REVIEW

An Individual Participant Data Meta-analysis: Behavioral Treatments for Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

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Objective: Behavioral interventions are well established treatments for children with attention-deficit/hyperactivity disorder (ADHD). However, insight into moderators of treatment outcome is limited.

Method: We conducted an individual participant data meta-analysis [IPDMA], including data of randomized controlled behavioral intervention trials for individuals with ADHD <18 years of age. Outcomes were symptoms of ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD) and impairment. Moderators investigated were symptoms and impairment severity, medication use, age, IQ, sex, socioeconomic status, and single parenthood.

Results: For raters most proximal to treatment, small- to medium-sized effects of behavioral interventions were found for symptoms of ADHD, inattention, hyperactivity/impulsivity (HI), ODD and CD, and impairment. Blinded outcomes were available only for small preschool subsamples and limited measures. CD symptoms and/or diagnosis moderated outcome on ADHD, HI, ODD, and CD symptoms. Single parenthood moderated ODD outcome, and ADHD severity moderated impairment outcome. Higher baseline CD or ADHD symptoms, a CD diagnosis, and single parenthood were related to worsening of symptoms in the untreated but not in the treated group, indicating a protective rather than an ameliorative effect of behavioral interventions for these children.

Conclusion: Behavioral treatments are effective for reducing ADHD symptoms, behavioral problems, and impairment as reported by raters most proximal to treatment. Those who have severe CD or ADHD symptoms, a CD diagnosis, or are single parents should be prioritized for treatment, as they may evidence worsening of symptoms in the absence of intervention.

Key words: behavioral interventions, ADHD, individual participant data meta-analyses, moderator analyses

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A ttention-deficit/hyperactivity disorder (ADHD)[1] in children and adolescents is highly prevalent[2] and impairing in multiple domains of functioning.[3] It is a heterogeneous disorder regarding etiology, symptomatology, functional impairments, developmental expression, and comorbid psychopathology; common comorbidities are oppositional defiant disorder (ODD), conduct disorder (CD), anxiety disorder, and depression.[4]

Pharmacological and behavioral interventions are well-established treatments for children and adolescents with ADHD,[5–7] with behavioral interventions often targeting comorbid pathology and ADHD-related impairments.[5] There is a clear need for behavioral treatments in clinic-based practice, as they may be preferred by patients and families[8,9] and can reduce the need for medication.[9–11] The heterogeneity of the symptomatology and comorbidity of

children with ADHD makes it unlikely that behavioral treatments will work equally for all individuals, emphasizing the need for more personalized treatment plans.

Moderation analysis allows the identification of subgroups of children (or families) that are more or less likely to respond to behavioral interventions.[12] To date, meta-analyses in ADHD samples could not consistently identify moderators of behavioral treatment response, most possibly due to lack of power or related to the diversity of sample compositions and study designs.[13] For example, child age was found to be a significant moderator in 1 meta-analysis[9] but not in 2 others.[14,15]

Individual treatment studies are mostly not designed or powered for moderation analyses.[12,16] An example of 1 of the few adequately powered studies for moderation analyses in ADHD samples is the Multimodal Treatment Study of ADHD (MTA),[16,17] which showed comorbid anxiety of the child to be a moderator of (better) behavioral treatment response.[9,18] The MTA study, however, was limited in age range (7—9 years) and in the comparability of the behavioral treatment arm to other behavioral treatments (ie, the MTA behavioral treatment was far more intense than most others). In sum, evidence regarding moderating factors is currently inconsistent or lacking, thereby hindering clinicians from personalizing treatment plans.

In contrast to individual randomized controlled trials, individual participant data meta-analysis (IPDMA) is particularly appropriate to run highly powered moderation analyses, as it uses individual data from the original studies, leading to uniform conclusions across studies.[19] The IPDMA approach has been shown to be of great advantage in the general field of medicine; for example, an IPDMA of Furukawa *et al.*[20] on treatment of depression resulted in an interactive Web tool that shows the individual predicted disease course when taking the participants' characteristics into account. However, this is the first IPDMA on the treatment of children and adolescents with ADHD. In the current study, we used IPDMA to identify behavioral intervention effects and moderators of outcomes for symptoms of ADHD, ODD, and CD, and global impairment in children and adolescents with ADHD (<18 years of age). We focused primarily on outcome measures taken from reporters most proximal to the delivery of the treatment: parent-rated outcomes for parent training and child-focused treatments, and teacher-rated outcomes for interventions that were primarily school based. Furthermore, we aimed to explore intervention effects on probably blinded measures, if available. We examined whether several variables that are routinely identified in everyday clinic-based practice moderated treatment effects. Identification of such moderators could yield a more personalized approach to intervention in

clinical settings. We used a hypothesis-generating approach, as the increased power of IPDMA may generate significant moderators that have never emerged in aggregated meta-analyses or individual studies.[12,16] Candidate moderators included clinical characteristics of the child (ie, severity of symptoms of ADHD, ODD, CD, and internalizing problems, and impairment; comorbidity with ODD, CD, anxiety disorder, and depression; and medication use) and demographic variables (ie, child's age, IQ, and sex; social economic status of the family, and single parenthood).

METHOD

This IPDMA has been registered in Prospero (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=69877). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) IPDMA guidelines for reporting were followed, and a checklist is available in Supplement 1, available online.

Identification and Selection of Studies

Inclusion and Exclusion Criteria. We included randomized controlled trials (RCTs) of behavioral treatments of individuals of individuals less than 18 years of age with ADHD (corroborated by clinical cutoffs on questionnaires or [semi]-structured interviews) and/or participants meeting clinical cutoffs on questionnaires or (semi)-structured interviews. RCTs had to compare behavioral interventions with a control condition (including active control conditions, except for medication; see below), or studies that compared 2 behavioral interventions. For the studies with head-to-head comparisons of 2 behavioral treatments, we coded both active interventions as intervention, but for studies with an active non-pharmacological control condition (eg, weekly support groups), we coded the control condition as an active control condition. Behavioral interventions were defined as interventions directed at changing children/adolescents' behaviors (ie, increasing desirable behaviors and decreasing undesirable behaviors), using (cognitive)—behavioral therapeutic techniques modeled to the definition used by Daley *et al.*[11] These include (cognitive)—behavioral interventions, such as parent- and teacher-mediated treatments, as well as (cognitive)—behavioral interventions aimed directly at the child/adolescent, such as behavioral skills training or (cognitive)—behavioral therapy. We excluded studies or intervention arms that used optimized medication treatment next to a behavioral intervention as part of their study design or as a control condition. English-, German-, and Dutch-language publications published in peer-reviewed journals were included. No date restriction was applied.

Selection and Screening of Studies. A 2-step approach was used to identify relevant articles. First, we searched Medline, CINAHL, PsycINFO, EMBASE+EMBASE CLASSIC, ERIC, Web of Science (Science Citation Index Expanded) up to July 2017 for relevant papers using a combination of the following search terms and their synonyms, as well as hierarchical family form (eg, MeSH terms): treatment specific terms (ie, behavioral treatment, psychosocial treatment, parent and/or teacher training), ADHD, child and adolescent, and randomized controlled trial (complete search criteria available in Supplement 2, available online). Two authors (APG, senior researcher, and RH, PhD student) performed the selection and screening of studies using Rayyan, a web and mobile app for systematic reviews[21]; disagreement was resolved by consensus with a third person (either ML, SvdO or BvdH, senior researchers). Second, literature lists of relevant articles (identified studies and previous systematic reviews and meta-analyses) were hand-searched to identify possible missing articles.

Data Collection and Management
Data collection. We contacted the corresponding authors of all selected trials by e-mail to ask to share their data, with a reminder after several weeks. If we failed to establish contact with the corresponding author, we emailed co-authors of the study. Furthermore, we contacted authors of selected papers during conferences and through our personal network. Each author signed an understanding agreeing that they were responsible for ethical clearance in using the data. To assess differences in results and baseline characteristics (age, sex, comorbidities) between the studies providing data and the studies not providing data, APG and RH also extracted the aggregated data from the published papers of the studies.

Data Checks and Harmonization. First, we checked the data of all studies as obtained, and harmonized measures. Regarding data checks, the number of participants in each study was compared to the number of participants in the published paper. We also checked the data by comparing intervention and control groups on sex, age and ADHD severity (if available) with the published data. Authors were contacted if any deviations from the reported data were found, and inconsistencies were resolved.

Regarding harmonization, for each dataset continuous measures (severity of total ADHD, inattentive, hyperactivity/impulsivity [HI], ODD, and CD symptoms; severity of internalizing problems, and global impairment) were converted into z scores, using pre-intervention−score SDs within studies (an overview of instruments per study used for each outcome domain can be found in Table S1,

available online). Conversion into z scores was necessary because of the large heterogeneity in instruments used between studies. The analyses for ADHD, ODD, and CD focused primarily on raters closest to the intervention: that is, parent ratings for parent training, multimodal interventions, and child-focused interventions and teacher ratings for pure school-based interventions; for impairment parent ratings were used or, if these were not available, a clinician or researcher ratings. Separate exploratory analyses were performed, if possible, on blinded ratings (ie, observations by a blinded rater) of ADHD, ODD, and CD symptoms. Coding of sex (men/women), age at baseline (in years), medication use at baseline (yes/no), IQ of the child, single parenthood (yes/no), socioeconomic status (low [<high school], medium [high school graduate or some college education], high [>college graduate], and diagnoses of ODD, CD, any anxiety disorder, and depression [including major depressive disorder and dysthymic disorder] [yes/no] were equalized across datasets.

Risk of Bias Assessment. Risk of bias assessment of the included studies was done independently by 2 authors (a combination of AG/ RH/LS) using the Cochrane risk of bias tool. Random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, vested interest, and selective outcome reporting were rated on a 3-point scale (no risk of bias, unknown, or risk of bias). Any disagreement was resolved by consensus.

Analyses
Analyses Between Studies Providing Data and Not Providing Data. To assess possible differences between studies that provided data and those that did not, we examined (available) demographic differences (percentage of male participants, ODD and CD, and mean age), region of origin (Europe, Northern America, other), sample size, type of intervention (parent, teacher, child, or multimodal treatment), and publication date based on data described in the manuscript using independent t tests. Furthermore, we examined whether there were differential intervention effects between studies that provided data and those that did not. For studies that provided data, we calculated ESs based on the IPD; for studies in which IPD was not available, ESs were calculated based on aggregated data from the manuscripts. ESs were compared using random effects meta-analysis with the "Metafor" package in R, for the main outcomes (ADHD, inattentive symptoms, HI, ODD, CD, and global impairment). It should be noted that these comparisons were possible only for those studies with a control group, and not for head-to-head comparisons (ie, comparisons of 2 active treatments). In studies performing

head-to-head comparison, both interventions were coded as intervention.

Analyses of Main and Moderator Effects. Analyses were conducted using the "LME4" package in R (version 1.2.1335).[22] We determined effects using a 1-stage IPDMA, in which data from participants across studies were analyzed in 1 stage, with a random intercept for study. First, linear multilevel analysis was used to examine effects of behavioral interventions on symptoms of total ADHD, inattentive, HI, ODD, and CD symptoms and global impairment. Post-measurements of total ADHD, inattentive, HI, ODD, and CD symptoms and global impairment were used as outcomes in these models, and pre-intervention measures and intervention group were added. Because all outcomes were transformed to *z* scores, the regression coefficients can be interpreted as effect sizes (ESs) (a coefficient of 1 is a change of 1 SD in the outcome measure) and can be interpreted as small $d = 0.2$; medium, $d = 0.5$; and large, $d = 0.8$.[23] Heterogeneity between studies with regard to the outcome measure was assessed using intraclass correlation (ICC). This measure varies between 0 (low clustering within studies) and 1 (high clustering between studies) and determines the proportion of variance accounted for by clustering within studies. Of note, this is not an appropriate indication of variance in effect sizes between studies, as we included both studies comparing 2 interventions and studies with a control group as comparison.

Second, to test effects of the candidate moderators, we added the interaction between intervention group and candidate moderator to the models, with separate models for each outcome and moderator. Benjamini−Hochberg[24] correction (based on 17 tests per outcome) was used to exert control over the false discovery rate.

Prespecified Additional Analyses. First, significant moderator effects were further explored by examining 3-way interactions between the moderator and possible explanatory variables included in the IPDMA. Second, analyses were rerun separately for parenting interventions and child/adolescent-focused treatments, to assess the effect of intervention type. Third, analyses were re-run on blinded measures. Fourth, in addition to dimensionally looking at age as a moderator, a categorical variable of age was also used to assess differential treatment effects by comparing 3 meaningful developmental stages: children <6 years; children between 6 and 12 years; and children >12 years. Finally, to examine whether the deterioration of ADHD symptoms depended on the type of control condition (WL or TAU/active control), we further tested whether there was a smaller intervention effect on the main outcome in studies with a TAU/active control condition, compared to a WL condition.

RESULTS

Collected Data

We identified 17,897 studies; after removal of duplicates, 10,351 studies were screened based on title and abstract. Authors AG and RH disagreed on 1.2% of decisions; these were resolved by consensus. From 284 full-text papers that were screened, 62 were deemed eligible. Regarding these, we received 23 datasets. A summary of unrecovered studies (n = 37) is available in Table S2, available online. In addition, we received data from 2 studies that were published at a later date than our initial search[25,26] (also see Figure 1 for PRISMA flow chart). To assess whether the addition of these 2 studies influenced the results all analyses were rerun excluding these studies (see Supplement 3 [Tables S3−S8], available online); results remained approximately similar). Data checks on the provided data led to only minor deviations that could be resolved with the corresponding author, and mostly considered the inclusion of more participants in the IPDMA compared to the reported data.

With a recent systematic search (up to May 13, 2020), using the same criteria and methods as for the current study, we verified whether we had missed more recent studies. We identified 8 new studies that met our inclusion criteria, of which 2 studies[25,26] were already identified when inquiring about older studies. Data from these 2 studies were included in the current IPDMA; the other 6 studies were not included.

A total of 2,885 participants (1,936 intervention and 949 control) with a mean age of 8.78 years (SD = 3.32 years; range 2−17.5 years) were included from a total of 25 studies (Table 1[27−48] for a summary of studies that provided data. In almost all studies, the informant was the parent, except for 1 school-based treatment for which teacher ratings were used.[31] For the current paper, 21 studies (n = 2,233) had most proximal ratings available. Only 3 studies of parenting interventions (all in preschool children) contained data on a probably blinded inattention measure (directly observed time on task, n = 295),[26,30,45] and only 4 studies (all in preschool children) contained data on blinded outcome measures for disruptive behaviors (child noncompliance, n = 175).[34,35,45,47] Given the small sample size, specific age group, and variability in measures, analyses on the probably blinded outcomes can be found in Supplement 4, available online. In short, no effects of behavioral interventions were found on these outcomes.

Q2

Q3

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Individual Participant Data (IPD) Flow Diagram
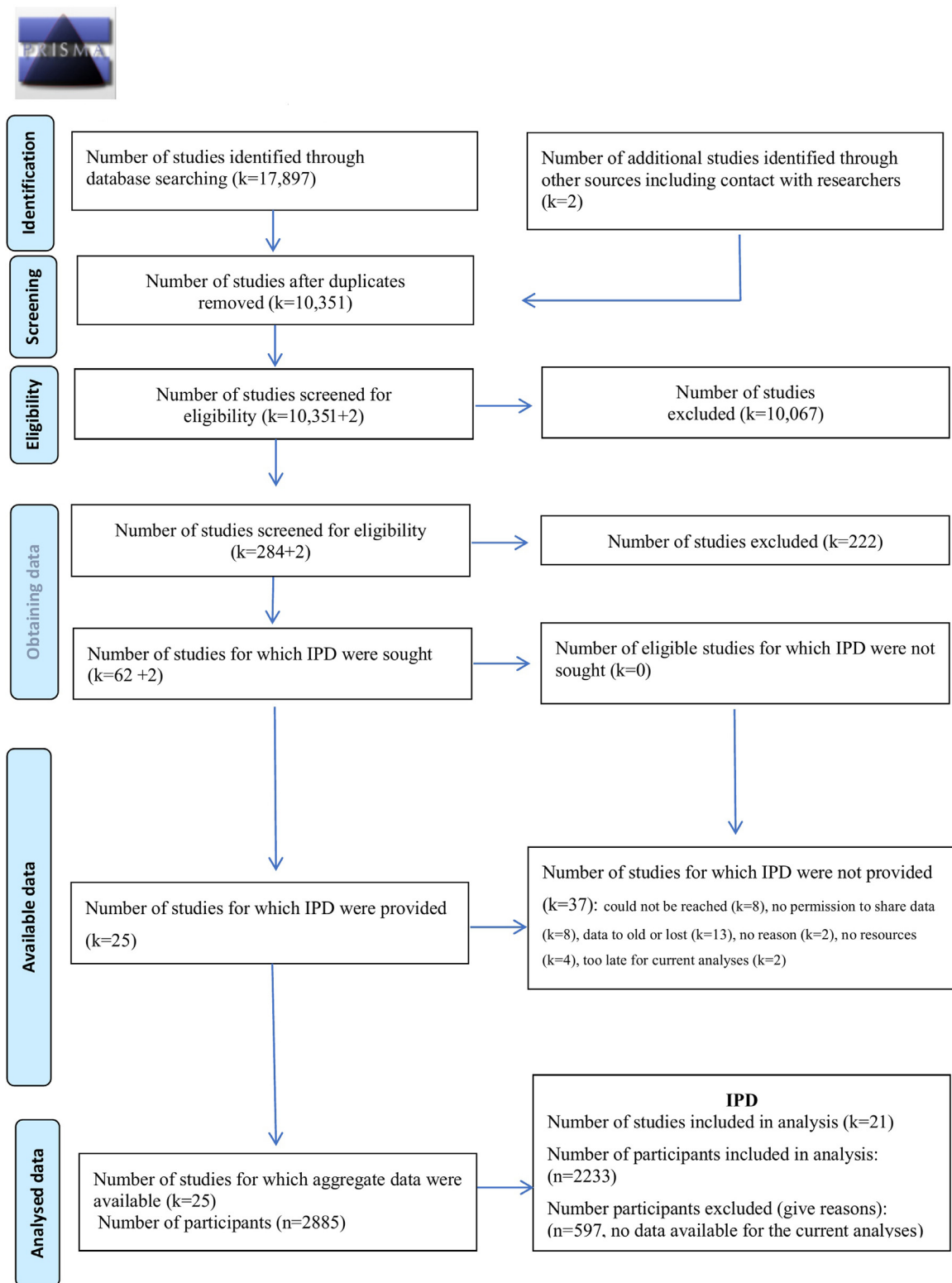
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TABLE 1 Characteristics of Included Studies

	Total	Intervention	Control	Intervention recipient	Age, mean (SD)	Medication use at baseline, yes, n (%)	Sex, female, n (%)	SES, n (%) Low	Medium	High	Single-parent family, yes, n (%)	ODD, n, (%)	CD, n (%)	Depression, n (%)	Anxiety, n (%)	Country of origin	Ethnicity[b]
Aghebati et al. 2014[27]	27	14 Triple P	13	Parent	8.04 (1.40)	27 (100)	11 (40.7)	7 (25.9)	11 (40.7)	9 (33.3)	0 (0)					Iran	
Boyer et al. 2015[28]	184	94 Plan My Life, 91 Solution-focused treatment,	0	Multimodal	14.45 (1.26)	141 (79.2)	53 (28.6)	31 (17.0)	84 (46.2)	67 (36.8)	25 (14.4)	57 (30.8)	0 (0)	32 (20.1)	14 (8.8)	Netherlands	
Chronis-Tuscano et al. 2013[29]	98	51 Standard BPT, 47 integrated parenting intervention (IPI-A)	0	Parent	8.78 (2.06)	58 (59.2)	33 (33.7)	1 (1.1)	30 (33.0)	60 (65.9)		51 (52)	17 (17.3)			USA	Caucasian (48.98%), African American (30.61), Other (20.41)
Daley et al. 2013[30]	43	19 New Forest Parenting Programme	24	Parent	7.28 (1.53)	0 (0)	8 (18.6)									UK	
Dupaul et al. 2006[31]	176		0	Teacher	8.58 (1.19)	51 (29)	43 (24.4)	18 (8.6)	136 (64.8)	56 (26.7)	0 (0)	0 (0)				USA	White (58.23)
Franke et al. 2016[32]	53	27 Triple P	26	Parent	3.97 (0.59)		38 (71.7)	10 (18.9)	14 (26.4)	29 (54.7)						New Zealand	New Zealand European ethnicity (79.2%)
Gershy et al. 2017[33]	57	23 Nonviolent resistance (NVR)	34	Parent	9.56 (2.49)		14 (17.7)	42 (28.0)	82 (54.7)	26 (17.3)						Israel	
Herbert et al. 2013[34]	31	17 Parenting Your Hyperactive Preschooler	14	Parent	4.58 (0.89)		8 (25.8)	8 (33.3)	4 (16.7)	12 (50.0)	15 (50)					USA	European American (83,87), African American (6,25) Latino (3,13) Multietnic (6,25)
Langberg et al. 2018[25]	280	111 Homework, organization, and planning skils 111 Completing homework by improving efficiency and focus	52	Multimodal	11.98 (1.03)	149 (53.2)	75 (26.8)	117 (45.9)	89 (34.9)	49 (19.2)	127 (45.4%)	85 (30.4)	10 (3.6)	12 (4.3)	73 (26.1)	USA	White (54.74%), Black (28.46%). Asian (1.46%), American Indian (1.1 %), Multiracial (0.58%)
Mautone et al. 2012[35]	61	29 Family school success early elementary	32	Multimodal	6.48 (0.60)	15 (24.6)	17 (27.9)	6 (4.9)	20 (16.4)	96 (78.7)	12 (19.7)	18 (29.5)	0 (0)	0 (0)	10 (16.4)	USA	Non-Hispanic (88%), Hispanic (12%), White (75%) Black/African American (21%) Multiracial (3%),
Mikami et al. 2010[36]	62	32 Parent friendship coaching	30	Parent	8.26 (1.21)	40 (64.5)	20 (32.3)	1 (1.6)	26 (42.6)	34 (55.7)	5(8.2)	20(32.2)		3(4.8)		USA	White (85%), African American (5%), Asian American (2%) Latino (1%), More than 1 race (7%)
Mikami et al. 2013[37]	24	12 Contingency management training, 12 making socially accepting inclusive classrooms	0	Teacher		9 (56.3)	11 (45.8)				0 (0)	12 (50)				USA	White (81%), Asian American (6%), Latino (2%), More than 1 ethnicity (8%)
MTA group 1999[17 a]	287	143 Parent training summer treatment program	144	Multimodal	7.76 (0.82)		57 (19.9)				121 (45.3)	41(14.3)	14(4.9)		96 (33.4)	USA	White (61%), African American (20%), Hispanic (8%),
Pfiffner et al. 2007[38]	69	36 Child life and attention skills program	33	Multimodal	8.67 (1.16)	2 (3.5)	23 (33.3)	1 (1.5)	17 (25.4)	49 (73.1)		16 (23.2)	0 (0)	1 (1.4)	8 (11.8)	USA	White (51%), Asian (16%), Hispanic (10%), African American (6%), mixed (17%)
Pfiffner et al. 2014[39]	199	74 Child life and attention skills program, 74 parent-focused treatment	51	Multimodal Parent	8.64 (1.16)	7 (3.5)	83 (41.7)	0 (0)	37 (18.8)	160 (81.2)	25 (12.6)	31 (15.6)	5 (2.6)	4 (2)	24 (12.1)	USA	Caucasian (54%), Latino (17%), Asian (8%), African American (5%), mixed race (17%)
Pfiffner et al. 2016[40]	135	72 Collaborative life skills	63		8.39 (1.13)	12 (8.9)	39 (28.9)	6 (4.5)	47 (35.1)	81 (60.4)	40 (29.6)	54 (40)	7 (5.2)			USA	White (26.8%), African American (8.93%), Asian (20.6%). Hispanic/ Latino (23.8%), Multiracial/multiethnic (19.87%)

(continued)

TABLE 1 Continued

	Total	Intervention	Control	Intervention recipient	Age, mean (SD)	Medication use at baseline, yes, n (%)	Sex, female, n (%)	SES, n (%)			Single-parent family, yes, n (%)	ODD, n, (%)	CD, n (%)	Depression, n (%)	Anxiety, n (%)	Country of origin	Ethnicity[b]
Power et al. 2012[41]	199	100 Family school success	99	Multimodal	9.42 (1.29)	85 (42.7)	63 (31.7)	4 (2.0)	28 (14.1)	167 (83.9)	42 (21.1)	54 (27.1)	0 (0)	5 (2.5)	46 (23.1)	USA	Non-Hispanic (93%), Hispanic (7%), White (72%), Black/ African American (22%), Multiracial (4%), Asian (2%)
Schramm et al. 2016[42]	113	40 Lerntraining für Jugendliche mit ADHS —LeJA (Learning Skills Training for Adolescents with ADHD)	73	Multimodal	13.99 (1.43)	56 (49.6)	16 (14.2)									Germany	
Sibley et al. 2013[43]	36	18 Supporting Teens' Academic Needs Daily	18	Multimodal	12.39 (1.02)	20 (55.6)	10 (27.8)	2 (5.6)	12 (33.3)	22 (61.1)		7 (19.4)	10 (27.8)	5 (15.6)	21 (63.6)	USA	White non-Hispanic (25%), Black non-Hispanic (8.35%), Hispanic, any race (61.15%), Mixed race (5.55%)
Sibley et al. 2016[44]	128	67 Supporting Teens' Academic Needs Daily	61	Multimodal	12.74 (0.86)	44 (34.3)	45 (35.2)	24 (19.4)	21 (16.9)	79 (63.7)	45 (35.2)	74 (57.8)	17 (13.3)			USA	Non-Hispanic white (7%), African American (10.8%), Hispanic (78.5%), other (3%)
Sonuga-Barke et al. 2018[26]	306	133 New Forest Parenting Programme, 131 Incredible Years	42	Parent	3.51 (0.58)	0(0)	82 (26.8)				92 (33)					UK	
Thompson et al. 2009[45]	41	21 New Forest Parenting Programme	20	Parent	4.18 (1.05)	0 (0)	50 (100.0)	32 (76.2)	7 (16.7)	3 (7.1)						UK	
Van Den Hoofdakker et al. 2007[46]	94	47 Behavioral parent training	47	Parent	7.43 (1.95)	47 (50.5)	18 (19.1)	32 (34.4)	38 (40.9)	23 (24.7)	10 (10.6)	71 (75.5)			41(43.6)	Netherlands	White (94.7%), African (2.1), Asian (2.1), unknown (1.1)
Webster-Stratton[47]	99	49 Incredible years, combined parent and child	50	Multimodal	5.36 (0.91)	0 (0)	24 (24.2)				20 (20.8)					USA	Minority (27.3%)
Xie et al. 2013[48]	22	13 Parent Training face to face, 9 Parent training video-conferencing	0	Parent	8.95 (1.89)		7 (31.8)									USA	

Note: CD = conduct disorder; n = number of participants; ODD = oppositional defiant disorder; SES = socioeconomic status.
[a]Some data were not available in the public access database of the Multimodal Treatment Study of ADHD (MTA) (ie, medication at baseline and single parenthood).
[b]Data extracted from the published manuscripts.

Risk of Bias

Risk of bias agreement was high ($\kappa = 0.92$) and is presented in Figure 2 (separate panels for those studies providing data and those not; see Figure S1 and Figure S2, available online). Results (based on manuscripts) showed that for many studies it was unclear how random sequences were generated (56%) and how allocation concealment took place (68%). In almost all studies, selective reporting was unclear (84%), as few studies preregistered their trials. A visual comparison between studies participating and those not participating showed that in the studies not participating, there were slightly more problems in allocation concealment, and more potential vested interests. Overall, 28% of studies had risk-of-bias violations (high risk of bias) on 2 or more items. Risk of bias (as measured by percentage of "no bias") was not associated with any of the results on the outcome measures (ADHD $p = .23$, inattention $p = .17$, HI $p = .31$, ODD $p = .92$, CD $p = .17$, impairment $p = .75$).

Analyses Between Studies Providing Data and Not Providing Data

Studies not providing data did not differ in age (mean = 8.48 versus mean = 8.87, $p = .70$), percentage of ODD (mean = 50.60% versus mean = 40.14%, $p = .29$), or CD (mean = 7.04% versus mean = 19.89%, $p = .12$), region of origin $p = .53$), type of intervention ($p = .42$), but studies

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FIGURE 2 Moderating Effects on Behavioral Treatment for Attention-Deficit/Hyperactivity Disorder
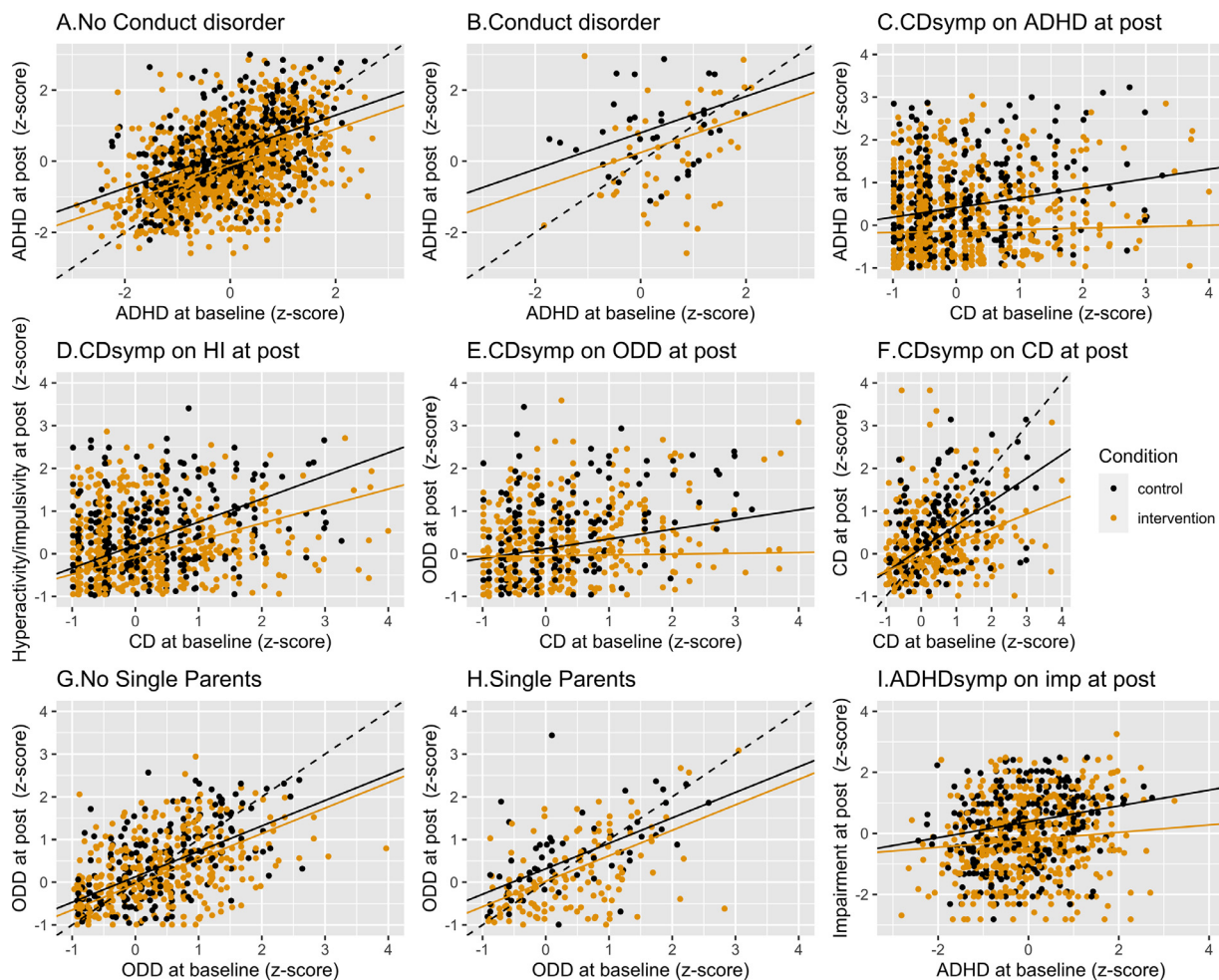
Note: (A, B) Moderating effect of CD diagnosis on ADHD symptoms post-intervention. (C) Moderating effects of CD symptoms at baseline on ADHD outcome post-intervention. (D) Moderating effects of CD symptoms at baseline on hyperactive impulsive outcome post-intervention. (E) Moderating effects of CD symptoms at baseline on ODD outcome post-intervention. (F) Moderating effects of CD symptoms at baseline on CD outcome post-intervention. (G, H) Moderating effect of single parents. (I) Moderating effects of ADHD symptoms at baseline on impairment post-intervention. The dashed black line was added for illustrative purposes; it represents the regression line where baseline severity is similar to post-intervention severity (ie, x = y). A regression line of the intervention and/or control group below the dashed black line at x = 0 indicates improvement at post-measurement compared to baseline, and a regression line above the dashed black line at x = 0 indicates deterioration at post-measurement. Number of individuals with CD with ADHD outcomes: n = 96. ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; HI = hyperactivity/impulsivity; imp = impairment; ODD = oppositional defiant disorder; symp = symptoms.

TABLE 2 Main Effects of Behavioral Interventions

		n	k	Estimate	SE	df	t	p
ADHD		2109	20	−0.42	0.05	716.90	−9.17	<.001
	Parent interventions	1689	17	−0.42	0.05	782.38	−8.8	<.001
	Child focused	423	3	−0.67	0.12	287.26	−5.68	<.001
Inattention		2,173	20	−0.46	0.05	662.48	−9.52	<.001
	Parent interventions	1,635	16	−0.45	0.05	758.61	−8.61	<.001
	Child focused	541	4	−0.64	0.10	290.02	−6.17	<.001
HI		2,233	21	−0.27	0.04	2230.00	−7.43	<.001
	Parent interventions	1,692	17	−0.31	0.04	1689	−7.40	<.001
	Child focused	544	4	−0.35	0.08	138.94	−4.52	<.001
ODD		1,798	16	−0.19	0.04	1413.62	−4.83	<.001
	Parent interventions	1,568	14	−0.20	0.04	1460.05	−4.93	<.001
	Child focused	[a]						
CD		1,229	12	−0.20	0.06	1226.00	−3.38	<.001
	Parent interventions	882	9	−0.23	0.05	879.00	−4.92	<.001
	Child focused	[a]						
Impairment		664	8	−0.59	0.10	661	−5.96	<.001
	Parent interventions	567	7	−0.68	0.11	564.00	−6.19	<.001
	Child focused	[a]						

Q4 *Note: Boldface type indicates models that remained significant after multiple testing correction. Full analyses on parent- and child-focused treatments are provided in Supplements 6 and 7 (Tables S15−S26), available online. ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; df = degrees of freedom; HI = hyperactivity/impulsivity; k = number of studies; n = number of individuals; ODD = oppositional defiant disorder; SE = standard error.*
[a]There were not enough observations to run these analyses.

not providing data did have a slightly larger percentage of male participants (mean = 79.64% versus mean = 70.93%, $p = .007$), smaller samples sizes (mean = 64 versus mean = 113, $p = .017$), and an earlier publication date (mean = 2008 versus mean = 2012, $p = .044$). No differences in ESs were found for the intervention effects on ADHD symptoms (difference in ESs [estimate] = 0.18, $p = .39$), inattentive symptoms (estimate = −0.04, $p = .80$), hyperactive/impulsive symptoms (estimate = 0.11, $p = .48$) or CD (estimate = −0.03, p = .89). However, studies that provided data appeared to have a smaller effect on ODD symptoms (estimate = 0.29, $p = .03$) compared to studies that did not provide data.

ADHD Symptoms
Behavioral interventions had a positive, small to medium ES on ADHD symptoms ($b = −0.42$, $p < .001$) (Table 2, and Supplement 5 [Tables S9−S14], available online). The proportion of variance accounted for by clustering within studies was low (ICC = 0.05). This effect remained significant in parenting interventions ($b = −0.42$, $p < .001$) and in child/adolescent focused interventions ($b = −0.67$, $p < .001$) (Table 2, and Supplements 6 and 7 [Tables S15−S26], available online). Symptoms of CD ($b = −0.19$, $p = .002$) and a diagnosis of CD at baseline ($b = −0.55$, $p =$

.008) moderated the intervention effect. Figures 2 and 3 show that this effect was driven by an increase in ADHD symptoms in the control group for children with more baseline symptoms of CD Figure 2C, and/or a baseline diagnosis of CD Figure 2A and B, compared to youths with fewer CD symptoms and/or no CD diagnosis, or youths in the intervention group. No other investigated candidate factor moderated the intervention effect on ADHD symptom severity (Table 3).

Additional analyses (see Supplement 8, available online) showed that the moderating effect of CD symptom severity and/or CD diagnosis did not vary as a function of any of the other variables, and remained significant in parenting interventions only ($b = −0.22$, $p = .002$; $b = −0.55$, $p = .008$, respectively).

Inattention Symptoms
Behavioral interventions had a positive, small- to medium-sized effect on inattention symptom severity ($b = −0.46$, $p < .001$), with low clustering within studies (ICC = 0.07). This effect remained significant in parenting interventions only ($b = −0.45$, $p < .001$) and child-focused interventions ($b = −0.64$, $p < .001$) (Table 2). None of the investigated variables moderated the intervention effect (see Table). Q5

TABLE 3 Moderating Effects of Child/Adolescent and Family Factors on Outcomes of Behavioral Interventions for Attention-Deficit/Hyperactivity Disorder (ADHD)

	ADHD			Inattention			HI			ODD			CD			Impairment		
	N	**k**	**ES**	**n**	**k**	**ES**	**n**	**k**	**ES**	**n**	**k**	**ES**	**n**	**k**	**ES**	**n**	**k**	**ES**
ADHD symptoms	2,109	20	−0.09	2035	18	−0.01	2112	20	−0.03	1786	16	−0.01	1104	11	−0.12	**659**	**8**	**0.50**
Age	2,109	20	0.10	2173	20	−0.03	2233	21	0.03	1798	16	−0.01	1229	12	0.01	664	8	−0.03
CD symptoms	**1,309**	**12**	**−0.19**	1405	12	−0.09	**1435**	**13**	**−0.14**	1092	10	−0.21	1229	12	−0.21	563	6	−0.17
Diagnosis anxiety	1,199	9	−0.05	1208	9	−0.25	1208	9	−0.15	1001	8	−0.13	647	5	−0.07	361	4	0.90
Diagnosis CD	**1,515**	**12**	**−0.55**	1528	12	0.20	1529	12	−0.37	1320	11	−0.36	1063	9	−0.44	604	6	−0.90
Diagnosis depression	1,105	8	0.01	1114	8	−0.47	1114	8	−0.46	907	7	−0.15	648	5	−0.19	360	4	−2.06
Diagnosis ODD	1,624	14	0.11	1636	14	0.09	1637	14	0.01	1428	13	−0.09	1051	9	−0.22	606	6	−0.31
Impairment	687	8	−0.17	692	8	−0.01	691	8	−0.05	519	6	−0.09	465	4	−0.16	664	8	0.1
Internalizing symptoms	1,203	11	−0.09	1227	12	−0.07	1215	11	−0.08	1010	10	−0.11	620	6	−0.16	588	6	−0.25
IQ	949	8	0.19	953	8	0.01	951	8	0.00	942	8	0.00	589	5	0.00	387	4	0.00
Medication use at baseline	1,738	16	−0.01	1827	16	0.05	1861	17	0.16	1466	13	−0.07	955	10	−0.16	645	7	−0.03
ODD symptoms	1,981	17	−0.06	1987	17	−0.06	1989	17	−0.03	1798	16	−0.08	1079	10	−0.05	615	7	−0.24
SES high vs low	1,386	15	−0.02	1342	14	−0.01	1399	15	0.03	1134	12	0.28	817	9	0.56	595	6	0.10
Sex	2,109	20	−0.55	2173	20	−0.42	2233	21	0.09	1798	16	0.01	1229	12	0.17	664	8	0.42
Single parent (yes)	1,306	10	−0.20	1309	10	−0.27	1314	10	−0.12	**1195**	**9**	**−0.29**	568	4	−0.13	539	5	0.11

Note: Boldface type indicates significant findings multiple testing correction. All linear multilevel analysis models have post-measurement score as outcome and are corrected for baseline impairment score. Every moderator was tested in an individual model. Full information on all models can be found in Supplement 5 (Tables S9−S14); correlation matrix between all moderators can be found in Table S27, available online. ADHD = attention-deficit/hyperactivity disorder, CD = conduct disorder; df = degrees of freedom; k = number of studies; n = number of individuals; ODD = oppositional defiant disorder; SE = standard error; SES = socioeconomic status.

Hyperactivity/Impulsivity Symptoms

Behavioral interventions had a positive, small effect on HI symptom severity ($b = -0.27$, $p < .001$), with low clustering within studies (ICC = 0.01) (Table 3). This effect remained significant in parenting interventions ($b = -0.31$, $p<.001$) and child/adolescent focused interventions ($b = -0.35$, $p < .001$) (Table 2). CD symptoms moderated intervention effect ($b = -0.14$, $p = .002$); Figure 2D shows that youths with higher CD symptom severity in the control group increased more in HI symptom severity compared to youths with fewer CD symptoms, or youths in the intervention group.

Additional analyses (see Figure S3, available online), showed a significant 3-way interaction among age, CD severity, and intervention condition ($p = .004$); a median split (age 8.6 years) showed that younger children with higher CD symptom severity in the control group had a worse outcome compared to younger children in the intervention group on HI symptom severity, but this effect was not significant in older children. The effect of CD symptom severity remained significant in parenting interventions only ($b = -0.20$, $p < .001$), but not in studies on child/adolescent-focused interventions ($b = 0.00$, $p = .99$).

ODD Symptoms

Behavioral interventions had a significant positive, small ES on symptoms of ODD ($b = -0.19$, $p < .001$), with low

clustering within studies (ICC = 0.02) (Table 3). This effect remained significant in parenting interventions ($b = -0.20$, $p < .001$); the number of studies was too low for analysis in child/adolescent-focused studies. Youths with more baseline CD symptoms ($b = -0.21$, $p < .001$; also see Figure 2E) and youths with single parents (Figure 2G and H) ($b = -0.29$, $p = .006$) showed a larger intervention effect. Figures 3 shows that both moderating effects were driven by a deterioration of those with high CD symptoms or single parents in the control group.

Additional analyses (see Supplement 8, available online), showed that the moderating effect of CD symptom severity and/or single parenthood did not vary as a function of any of the other variables. The moderating effect of baseline CD severity and single parenthood remained significant in studies on parenting interventions only ($b = -0.21$, $p < .001$; $b = -0.31$, $p = .004$ respectively).

CD Symptoms

Behavioral interventions had a positive, small ES on CD symptom severity ($b = -0.20$, $p < .001$). The proportion of variance accounted for by clustering within studies was low (ICC < 0.001) (Table). This effect remained significant in **Q6** parenting interventions ($b = -0.23$, $p < .001$) (Table 2); the number of studies was too low for analysis in child-focused studies. Youths with higher baseline CD symptom

severity showed a larger intervention effect ($b = -0.21$, $p < .001$), although this seems to be driven by a larger deterioration of those with high CD symptoms in the control group (Figure 2F).

Additional analyses showed a significant 3-way interaction among baseline ADHD severity, baseline CD severity, and intervention condition ($p = .02$); those with high ADHD and high CD symptom severity, but not those with low ADHD symptoms and high CD symptoms, showed worse outcome post-intervention in the control group (see Figure S3, available online) The effect of baseline CD symptom severity remained significant in studies on parenting interventions only ($b = -0.29$, $p < .001$).

Global Impairment
Behavioral interventions had a positive, medium-sized effect on global impairment ($b = -0.59$, $p < .001$). The proportion of variance accounted for by clustering within studies was low (ICC < 0.001) (Table 3). This effect remained significant in parenting interventions ($b = -0.68$, $p < .001$); the number of studies was too low for analysis in child-focused studies. Individuals with higher baseline ADHD symptom severity showed smaller intervention effects ($b = 0.50$, $p < .001$) than those with low baseline ADHD symptoms, although this effect seems to be driven by a larger deterioration in impairment in the control group (Figure 2I). Additional analyses (see Supplement 8, available online), showed that the moderating effect of ADHD symptom severity did not vary as a function of any of the other variables (including control condition). The effect of baseline CD symptom severity remained significant in studies on parenting interventions only ($b = 0.51$, $p < .001$).

Additional Analysis Regarding Age and Control Condition
Age as a dimensional variable did not moderate intervention outcome on any of the outcome variables (see Supplement 8, available online).

When compared to TAU/active controls, the effect of behavioral intervention on the outcome variables we found that the intervention effect was smaller compared to those in a WL condition on symptoms of ADHD ($b = 0.47$, $p < .001$), inattention ($b = 0.66$, $p < .001$), HI ($b = 0.25$, $p = .002$), ODD ($b = 0.28$, $p < .001$), and CD ($b = 0.35$, $p < .001$), but not impairment ($b = 0.06$, $p = .79$). Of the previously identified moderators, the control condition affected only the relation between CD symptoms on CD symptoms; individuals

in the WL condition performed worse than those in a TAU/active control group ($b = 0.27$, $p = .009$).

DISCUSSION
The present study is the first IPDMA on behavioral interventions for children and adolescents with ADHD. Its large database, including data from 21 randomized controlled studies and behavioral treatment outcomes of 2,233 children and adolescents with ADHD, enabled moderator analyses of sufficient statistical power. Results showed robust evidence that behavioral interventions reduced ADHD symptoms, behavioral problems, and global impairment according to reports of raters most proximal to the delivery of the intervention, with small- to medium-sized effects. The intervention effect size in this IPDMA was highest for impairment, which, for most interventions, is the primary treatment target.[5,27] Moreover, on total ADHD symptom severity reduction, we found a seemingly larger effect size compared to those of aggregated data meta-analyses (eg, Boyer *et al.*[28]). Our analyses clearly showed the added value of IPDMA compared to other designs, as we uncovered moderators that could not be identified in earlier meta-analyses or randomized controlled trials. CD (baseline symptoms as well as comorbid diagnosis) moderated treatment effects. For all outcome measures except inattention and global impairment, higher baseline CD symptomatology (and/or a diagnosis of CD) was associated with larger treatment effects. For HI symptoms, this moderating effect was found only in younger individuals (<8.6 years of age, using a medium split). For CD, the moderating effect was present **Q8** only in those with more severe (z scores >0) baseline ADHD symptom severity.

The larger benefit of behavioral interventions in children with more severe CD may seem consistent with some of the existing literature on intervention effects for children with conduct problems; however, most studies did not report whether effects were driven by the intervention or control condition.[29] Our results clearly show that positive intervention effects in children with elevated CD symptoms were driven by larger symptom deterioration in the control condition (mostly TAU or WL). These findings suggest that youths with more severe CD symptoms are more likely to suffer an increase in symptoms of ADHD and behavioral problems over time, particularly when not treated, emphasizing the importance of direct access to care. A similar moderating effect was found for ADHD symptoms on global impairment. In addition, this group did not improve (and even seems to deteriorate for HI and CD outcomes) from pre- to post-assessment in the active treatment condition, suggesting a protective rather than an ameliorative effect of

behavioral interventions for those with more severe CD symptoms or ADHD symptoms. Perhaps treatments for this subgroup of children with severe behavioral problems should be more intensive than routine ADHD interventions and enhanced with CD-specific components.[32]

With respect to the moderation effect of single parenthood, a similar pattern emerged. The data suggest that youth from single-parent families deteriorated with regard to ODD symptoms in the control condition, indicating that children and adolescents from single-parent families should also be treated immediately. Moreover, this particular subgroup did not improve substantially in terms of ODD symptoms in the behavioral treatment condition, again indicating a protective rather than an ameliorative effect of behavioral interventions. Treatments that are tailored to the specific needs of single-parent families may therefore be more suitable for this subgroup. For example, a study by Chacko *et al.*[37] in families of children with ADHD showed that children's ODD symptoms reduced significantly only after a behavioral parent training program that was specifically designed for single mothers, whereas this effect was not present in children whose mothers received standard parent training.

Other potential moderators were not significant, suggesting equal effectiveness of behavioral interventions across children's age, IQ, sex, medication status, and child's comorbidity with ODD, anxiety, and depression, as well as socioeconomic status and impairment severity. For age, additional analyses showed no differential effect of behavioral interventions on any of the outcome measures in individuals less than 6 years of age, between 6 and 12 years, and more than 12 years. The lack of a moderating effect of age or socioeconomic status is in line with the only currently available IPDMA on effects of 1 specific parenting program for behavioral problems (no specific ADHD sample) in young children (<12 years),[36] suggesting equal effectiveness of behavioral treatments in ADHD across age groups and socioeconomic status.

In addition, we found evidence for a specific waitlist effect,[39] as we found that children in the waitlist control group performed worse on almost all outcomes than those in the TAU/active control condition.[39,40] Given the negative effects of waiting for behavioral intervention, efforts should be made to make behavioral interventions easily and quickly accessible to all, for example, by integrating them into regular services and daily lives of parents and children (eg, in schools, primary care practice, or community services) and to reduce waitlists to a minimum, especially for those with severe behavioral problems. Telehealth and digital approaches may also be of value in increasing access and uptake of behavioral interventions,[40,41] and moreover could be cost-effective.

Major strengths of our IPDMA are that we rigorously analyzed a large database, thereby covering a range of outcomes and potential moderators. Although we included just over one-third of eligible studies, our database was representative of all eligible behavioral intervention studies, given the similar ESs reported in included and not included studies. Moreover, as in IPDMA the number of participants is of importance, our IPDMA did include over one-half of the total number of participants of the eligible studies. Most of the missing studies were older studies for which the data were no longer available.

Limitations of our IPDMA include, first, in line with other meta-analyses[11,28] that we examined, a heterogeneous group of behavioral interventions (eg, parent training, classroom interventions, or skills training) that targeted different outcomes, whereas intervention effects and moderators of outcome may differ between intervention types.[5] Future meta-analyses, preferably using IPD, should focus on different intervention types. Nevertheless, robust effects of behavioral interventions on ADHD, behavioral problems, and impairment were obtained, and effects remained significant in parenting interventions only as well as child/adolescent-focused interventions only. Second, as cannot be avoided in an IPDMA, several assumptions had to be made in the process of data harmonization, for example, that different measures from different trials actually measured the same construct. However, we did find low clustering of outcomes within studies (ICCs < 0.07), which is indicative of low heterogeneity of constructs across studies. A third limitation concerns the blinded measures. The number of studies using objective measures of symptom change or impairment that met inclusion criteria was very limited. We only included 4 parent training studies that used objective observational measures. In addition, the measures used were diverse (from structured play observations to audio-tapes of problem situations), and not all were well validated, reflecting the absence of appropriate objective measures for behavioral interventions, which should be developed in future studies. These should not only include behavioral measures but impairment measures as well. Previous meta-analyses have shown that effects of behavioral interventions on ADHD symptoms assessed by blinded raters were not significant.[28] Thus, it remains unclear whether intervention effects reflect actual changes in ADHD symptoms or are limited to the perceptions of parents or teachers. However, such changes in perceptions may, of course, be important psychological indicators of the rater's beliefs about child behavior (even if not accompanied by actual changes in core symptoms). It could also be argued that intervention recipients themselves (parents or teachers in the instance of children) are the best raters of the child's problems.[42]

Furthermore, parent- and teacher-reported outcomes are better translatable to clinic-based practices, as they are nearly always the only available information source in clinical care. Another limitation is that we included only peer-reviewed published work, which may have been biased by a possible exaggerated estimate of intervention effect,[43] although moderator analyses on individual data may be less influenced by this bias. Moreover, we did not have permission, which is required under the European General Data Protection Regulation (GDPR), to include ethnicity in our moderator analyses. Also, many studies (in fact, all of the European studies except for 1 older study) did not collect data on ethnicity. The majority of the American studies reported on ethnicity; it appeared that most of the included populations were a reasonable representation of the United States. Finally, the systematic search of the current IPDMA was 3 years old. Preparing and gathering the data for IPDMA takes time (in the instance of this study, more than 2 years). However, with a recent systematic search, using the same criteria and methods as the current study, we identified 6 datasets that were not included in the current analyses. Unfortunately, as collection, preparation, and harmonizing of those data would have taken substantial time, we could not include these in the current study. Future IPDMA studies should focus on parenting measures, long-term outcomes, mediators of treatment effects (eg, increase in parenting skills), and moderators of behavioral treatments in relation to other treatments for ADHD, such as medication. Future studies also need to address how to sequence and combine behavioral and cognitive treatment to medication and other interventions, to reduce impairment and improve functioning of children and adolescents with ADHD.[44]

This IPDMA showed that behavioral interventions for ADHD are effective treatments, significantly reducing core ADHD symptoms, associated behavioral problems, and global impairment, as perceived by parents or teachers post-treatment. Improvement in impairment is notable, as impairment in functioning is generally what prompts treatment seeking and is arguably the most salient outcome in behavioral treatment. We found significant moderators of outcome that can be translated to a clear clinical message, although these moderators seemed to have the strongest impact on the control condition rather than the active treatment condition; in particular, children with high levels of CD symptoms or diagnosis, children with single parents, and children with high levels of ADHD symptoms, should be prioritized for behavioral treatment. For these children, treatment seems to prevent them from further deterioration in terms of ADHD symptoms, behavioral problems, and/or impairment.

UNCITED REFERENCES:

[49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62]

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