; Daley et al., 2014; Klassen et al., 1999; Rimestad et al., 2019; Sonuga-Barke et al., 2013) applied the Jadad scale (Jadad et al., 1996) and seven the Cochrane Risk of Bias Tool for rating study quality or risk of bias of included primary studies (Otasowie et al., 2014; Punja et al., 2016; Riera et al., 2017; Storebø et al., 2015, 2019; Wang et al., 2017; Ward et al., 2020). The remaining four meta-analyses used an adaptation there of or did not assess study quality or any potential bias (Iznardo et al., 2020; Richardson et al., 2015; Schwartz & Correll, 2014; Van der Oord et al., 2008). Test of publication bias was considered in 11 meta-analyses (69 %); one meta-analysis (Punja et al., 2016) originally planned to analyze bias but was unable to do so because of the low number of studies included. Thirteen meta-analyses (87 %) (Cheng et al., 2007; Daley et al., 2014; Iznardo et al., 2020; Otasowie et al., 2014; Punja et al., 2016; Richardson et al., 2015; Riera et al., 2017; Rimestad et al., 2019; Schwartz & Correll, 2014; Sonuga-Barke et al., 2013; Storebø et al., 2015, 2019; Van der Oord et al., 2008; Ward et al., 2020) performed additional subgroup and sensitivity analyses to identify subgroups or moderators or to test the robustness of their results.

Quality of evidence in meta-analyses

Only four meta-analyses (Otasowie et al., 2014; Punja et al., 2016; Storebø et al., 2015, 2019) (also all Cochrane reviews) assessed the quality of evidence on outcome-level via the GRADE approach and provided a "Summary of Findings" table.

Primary Study Overlap

The CCA represents the primary study overlap and ranged from slight for pharmacological intervention to very high for parent-rated psychological interventions (see Table 1). The CCA measure was not computable for combined interventions. A citation matrix including the visually demonstration of the amount of overlap is provided in Appendix C.

Insert Table 1 about here

Effect of interventions

eTable 3 and eTable 4 in Appendix provide a summary of each outcome's results.

Pharmacological interventions

ADHD symptoms – parent ratings. Eight meta-analyses (Cheng et al., 2007; Klassen et al., 1999; Otasowie et al., 2014; Punja et al., 2016; Riera et al., 2017; Schwartz & Correll, 2014; Storebø et al., 2015; Wang et al., 2017) met our inclusion criteria for quantitative analysis, investigating primary studies with only stimulant medication, only non-stimulant medication or both versus placebo-control groups based on parent-rated ADHD symptoms. The quality scores of these eight meta-analyses ranged from 27 to 49 (M = 38.9) and none thereof described effects sizes for follow-up data. The overall effect in our meta-meta-analysis resulted in an effect size of SMD = 0.67 (95 % CI, 0.60 to 0.74; z = 18.11, p < .001) with τ^2 = 0.002 and I^2 = 30.7 % indicating low to moderate heterogeneity between results from individual meta-analyses (Figure 3). Sensitivity analysis identified one meta-analysis (Otasowie et al., 2014) as an outlier, and heterogeneity was reduced to zero with no change in

overall SMD when that study was excluded. Meta-analyses of stimulants showed no significant differences in effect sizes compared to non-stimulants or mixed medication (stimulants and non-stimulants) in our subgroup analysis ($Q = 1.01$, $df = 2$, $p = .605$). The influence of meta-analyses' study quality on effect sizes did not reach significance in our meta-regression ($\beta = -0.004$, $z = -0.673$, $p = .501$).

Insert Figure 3 about here

ADHD symptoms – teacher ratings. The same eight meta-analyses as those included in the previous analysis on parent ratings reported pharmacological-treatment effect sizes compared to placebo based on teacher-rated symptoms (Figure 4) and resulted in an overall SMD of 0.68 (95 % CI, 0.54 to 0.82; $z = 9.29$, $p < .001$) with low to moderate heterogeneity among meta-analyses ($\tau^2 = 0.029$). One meta-analysis (Klassem et al., 1999) was identified as an outlier contributing the most to between-study heterogeneity. Re-analysis excluding that outlier resulted in an overall SMD of 0.62 (95 % CI, 0.49 to 0.75; $z = 9.39$, $p < .001$) and reduced heterogeneity to $I^2 = 73.6$ %.

Significant differences were revealed in subgroup-analyses between meta-analyses including only stimulants, only non-stimulants, or both treatments ($Q = 19.35$, $df = 2$, $p < .001$). Meta-analyses reporting effect sizes of stimulant medication (Klassen et al., 1999; Punja et al., 2016; Storebø et al., 2015; Wang et al., 2017) resulted in SMD of 0.79 (95% CI, 0.64 to 0.94), and meta-analyses of non-stimulant medication only in SMD of 0.42 (95% CI, 0.29 to 0.55). (Cheng et al., 2007; Otasowie et al., 2014; Schwartz & Correll, 2014) Lastly, meta-analyses of mixed (stimulant and non-stimulant) yielded a SMD of 0.75 (95% CI, 0.64 to 0.86). (Riera et al., 2017) Meta-regression analysis indicated no influence of the study-quality score on meta-analytic effect size ($\beta = -0.002$, $z = -0.202$, $p = .839$).

Insert Figure 4 about here

Psychological Interventions

ADHD symptoms – parent ratings. Five meta-analyses (Daley et al., 2014; Richardson et al., 2015; Rimestad et al., 2019; Sonuga-Barke et al., 2013; Storebø et al., 2019) of different psychological interventions such as parent training, school-based treatments, (cognitive) behavioral therapy and social skills training compared with a control group reported pooled effect sizes for parent-rated ADHD symptoms. Control groups are indicated in eTable 4. The study-quality scores ranged from 39.5 to 49.5 with a mean quality index of $M = 44.3$. Two of the included meta-analyses (Rimestad et al., 2019; Storebø et al., 2019) reported effect sizes based on follow-up data. The random effects data synthesis yielded an overall effect size of SMD = 0.42 of psychological interventions compared with control (95 % CI, 0.33 to 0.51; z = 8.91, p < .001) with $\tau^2 < 0$ and $I^2 = 0.0$ % indicating no substantial heterogeneity between results from individual meta-analyses (Figure 5). Our sensitivity analyses detected no outlier contributing to heterogeneity.

Two meta-analyses provided effect sizes for post-treatment to follow-up changes in parent-rated ADHD symptoms (Rimestad et al., 2019; Storebø et al., 2019) with SMD between 0.5 (95 % CI, 0.14 to 0.87, $I^2 = 0\%$) and 1.36 (95 % CI, 0.25 to 2.48, $I^2 = 95\%$) favoring treatment.

After inspecting the citation matrix, we excluded the meta-analysis with the highest overlap to others[19] and could reduce the CCA to 4.76 indicating “low” overlap. The sensitivity analysis including only low overlap meta-analyses yielded no difference in overall SMD, indicating that the excluded meta-analysis had no substantial influence on the overall effect size. The study-quality score did not reach significance in meta-regression analysis ($\beta = 0.003$, z = 0.206, p = 0.837) showing no influence on effect sizes.

Insert Figure 5 about here

ADHD symptoms – teacher ratings. Seven meta-analyses (Daley et al., 2014; Iznardo et al., 2020; Klassen et al., 1999; Richardson et al., 2015; Rimestad et al., 2019; Sonuga-Barke et al., 2013; Storebø et al., 2019; Ward et al., 2020) investigating the effectiveness of school-based, behavioral, psychological interventions or a combination of these reported significant effects for teacher rated ADHD symptoms compared to a control group (see eTable 4). To fulfill the highest quality standards, we extracted only the effect size based on between-subject design of the relevant meta-analysis (Ward et al., 2020) and not within-subject effects (e.g., change from pre- to post-treatment). Two meta-analyses (Daley et al., 2014; Sonuga-Barke et al., 2013) consisted of exactly the same primary studies (k = 7), therefore this effect size was included only once for meta-meta-analytic calculation. PRISMA scores ranged from 27 to 49.5 (*M* = 41.6). The overall synthesis of these seven effect sizes resulted in an SMD of 0.25 (95 % CI, 0.12 to 0.38; z = 3.82, p < .001) with $\tau^2 < 0$ and $I^2 = 0.0$ % indicating no heterogeneity (Figure 6). No statistical outliers were detected in our sensitivity analysis.

Follow-up data results of two meta-analyses (Storebø et al., 2019; Ward et al., 2020) ranged from SMD of 0.07 (95 % CI, -0.01 to 0.15, $I^2 = 0\%$) to 0.11 (95 % CI, -0.06 to 0.28, $I^2 = 0\%$) favoring treatment. Meta-regression analysis indicated no influence of study quality on effect sizes (β = -0.002, z = -0.178, p = .859).

Insert Figure 6 about here

Sensitivity analyses

Omitting the meta-analysis (Iznardo et al, 2020) based on mixed design studies (i.e., including three between-subject and two within-subject design primary studies) the overall effect size

for the remaining meta-analyses based on between-subject designed changed to 0.21 (95 % CI, 0.05 to 0.36, I^2 = 0.0 %) for teacher-rated ADHD symptoms. Meta-Regression Analyses can be found in supplemental material eFigure 1. Detailed information on figures of subgroup and sensitivity analyses can be requested from the authors.

Combined Interventions

Within all identified meta-analyses, only three articles examined the combination of pharmacological and psychological treatment. Of these, Majewicz-Hefley (2007) considered symptom categories separately (inattention, hyperactivity, impulsivity) but did not specify the rater (and therefore do not meet our inclusion criteria), whereas Van der Oord et al. (2008) and Klassen et al. (1999) reported outcomes for clustered ADHD symptoms overall rated by parent and teachers. As one of the meta-analyses (Klassen et al., 1999) had been conducted relying on two primary studies also included in the other meta-analysis (Van der Oord et al., 2008), and failed to report a standardized effect size, we were unable to analyze data on the meta-meta-level. The latter meta-analysis (Van der Oord et al., 2008) was based on within-subject design only (no control group) and resulted in effect sizes (standardized mean change) of 1.89 (95 % CI, 1.39 to 2.40, *Q*-stat = 12.3) for parent and 1.77 (95 % CI, 1.08 to 2.46) for teacher rated ADHD symptoms indicating heterogeneity between studies (*Q*-stat = 31.47).

Discussion

Summary of results

This umbrella review entailing meta-meta-analysis provides an overview of the latest meta-analytical evidence on the effectiveness of pharmacological and psychological interventions for treating ADHD in children and adolescents. As no previous research has examined the literature in this way, no systematic review summarizing meta-analyses of interventions for children and adolescents with ADHD was available before the present study. To ensure a high scientific standard, we followed the latest recommendations from the Cochrane Collaboration for reporting a second-order meta-analysis (see Pollock et al., 2020). In addition to our narrative summary of specific characteristics of the different meta-analyses, we aggregated the current evidence on a quantitative level and conducted meta-meta-analyses. These kinds of analyses reveal variation between results from individual meta-analyses and may thus contribute to explaining observed heterogeneity between results from individual meta-analyses.

Note that direct comparisons of effect sizes of pharmacological versus psychological treatment over meta-meta-analyses concerning which intervention works best when treating ADHD are inappropriate (Pollock et al., 2020). This is because meta-meta-analytical procedures do not combine evidence on primary study level (first level) and effect sizes do not reflect the effectiveness of the intervention applied. Instead, we rather aggregated results from extant meta-analyses to analyze the second level. This is in line with our claim to summarize meta-analyses that assess the effects of the most common ADHD treatment options for children and to identify factors contributing to heterogeneous results.

Our analysis of eight meta-analyses for pharmacological interventions (Cheng et al., 2007; Klassen et al., 1999; Otasowie et al., 2014; Punja et al., 2016; Riera et al., 2017; Schwartz & Correll, 2014; Storebø et al., 2015; Wang et al., 2017) resulted in significant moderate to large effects with moderate heterogeneity for parent-rated ADHD symptoms.

This finding is consistent with research findings high on the evidence pyramid, such as network-meta-analysis or individual patient data analysis (see Cortese et al., 2018 for children, adolescents and adults and Groenman et al., 2021 for children and adolescents) and confirms recommendations in current treatment guidelines (AWMF, 2017; NICE, 2018). An exploratory subgroup analysis revealed significant results for stimulant and non-stimulant medication, suggesting that pharmacotherapy with different substances is effective according to parents' ratings. However, given the small number of meta-analyses and their exploratory nature, conclusions based on their findings are limited. Results for teacher ADHD symptom ratings are similar, though their heterogeneity was substantially larger than parent ratings were. Therefore, these analyses do not enable any final conclusions about the treatment effect's precise magnitude. Overall, study quality and effect sizes revealed no association in our meta-meta-analysis on pharmacological ADHD interventions. Note that with these results, the PRISMA items are not intended and not validated for use in such analyses. It is therefore possible that associations between study quality and observed treatment effects remained undetected in our analyses. No follow-up data of pharmacological interventions have been available for meta-meta-analytic use. Results of the CCA indicated a slight overlap of primary studies within our meta-meta-analyses.

The current meta-meta-analysis of psychological interventions (such as behavioral therapy, parent training and school-based treatments) demonstrated small effects on parent ratings across the five included meta-analyses (Daley et al., 2014; Richardson et al., 2015; Rimestad et al., 2019; Sonuga-Barke et al., 2013; Storebø et al., 2019) and zero between-meta-analytic heterogeneity. Narratively analyses of two meta-analyses (Storebø et al., 2019; Ward et al., 2020) showed medium to large effect sizes in long-term. Our assessment of primary study overlap resulted in a CCA of 12.5 % (high overlap).

There are seven meta-analyses (Daley et al., 2014; Iznardo et al., 2020; Klassen et al., 1999; Richardson et al., 2015; Rimestad et al., 2019; Sonuga-Barke et al., 2013; Storebø et al.,

2019; Ward et al., 2020) of ADHD symptoms based on teacher ratings that compared the psychological intervention with a control group (one exception with a mixed design) (Iznardo et al., 2020). Our analyses yielded significant small effects with no heterogeneity for teacher ratings with high primary study overlap. This may reveal more research efforts of new primary studies based on teacher-rating. Two meta-analyses provided follow-up data with small effect sizes for teacher-rated ADHD symptoms in long-term. However, given the paucity of meta-analyses and their exploratory nature, conclusions based on their findings are limited. Effect sizes of previous analyses and comprehensive overviews ranged from small to medium across different psychological interventions such as parent training, psychotherapy or classroom interventions and aggravated recommendations. For instance, the German guidelines (AWMF, 2017) and NICE guidelines (NICE, 2018) indicated that psychological interventions carried out as monotherapy may not be effective for all individuals with ADHD to reduce ADHD symptoms to non-clinical levels (e.g., for school-aged children).

While our meta-analyses of medical therapies showed no descriptive difference between parent- and teacher-rated ADHD symptoms, our meta-analyses of psychological treatments indicated somewhat lower effect sizes for symptoms based on teacher ratings. Such reduced effects are in line with findings that established smaller and partly non-significant effects for psychological ADHD treatments according to probably blinded (thereby including teacher ratings), while proximal (i.e., parental) ratings did result in significant, although small effects (Daley et al., 2014; Sonuga-Barke et al., 2013). However, unlike a meta-analysis of nonpharmacological interventions of Sonuga-Barke et al. (2013), our results indicate that meta-analyses examining psychological interventions based on teacher ratings do reveal small and significant effect sizes underlining the importance of such treatments. It is not surprising that meta-analyses on teacher-rated-ADHD symptoms yielded lower effect sizes as not all psychological interventions included a specific teacher or school component. Although teacher ratings seem to be a valid measure to assess ADHD in classrooms (Staff et al., 2021),

we cannot expect that effects of, for example, behavioral parent training programs will generalize to the child's behavior in school settings.

Overall, meta-analyses of pharmacological interventions resulted in moderate to high effect sizes indicating significant symptom reduction in both parent and teacher ratings. An important finding of ours is, however, that we were unable to analyze meta-data on combined treatments as too few meta-analyses met our inclusion criteria, even though the narrative results are promising with large effect sizes of combined treatment on parent and teacher-rated ADHD symptoms. This reveals a general lack of primary studies on combined treatments, despite preliminary evidence that additional behavioral treatment may lead to lower medication doses. In addition, the definition of "combined treatments" is not similarly implemented in every primary study. For instance, some studies initiated pharmacological treatment first, followed by psychosocial treatment, while in others the treatments were applied simultaneously or the other way round. The pattern of carrying out pharmacological and psychosocial treatments might influence combined treatments' effectiveness (Pelham et al., 2017). Thus, large-scale primary studies are urgently needed that specifically compare combined treatments to pharmacological and psychological therapies to enable conclusions for decision-making clinicians as to which treatment is the most effective for whom as first-line treatment.

Implications for ADHD treatment research

With focus on the *participants* in the included meta-analyses, one of the most important findings is that we identified no meta-analyses that focused specifically on adolescents, i.e., children more than 12 years old. The average age of participants in the included meta-analyses ranged from four to 11 years. Among the meta-analyses not fulfilling all our inclusion criteria, however, we found some meta-analyses that focused on youths as participants (e.g., Hirota et al., 2014). However, either the reported outcomes in those studies

did not correspond to our protocol, or the examined intervention was not pharmacological or psychological (e.g., Chan et al., 2016; Chang et al., 2018 or Chimiklis et al., 2018). Adolescence represents a vulnerable age in terms of demands at school, and from parents, peers and society, and such vulnerability increases when treatment is discontinued. Previous research pointed out that many participants with ADHD, who enter adolescence, often discontinue therapy, resulting in a discrepancy of support vs. demand ('lost in transition', Buitelaar, 2017). This might contribute to the disorder's exacerbation specifically during adolescence (Buitelaar, 2017; Montano & Young, 2012; Robb & Findling, 2015). Future research should therefore focus on developing and evaluating interventions for adolescents, as this is a crucial age range during which the disorder's negative course may be prevented or impeded, and to prevent a persisting impairment into adulthood, as there is evidence that comorbidities and impairments in adolescence caused by the disorder worsen substantially (Keshavan et al., 2014; Manfro et al., 2019).

Second, the percentage of male participants amounted to over 90% in individual meta-analyses, although research has revealed a male-female-ratio of only 2:1 to 4:1 in population-based studies (Huss et al., 2008; Ramtekkar, et al., 2010). Specific sex effects may be present, and our ability to generalize meta-analytic findings to the under-represented female population might be limited. Although previous (IPD) meta-analyses detected no association between sex and intervention response (Arnold et al., 2015; Groenman et al., 2022; Jensen et al., 2007; Owen et al., 2003), many failed to conduct appropriate analyses due to low power or too few included studies (but Groenman et al., 2022). To adequately estimate any association between sex and treatment effects, future meta-analyses should therefore include individual patient data (on psychological, pharmacological and combined treatment) with adequate power across individual studies in individual patient-data meta-analyses.

Another important limitation of the latest meta-analytic literature is the investigation of the role that comorbid disorders may play in treatment effectiveness. Comorbid disorders,

e.g., comorbid oppositional defiant disorder/conduct disorder (Groenman et al., 2022), are very common in children with ADHD and are known to have a substantial impact on the treatment effectiveness (Jensen et al, 2001; Larson et al., 2007; Reale et al., 2017). Our study showed that 71% of included meta-analyses examined samples presenting comorbid disorders. None of these meta-analyses specified comorbid disorders or their influence on treatment effectiveness results, perhaps for statistical reasons (lack of studies). Therefore, another recommendation for future research is to conduct individual patient data meta-analysis especially concerning medication and combined treatments, as these are adequately powered to systematically assess potential associations between the presence of comorbid disorders on the effectiveness of pharmacological and psychological treatments and of the two combined.

Our last finding to be addressed regarding the sample is the high number of participants in psychological studies who underwent parallel medical therapies (in 70 % of the included meta-analyses). This may be due to the fact that pharmacological treatment often serves as first-line therapy in clinical practice, which would make it difficult to recruit enough medication-naïve participants in psychological treatment studies. It differs from the so-called combined treatment, such that medication in psychological studies represents only a statistical variable and not an active intervention. Many different combinations of medication and psychological treatments are possible in the studies (e.g., providing medication before starting psychological treatment, or only including participants in the study who are stable on medication) and should be consistently designed (with medication as part of the intervention and defined as “combined treatment” as mentioned above). The effects of different combinations of medication and psychological treatment on ADHD symptoms remain unclear (Pelham et al., 2017). Future meta-analyses should therefore be more specific with regards to defining inclusion criteria for participants in primary studies, and should clearly describe how psychological interventions and medication treatment coincide in the participants included

(e.g., if only participants on stable medication were included, or if the treatment consisted of a combination of medication and psychological treatment in treatment-naïve participants, for instance). Such a differentiated report could then also help us estimate the cost-effectiveness of treatment options, their sequence, and combination (e.g., Page et al., 2016).

Our results enable few conclusions about *outcome data* defined in meta-analyses. The included meta-analyses often summarized ADHD core symptoms (inattention, hyperactivity/impulsivity) in general outcomes like 'ADHD overall'. As different meta-analyses could have shown various effects on different core symptoms, future meta-analyses should investigate the effectiveness of treatment options on categories of symptom-based outcomes, for instance by analyzing inattention and hyperactivity/impulsivity separately (Groenman et al., 2022). Closely linked to this recommendation is that many included meta-analyses used screening questionnaires as measurements to analyze change in ADHD symptoms (e.g., SDQ, Goodman, 1997 or CBCL/TRF/YSR, Achenbach & Dumenci, 2001). Such screening instruments, however, do not reflect the entire range of ADHD-specific symptoms and may therefore not adequately capture intervention-triggered changes. One potential option to fulfill this need for standardized, valid measurement tools into practice is to employ subscales from ADHD-specific questionnaires (like Conners 3^{TM}, Conners, 2008) or of structured clinical interviews that capture symptoms reflected in the two main classification systems DSM-5 and ICD-10 in a more differentiated way (Neuschwander et al., 2017; Rettew et al., 2009). As meta-analyses depend on individual studies, future ADHD treatment studies should aim to employ ideally the same questionnaire across countries and studies (disorder-specific questionnaires, rather than broad screenings) and report change in ADHD symptoms separately for each measurement (such as questionnaire vs. interview vs. observation).

Further, children's self-ratings were not reported in all included meta-analyses. Self-rated symptoms are important to gain insight into understanding a disorder and thus, treatment

motivation and change in impairment and functioning (Brakemeier et al., 2019). This harmonizes with work that highlighted the need for combining self- and informant-reported symptoms when diagnosing ADHD (Barkley et al., 2010; Sibley et al., 2016). A possible explanation for this lack is the usually young age of children included in primary studies and controversy about the validity of self-assessments by young children (Volz-Sidiropoulu et al., 2016). There are nevertheless standardized and validated self-rating questionnaires for children eight years old and older (e.g., Conners 3^{TM}; Conners, 2008).

Lastly, unfortunately only three of the 16 included meta-analyses yielded any follow-up data on long-term effects of treatment on ADHD symptoms; all three thereof investigated psychological interventions. Researchers have emphasized the need for longer-term follow-up data (Cortese et al., 2018; Elliot et al., 2020; Ward et al., 2020). The most frequent criticism in the meta-analyses we included was the paucity of primary studies assessing long-term data. Therefore, future primary studies, especially those investigating the effects of pharmacological interventions, should assess long-term as well as short-term effects after treatment termination.

With regard to *study design*, meta-analyses should specify their treatment and control-group before conducting a literature search. Our study demonstrates that the meta-analyses we included did not always specify their control group (active vs. semi-active vs. passive comparator). This lack of information hampers valid conclusions for clinical practice, as the effects of treatments vs. control can differ depending on the type of control used. Mixing different control groups together in one meta-analysis will likely encourage between-study heterogeneity, making it harder to interpret the results obtained because effect sizes can vary because of the nature of the comparator (Mohr et al., 2014). Future meta-analyses on psychological studies should therefore focus on homogeneous comparators to enable valid interpretations.

With respect to *methodological quality* the well-known 'garbage-in, garbage-out' problem highlights the fact that a meta-analysis is only as good as the primary studies it includes. To interpret effects sizes and draw firm conclusions, it is crucial to assess every primary study's quality to enable a fruitful evaluation of the bias risk on the meta-analytic level. The current guidelines for conducting meta-analyses recommend different tools (e.g., Jadad scale, Cochrane risk of bias tool) and approaches (e.g., GRADE approach) but approximately 25 % of the meta-analyses included in this overview did not engage in any evidence-quality assessments. Specifically, the GRADE approach enables a clear and transparent overview for readers by rating the certainty of the available evidence (Guyatt et al., 2008), which facilitates implications for clinical practice and the development of guidelines. Future meta-analyses should focus on adopting validated quality-measurement tools and describe the certainty of evidence in addition to estimating effect sizes.

Another point to make regarding methodological quality is that our results reflect substantial heterogeneity in conducting and reporting meta-analyses in the field of ADHD intervention research; i.e., our quality index ranged from 27.5 to 49.5 with a mean of 40. None of the meta-analyses scored the maximum 54 points and thus completely fulfill the standards required in the PRISMA statement (2009). Future meta-analyses should thus apply state-of-the-art guidelines like the Cochrane handbook (Higgins et al., 2021) or the updated PRISMA 2020 statement (Page et al., 2021) to improve the methodological quality of meta-analyses and in how findings are reported to ultimately enable valid conclusions to be drawn.

Taken together, to address the aforementioned issues such as the use of different control groups, lack of direct comparisons between pharmacological, psychological, and combined interventions, and factors associated with participant-level variables (such as sex or the presence of comorbidities), future ADHD research should apply additional advanced meta-analytic methods in addition to meta-meta-analysis, e.g., individual participant-data meta-analysis (e.g., Groenman et al., 2021) or network meta-analysis (e.g., Cortese et al.,

2018). eTable 3 in supplemental material summarizes all implications described above for a detailed overview.

Limitations

One key challenge in conducting the present meta-meta-analysis was how to manage study overlap across different meta-analyses, because diverging views about dealing with this were involved (Munder et al. 2013; Pollack et al. 2019). Although we had initially planned to apply Munder's formula (2013), we could not, as that would have dramatically reduced the number of meta-analyses we could include. We thus followed recommendations by Pollock and colleagues (2020) instead, who argue "if the purpose is to present and describe the current body of systematic review evidence on a topic, it may be appropriate to include the results of all relevant systematic reviews, regardless of topic overlap" (p. 9).

Another limitation is that several meta-analyses included primary studies with heterogenous control-groups, especially in the psychological treatment meta-analyses. There is evidence that diverging effects between treatment and control are strongly dependent on the nature of the control condition (Mohr et al., 2014). Therefore, future meta-analyses should focus on homogeneous comparators as the Cochrane Handbook explicitly requires (see Pollock et al., 2020) or should clearly distinguish between different types of control groups in their analyses, for instance by using network-meta-analysis techniques (e.g., Catalá-López et al., 2017 or Cortese et al., 2018).

Another limitation is that we focused on the outcome ADHD symptoms and not on other important areas such as comorbidities (e.g., Daley et al., 2014) or functional impairments (like academic and educational outcomes, e.g., Loe et al., 2007), while the primary outcome of psychological treatments is often not to alleviate ADHD symptomatology, but rather to reduce an impairment's severity. The data for such additional analyses have been extracted, and we will present it elsewhere (Korfmacher et al., in prep).

Finally, we started planning and conducting our meta-meta-analysis at a time in which no standard tool existed to assess the study quality of an individual meta-analysis. We based our assessment therefore on PRISMA criteria applied in two previous meta-meta-analyses (Mingebach et al., 2018; Weber et al., 2019). Nonetheless, summary scores should be interpreted with caution (Herbison et al., 2006).

Conclusion

This paper reveals meta-meta-analytical knowledge on the efficacy of pharmacological and psychological interventions and their combination for children with ADHD. Our overview advances the field of ADHD intervention research by identifying evidence gaps, thereby contributing to standardization and providing recommendations for future ADHD treatment studies and meta-analyses. Pharmacological and psychological treatment options seem to be effective in treating ADHD according to parental and teacher ratings. There is a dearth of studies on combined pharmacological and psychological treatments, although such therapies are often considered the "gold-standard" in treatment guidelines (AWMF, 2017; NICE, 2018). There is an obvious shortage of studies on the long-term treatment effects of pharmacological and psychological interventions on adolescents, and there is a lack of standardized primary studies. Furthermore, meta-analyses should focus on primary studies investigating treatments for adolescents, as this is a very vulnerable age group and at risk of developing persisting symptoms – moreover, they often fail to benefit from current interventions (Buitelaar, 2017). Despite the presence of many primary studies investigating the effects of psychological and pharmacological ADHD treatments and their combination, we observed a lack of international standardization regarding inclusion criteria, sample definition, outcome data, study design, and quality assessment, all of which are urgently required to enable evidence-based recommendations for pediatric ADHD treatments. To compare the effectiveness of ADHD treatment options, our work highlights the need for meta-analyses based on standardized primary studies and investigating long-term effects, network meta-analyses and individual patient data analysis as encouraged by leading ADHD research organizations (Hussong et al., 2013; Kanters et al., 2016).

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Table 1

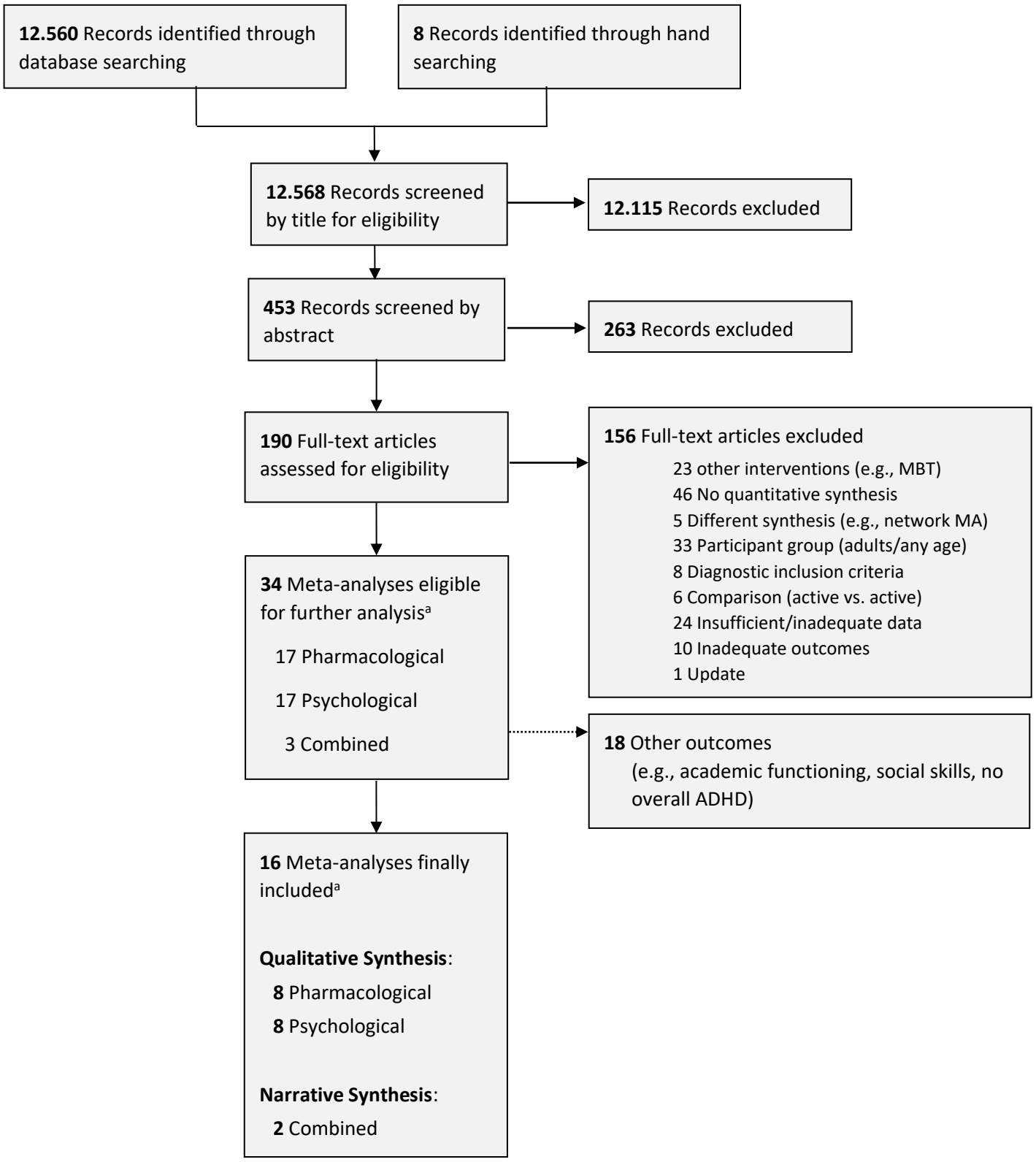
Overview of CCA Score as Measure of Primary Study Overlap

Outcome	k	CCA	Overlap[a]
Pharmacological Interventions			
Parent	9	3.36	Slight
Teacher	9	1.17	Slight
Psychological Interventions			
Parent	6	12.50	High
Teacher	7	4.63	Slight
Combined			
Parent	2	-	-
Teacher	2	-	-

Note. k = number meta-analyses; CCA = corrected covered area; "-" = CCA not computable.
[a] Interpretation of CCA by Pieper et al. (2014)

Figure 1

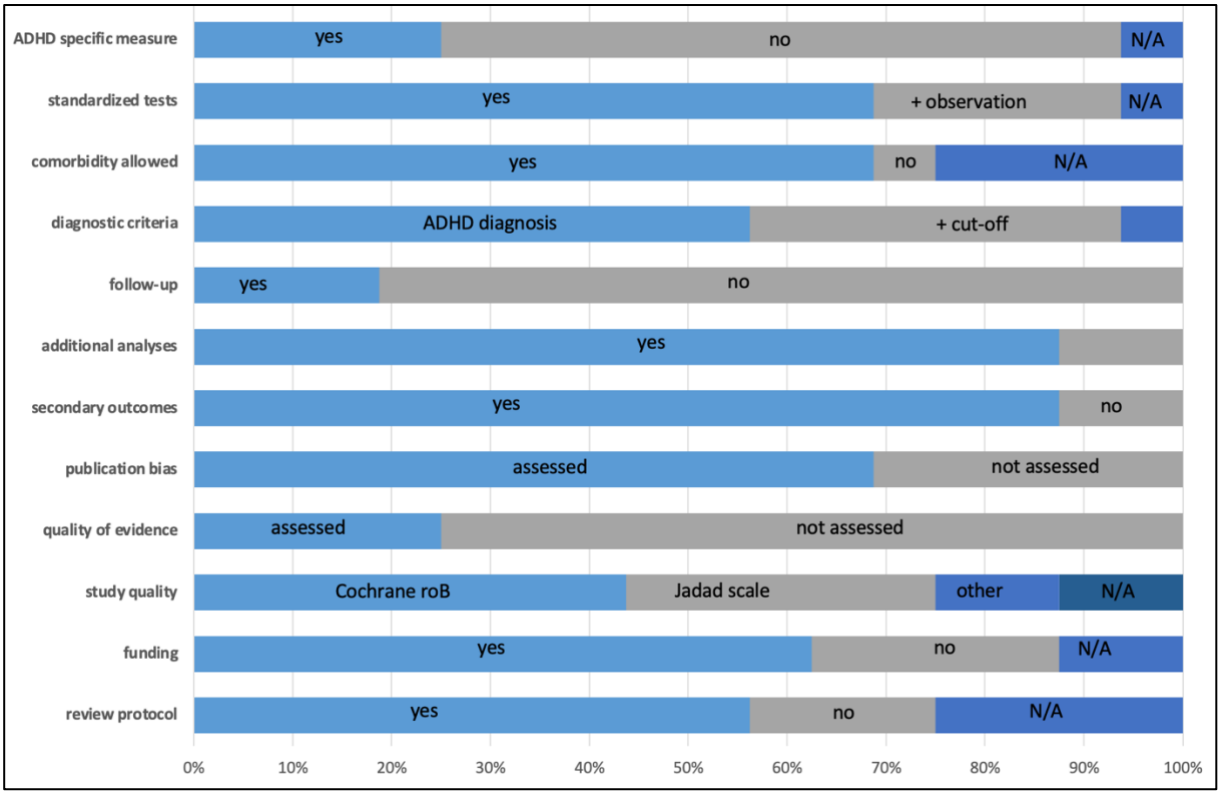
Flow Chart of Literature Search and Screening Process



[a] Number of overall included papers: the following numbers represent intervention-specific results as two meta-analyses provided effect sizes for more than one intervention

Figure 2

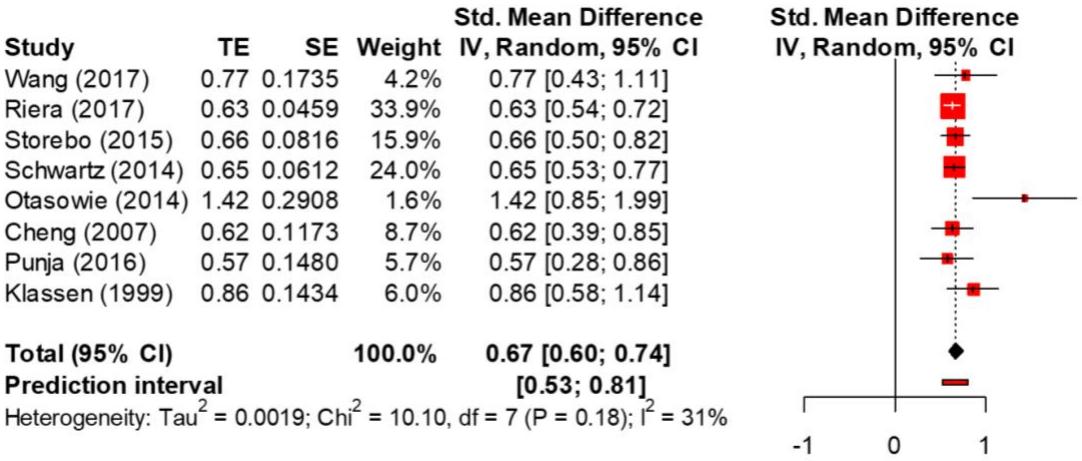
Descriptive characteristics of N =16 meta-analyses



Note. ADHD = attention deficit/hyperactivity disorder; + cut-off = ADHD diagnosis plus cut-off value on a measurement scale; CPT = Continuous Performance Test; N/A = not assessed; RoB = Cochrane risk of bias tool

Figure 3

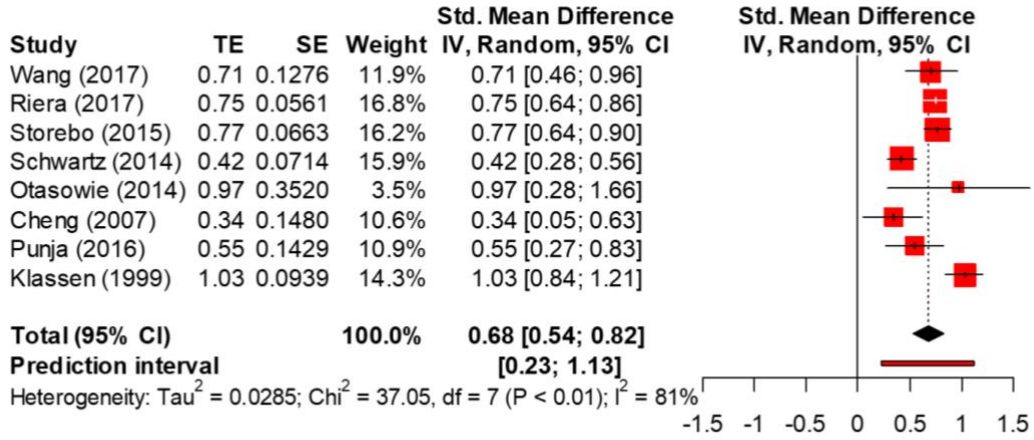
Forest Plot of Meta-Meta-Analysis of Pharmacological Interventions as Compared with Placebo for Parent-Rated ADHD



Note. TE = effect size of meta-analysis; SE = standard error of effect size; random = random-effects model; CI = Confidence Interval

Figure 4

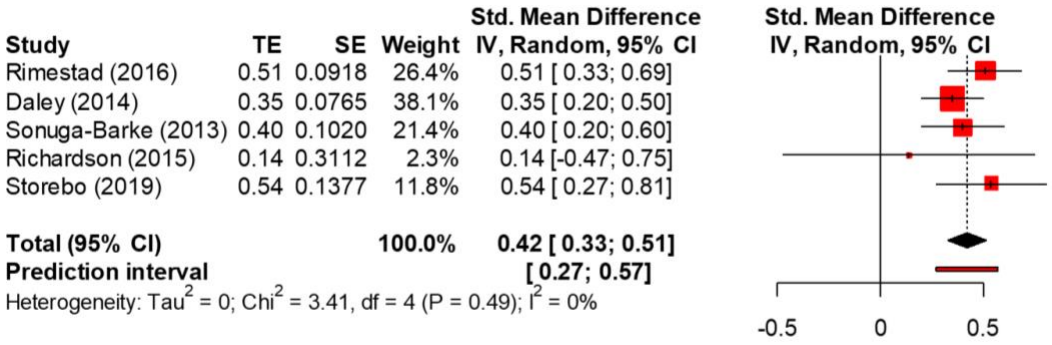
Forest Plot of Meta-Meta-Analysis of Pharmacological Interventions as Compared with Placebo for Teacher-Rated ADHD



Note. TE = effect size of meta-analysis; SE = standard error of effect size; random = random-effects model; CI = Confidence Interval

Figure 5

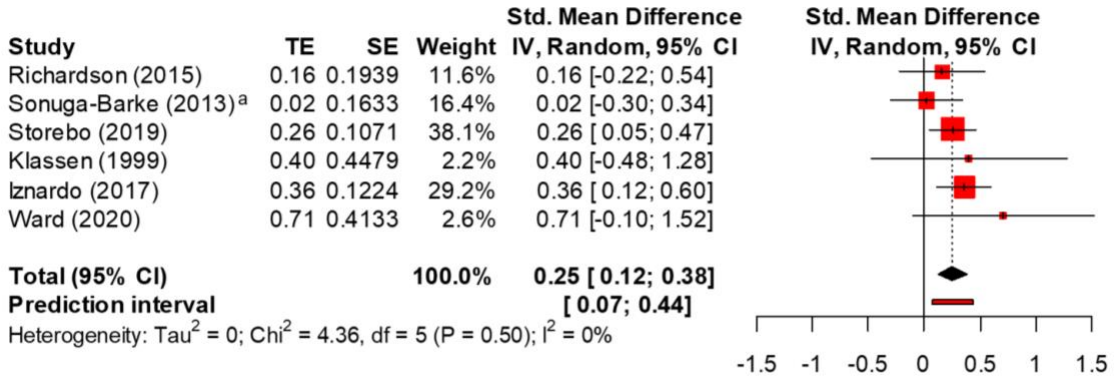
Forest Plot of Meta-Meta-Analysis of Psychological Interventions as Compared with Control on Parent-Rated ADHD



Note. TE = effect size of meta-analysis; SE = standard error of effect size; random = random-effects model; CI = Confidence Interval

Figure 6

Forest Plot of Meta-Meta-Analysis of Psychological Interventions as Compared with Control on Teacher-Rated ADHD



Note. TE = effect size of meta-analysis; SE = standard error of effect size; random = random-effects model; CI = Confidence Interval

[a] Sonuga-Barke (2013) and Daley (2014) are only counted once in this meta-meta-analysis as they represent exactly the same effect size based on the same primary studies.