Executive functions in children with heart disease: a systematic review and meta-analysis

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Abstract

Context: People with CHD are at increased risk for executive functioning deficits. Meta-analyses of these measures in CHD patients compared to healthy controls have not been reported. *Objective:* To examine differences in executive functions in individuals with CHD compared to healthy controls. *Data sources:* We performed a systematic review of publications from 1 January, 1986 to 15 June, 2020 indexed in PubMed, CINAHL, EMBASE, PsycInfo, Web of Science, and the Cochrane Library. *Study selection:* Inclusion criteria were (1) studies containing at least one executive function measure; (2) participants were over the age of three. *Data extraction:* Data extraction and quality assessment were performed independently by two authors. We used a shifting unit-of-analysis approach and pooled data using a random effects model. *Results:* The search yielded 61,217 results. Twenty-eight studies met criteria. A total of 7789 people with CHD were compared with 8187 healthy controls. We found the following standardised mean differences: -0.628 (-0.726, -0.531) for cognitive flexibility and set shifting, -0.469 (-0.606, -0.333) for inhibition, -0.369 (-0.466, -0.273) for working memory, -0.334 (-0.546, -0.121) for planning/problem solving, -0.361 (-0.576, -0.147) for summary measures, and -0.444 (-0.614, -0.274) for reporter-based measures ($p < 0.001$). *Limitations:* Our analysis consisted of cross-sectional and observational studies. We could not quantify the effect of collinearity. *Conclusions:* Individuals with CHD appear to have at least moderate deficits in executive functions. Given the growing population of people with CHD, more attention should be devoted to identifying executive dysfunction in this vulnerable group.

There are approximately 2.5 million children and adults living in the United States with CHD today.[1] CHD is the most common congenital anomaly, affecting approximately 1% of births.[2] An additional 40,000 children are born in the United States every year with heart defects,[3] and many more are born throughout the world, resulting in a significant public health issue. Improvements in medical and surgical management have greatly improved survival in children with heart disease[4]; since the majority of these children are now expected to survive into adulthood, research has increasingly focused on the comorbidities faced by this population.

Deficits in cognitive functioning were recognised as a potential problem for children and adults with CHD many years ago.[5–7] Children born with heart anomalies are exposed to anaesthesia, surgery, and cardiopulmonary bypass at a very early age, all of which could potentially result in damage to the developing brain. Further, children with critical CHD, defined as a heart defect requiring intervention in the first year of life,[1] are at higher risk for chronic hypoxaemia,[8] poor feeding and growth,[9] intrauterine growth restriction,[10] and a high physiologic stress response in early development.[11] These combined factors may potentially increase the risk for developing cognitive problems, which could lower academic success,[12] educational attainment,[13] and quality of life.[14–16]

Individuals with CHD may present with several neurodevelopmental vulnerabilities. Deficits in executive functions are among the most prevalent long-term morbidities in children and adolescents with CHD who underwent cardiac surgery in infancy.[17–19] Executive functions refer to an umbrella of higher order neurocognitive processes that allow an individual to adapt to new situations. Executive functions can be categorised into core components including inhibitory control, working memory, and cognitive flexibility (or set-shifting), as well as higher order functions such as planning and problem-solving abilities. They help to temporarily retain information so it can be manipulated, inhibit attention to irrelevant stimuli, and help plan a complex series of thoughts or actions. Executive functions undergo a protracted development throughout childhood, and they continue to develop into early adulthood. They are essential to learning processes as well as social and emotional development.[20] Recent studies have reported

significant deficits in these functions for children, adolescents, and adults with CHD as observed in standardised and experimental neuropsychological assessments. People with CHD performed especially poorly on measures of cognitive flexibility,[21] verbally mediated tasks,[21] and inhibition.[22] Performance on measures of working memory was relatively preserved.[22] Likewise, data from neuroimaging studies have corroborated these findings and have indicated that adolescents and young adults with CHD have altered brain activation patterns in regions related to executive function.[23]

The number of studies reporting measures of executive functions in people with CHD has greatly increased in the last several years. These studies have incorporated a wide variety of designs, populations, and clinical variables into their study populations, and many studies examined executive functions. We chose to conduct a systematic review and use meta-analytic methods to assess whether there are differences in executive functioning between people with CHD and controls, and whether we could identify variables, such as early surgical repair versus conservative management, that could explain some of the differences in scores between the CHD population and controls. The aim of this study was to conduct a systematic review of the literature and subsequent meta-analysis with the hypothesis that children and adults with CHD would score worse on measures of EF compared to control groups or normative population samples. Specifically, we hypothesised that children would perform worst on measures of cognitive flexibility and inhibition, while a smaller difference would be identified in measures of working memory and planning/problem solving.

Materials and methods

Study selection

We conducted our systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement and Checklist.[24] We searched PubMed, CINAHL, EMBASE, PsycInfo, Web of Science, and the Cochrane Library for results published between 1 January, 1986 and 15 June, 2020. Our final search term was developed in consultation with a trained research librarian to maximise search results (Supplemental Information, Figure S1).

We included randomised controlled trials, observational studies, and cross-sectional studies that included a measure of executive function in a cohort with CHD evaluated at >3 years of age. We chose the age of three as the lower limit where executive functions could be meaningfully tested.[25] We excluded reports that were published earlier than 1 January, 1986 in order to reflect more modern practice in paediatric cardiac surgery and paediatric cardiology. Finally, we chose to exclude studies that included heart transplant recipients due to the high proportion of patients who were not born with CHD or might have presented a different neuropsychological profile.

Screening of search results

Studies were screened by title and abstract by two authors independently (WMJ, JJL). Further, we screened the bibliographies of the screened manuscripts and abstracts. Once our systematic review was complete, two authors (WMJ and ND) then independently read the screened manuscripts and abstracts in full to identify whether they met the full inclusion and exclusion criteria. Each potential entry was then discussed, and disagreements were adjudicated by a third author (LSS).

Data extraction

The scores for measures of executive functions that were reported in each manuscript were then extracted manually, and the measures were categorised into six main domains: planning and problem solving, inhibition, cognitive flexibility, working memory, summary measures, and reporter-based measures of executive function. Summary measures were defined as measures that combined multiple different domains into a single summary score, and reporter-based measures were self-report measures completed by either the subject or a caretaker. The included measures were categorised by consensus among authors. Different measures administered to the same cohort were included if the measures were different tests, tested different domains of executive function, or tested the same cohort at different ages. We allowed inclusion of longitudinal data because executive functions develop and change continuously throughout childhood.[26] If there were multiple reports of identical data, we judged which data to use on an individual basis, with the goal of using the largest cohort reported. Authors were contacted if there was confusion regarding duplication, and if no response was received, those measures were discarded.

We extracted the following data from manuscripts: First author, year of publication, journal of publication, title, number of study subjects, number of control subjects if applicable, age at testing, CHD diagnosis, the name of the neuropsychological test, and the reported scores for the neuropsychological measures. The reported data were extracted as means with standard deviations or medians with ranges. The extracted data were checked twice more by one author (WMJ) in separate sessions to ensure correctness.

Bias assessment

Publication bias was assessed visually through the use of funnel plots. Assessment of the quality of evidence and other sources of bias were conducted by two authors independently (WMJ and NSF) using a modified Newcastle-Ottawa Scale for nonrandomised cohort studies. The results were discussed, and disagreements were adjudicated by a third party (LSS).

Dealing with dependent data

We chose to deal with correlation in the data using the method of Graham and Hebert,[27] which is an adaptation of Cooper's shifting unit-of-analysis approach.[28] This method recommends an independent meta-analysis for each individual domain of a construct such as executive function, as opposed to calculating a combined overall effect size for all of the measures included in the analysis. We chose not to perform more complex methods of dealing with dependence, such as robust variance estimation[29] or three-level meta-analysis,[30] based on the conclusions of Scammacca et al,[31] who found that most methods of dealing with data dependence result in similar conclusions regarding the effect size. Further, since a weighted average of related but distinct executive functions domains would not be meaningful, we chose to employ Graham and Hebert's approach in our analysis.

Data analysis

Analyses for each domain were performed with Comprehensive Meta-Analysis software (Biostat, Inc., Englewood, NJ). We chose *a priori* to use a random-effects model to estimate the effect size because we felt it was likely that age and CHD diagnosis would

contribute to a range of effect sizes, contributing to between-study heterogeneity.[26] Further, previous work by our group showed that measures of intelligence varied based on the CHD diagnosis of the study population.[32] Therefore, a random-effects model seemed most appropriate. We assessed heterogeneity using the I^2 statistic. We calculated a pooled standardised mean difference between scores of children with CHD and scores of healthy controls. A negative standardised mean difference was standardised to mean worse performance on the measure in the CHD group compared to controls. A standardised mean difference of 0 to −0.3 indicated a mild decrease in performance, a standardised mean difference of −0.3 to −0.6 indicated a moderate deficit in performance, and a standardised mean difference of −0.6 or below indicated a severe deficit in performance in the CHD group relative to controls.

We explored sources of heterogeneity if the I^2 statistic exceeded 50% in any domain-level effect size calculation, indicating at least moderate between-study heterogeneity. Techniques we planned to use included meta-regression on clinical variables such as age and CHD type, "one-study-removed" analysis, and "one-measure-removed" analysis.

"One-study-removed" analysis is a technique for exploring each individual study's impact on the effect size estimate and between-study heterogeneity. One study at a time is removed and the model is recalculated. If there are large differences in the effect size estimate or in the I^2 statistic between the two models, one could explore differences in that study compared to others.

We also explored whether removing one individual measure, such as the Trail Making Test Part B or the DKEFS Sorting Test, and recalculating the model would result in significant changes in effect size estimate and I^2. Significant changes could potentially indicate that the particular measure being tested may not have appropriate construct validity for the EF domain in our population of interest.

If less than 10 studies were included in any of the individual domain-level analyses, forest plots would be inspected visually for potential drivers of the heterogeneity. Potential moderator variables that would be considered for meta-regression included the specific measures used for each domain, the quality of evidence, age at evaluation, CHD diagnosis, and for the reporter-based measures analysis, the reporter.

We used the means, standard deviations, and sample sizes of control groups where presented. Data reported as medians with interquartile ranges or overall ranges were converted to means and standard deviations using standard methods.[33] If data were reported as subgroups, the means and variances were pooled using the method reported by Hedges and Olkin.[34] When no control group was included as part of the study, normative scores provided by the assessment battery were used.

Finally, we chose to consider the effect of normative data in our analysis. While normative data samples are large and validated in a broad sample, they often fail to take into account local variation in important confounders that could affect performance on measures of EF, such as socioeconomic status, parental education, and educational quality. Given that many of our studies contained small, geographically restricted convenience samples, and since many normative samples contain sample sizes in the thousands, an artificially large effect size in one cross-sectional study due to confounding variables could potentially drastically and incorrectly alter the overall effect size estimate. For this reason, we compared scores for participants in studies with no control group to a
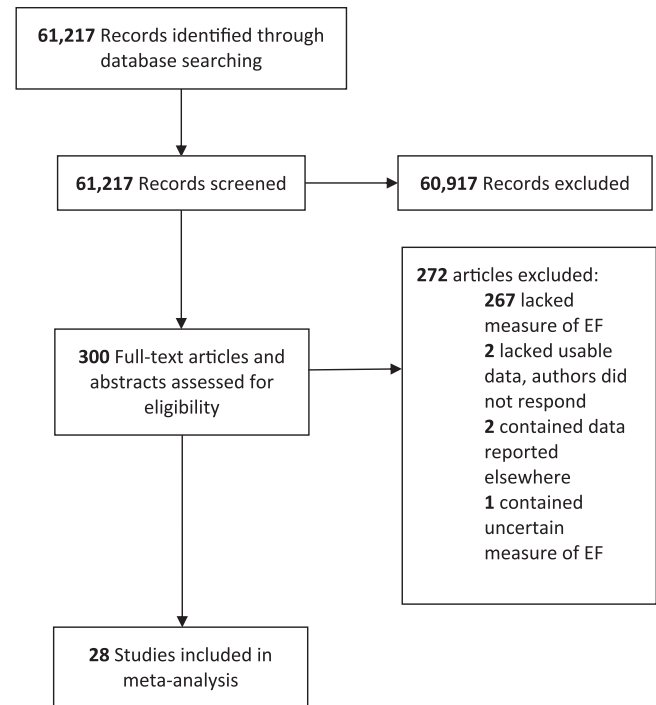
Figure 1. PRISMA flow diagram illustrating screening process and assessment of articles and abstracts for inclusion.

standardised control group utilising the expected scores for healthy children as per the testing manual (scaled score: mean 10, standard deviation 3; T-score: mean 50, standard deviation 10; standard score: mean 100, standard deviation 15), and limited the number of participants in each individual study's control group to 200.

Results

Study characteristics

A total of 61,217 results were screened by title and abstract. Three hundred articles were identified for full-text screening from these search results. After independent review, 28 articles met the inclusion criteria for the analysis (Fig 1). Two hundred sixty-seven articles and abstracts were excluded due to the lack of a reported measure of executive function. Two manuscripts were excluded due to the failure to report a usable centrality and variance estimate of the executive function measure scores.[35,36] Two manuscripts were excluded because the data were reported in another included manuscript.[37,38] Finally, one manuscript was rejected because it was not clear whether the measure included was a measure of executive function.[39]

The 28 included studies contained a total of 91 scores for measures of executive functions across the six domains (cognitive flexibility, inhibition, working memory, planning and problem solving, summary measures, reporter-based measures) that we planned to analyse. The characteristics of the included studies and measures are described in the Supplemental Information (Tables S1 – S6). A total of 16 scores on measures of executive function reported in eight manuscripts were excluded (Supplemental Information, Table S7). A brief description of the neuropsychological measures included in the analyses is presented in the Supplemental Information (Table S8).

Standardized Mean Difference in Measures of Cognitive Flexibility and Set Shifting

Study name	Std diff in means	Standard error		Variance	Lower limit	Upper limit	Z-Value	p-Value
Bellinger et al 2003	−0.271	0.134	Trails B	0.018	−0.534	−0.007	−2.016	0.044
Bellinger et al 2003	−0.120	0.263	WCST - Number cat achieved	0.069	−0.635	−0.395	−0.456	0.649
Bellinger et al 2003	−0.551	0.109	WCST - Perservr errors	0.012	−0.765	−0.337	−5.044	0.000
Bergemann et al 2015	−0.963	0.513	Trails B - HLHS	0.263	−1.969	−0.043	−1.876	0.061
Calderon et al 2014	−0.527	0.214	5y cohort - DCCS part 2	0.046	−0.947	−0.107	−2.457	0.014
Calderon et al 2014	−0.726	0.229	6y cohort - DCCS part 2	0.053	−1.175	−0.276	−3.163	0.002
Calderon et al 2014	−0.622	0.248	7y cohort - DCCS part 2	0.061	−1.107	−0.136	−2.510	0.012
Cassidy et al 2015	−0.599	0.133	Cat Sw - SV	0.018	−0.859	−0.338	−4.501	0.000
Cassidy et al 2015	−0.789	0.138	Cat Sw - TGA	0.019	−1.059	−0.519	−5.731	0.000
Cassidy et al 2015	−0.677	0.165	Cat Sw - ToF	0.027	−1.001	−0.353	−4.094	0.000
Cassidy et al 2015	−0.536	0.132	CCS - SV	0.018	−0.796	−0.277	−4.049	0.000
Cassidy et al 2015	−0.822	0.138	CCS - TGA	0.019	−1.093	−0.551	−5.950	0.000
Cassidy et al 2015	−0.744	0.166	CCS - ToF	0.028	−1.070	−0.418	−4.477	0.000
Cassidy et al 2015	−0.858	0.136	Dot - SV	0.018	−1.124	−0.591	−6.311	0.000
Cassidy et al 2015	−0.389	0.134	Dot - TGA	0.018	−0.652	−0.126	−2.904	0.004
Cassidy et al 2015	−0.640	0.165	Dot - ToF	0.027	−0.963	−0.317	−3.883	0.000
Cassidy et al 2015	−1.008	0.138	SR - SV	0.019	−1.278	−0.737	−7.302	0.000
Cassidy et al 2015	−0.869	0.139	SR - TGA	0.019	−1.141	−0.597	−6.259	0.000
Cassidy et al 2015	−0.645	0.165	SR - ToF	0.027	−0.968	−0.321	−3.909	0.000
Iardi et al 2016	−0.219	0.161	DKEFS Trails Switching	0.026	−0.535	−0.096	−1.361	0.174
Kasmi et al 2018	−0.653	0.200	WCST - Perseverative errors	0.040	−1.046	−0.261	−3.261	0.001
	−0.628	0.050		0.002	−0.726	−0.531	−12.625	0.000

Full Model

Figure 2. Forest plot of measures of cognitive flexibility and set shifting. Meta-analysis shows a moderate decrease in scores on measures of cognitive flexibility and set shifting ($I^2 = 49.6\%$, $p < 0.001$). Sensitivity analysis did not show any significant effects of a particular measure or with one study removed.

Assessment of publication bias and quality of evidence

Funnel plots for each of the six analyses were generated and visually inspected. None of the plots indicated substantial publication bias. The quality of evidence was rated as moderate by the modified Newcastle-Ottawa scale and by qualitative impression (Supplemental Information, Tables S1 – S6).

Measures of cognitive flexibility and set shifting

Six manuscripts contained 21 measures of cognitive flexibility and set shifting.[17,19,21,22,40,41] A total of 2165 scores on measures of cognitive flexibility and set shifting were reported in 548 children and adults with CHD. A total of 2170 scores on measures were reported for 607 healthy controls. Meta-analysis showed a standardised mean difference of −0.628 (95% confidence interval: −0.726, −0.531) between populations with CHD and healthy controls in the full model (Fig 2). I^2 was 49.62%, indicating a moderate amount of heterogeneity. Sensitivity analysis was performed to attempt to explain some of the between-study heterogeneity, including techniques such as meta-regression on age and type of CHD, "one-study-removed" analysis, and removal of one neuropsychological measure (e.g. Trails B or the DKEFS Sorting Test Confirmed Correct Sorts) from the analysis. None of those analyses decreased the I^2 statistic by more than 10%, so the initial model was kept in place.

Measures of inhibition

Seven manuscripts contained 16 measures of inhibition.[17,22,42–46] Totally, 1273 scores on measures of inhibition were reported in 1038 children with CHD, and 986 scores on measures of inhibition were reported in 759 healthy controls. Meta-analysis revealed a standardised mean difference of −0.469 (95% confidence interval: −0.606, −0.333, Fig 3a), and I^2 was calculated to be 51.98%. Two of the measures reported were the Statue test, a test commonly used to assess motor inhibition, whereas the other measures were

assessments of cognitive inhibition, similar to the Stroop task.[47] After eliminating the two Statue measures, the standardised mean difference was −0.486 (95% confidence interval: −0.617, −0.355, $I^2 = 34.62\%$, Fig 3b).

Measures of working memory

Twelve manuscripts reported 21 measures of working memory.[19,22,23,41–43,48–53] Authors reported 835 scores on measures of working memory in 501 children with CHD and 1565 scores on measures of working memory in 1095 healthy controls. The standardised mean difference was −0.369 (95% confidence interval: −0.466, −0.273, Fig 4), indicating a mild-to-moderate decrease in performance on measures of working memory in subjects with CHD compared to healthy controls. I^2 was 6.4%, indicating low between-study heterogeneity.

Measures of planning and problem solving

Three manuscripts contained 11 measures of planning and problem-solving abilities.[21,43,54] Two manuscripts reported an overall score for a variant of the Tower of London task, while the other manuscript reported three different metrics calculated to measure planning and problem-solving abilities during the Delis-Kaplan Executive Function System Tower task. There were 1145 scores on measures of planning and problem solving reported in 419 children with CHD, and 1032 scores on measures of planning and problem solving reported in 144 healthy controls. The overall standardised mean difference was calculated as −0.334 (95% confidence interval: −0.546, −0.121, Fig 5a), indicating moderate decreases in planning and problem-solving abilities in populations with CHD compared to healthy controls. I^2 was 82.83%, and upon visual inspection, measures of the Delis-Kaplan Executive Function System Tower Test move accuracy ratio appeared to vary substantially from the other measures. When these measures were
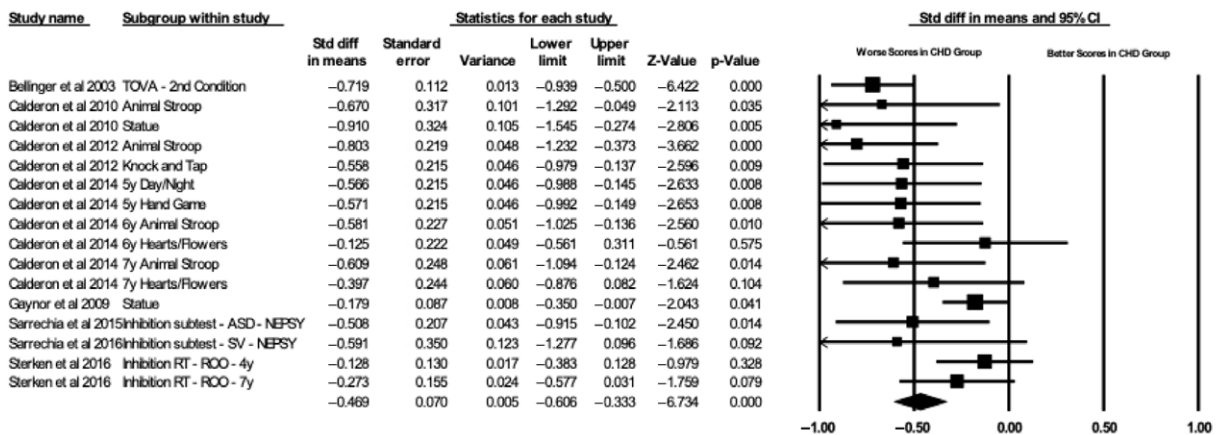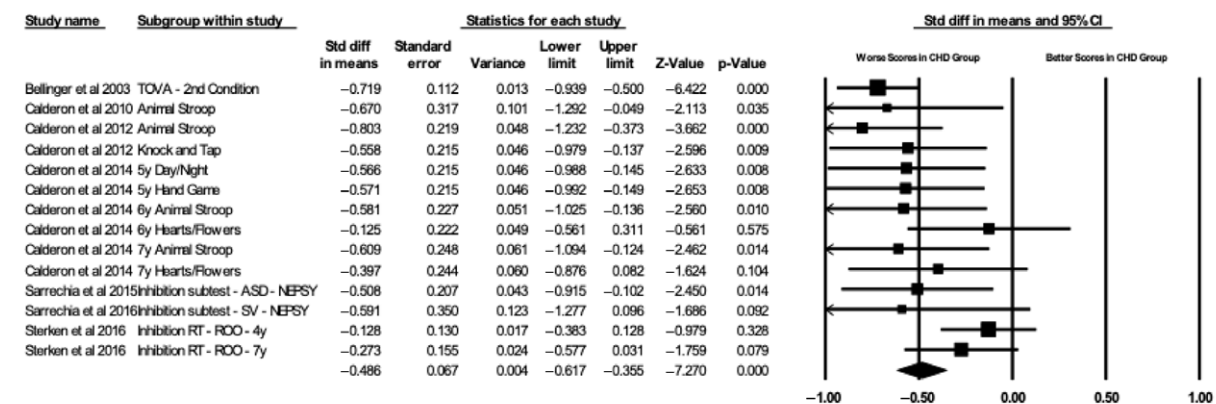
(a)

Standardized Mean Difference in Measures of Inhibition

Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bellinger et al 2003	TOVA - 2nd Condition	−0.719	0.112	0.013	−0.939	−0.500	−6.422	0.000
Calderon et al 2010	Animal Stroop	−0.670	0.317	0.101	−1.292	−0.049	−2.113	0.035
Calderon et al 2010	Statue	−0.910	0.324	0.105	−1.545	−0.274	−2.806	0.005
Calderon et al 2012	Animal Stroop	−0.803	0.219	0.048	−1.232	−0.373	−3.662	0.000
Calderon et al 2012	Knock and Tap	−0.558	0.215	0.046	−0.979	−0.137	−2.596	0.009
Calderon et al 2014	5y Day/Night	−0.566	0.215	0.046	−0.988	−0.145	−2.633	0.008
Calderon et al 2014	5y Hand Game	−0.571	0.215	0.046	−0.992	−0.149	−2.653	0.008
Calderon et al 2014	6y Animal Stroop	−0.581	0.227	0.051	−1.025	−0.136	−2.560	0.010
Calderon et al 2014	6y Hearts/Flowers	−0.125	0.222	0.049	−0.561	0.311	−0.561	0.575
Calderon et al 2014	7y Animal Stroop	−0.609	0.248	0.061	−1.094	−0.124	−2.462	0.014
Calderon et al 2014	7y Hearts/Flowers	−0.397	0.244	0.060	−0.876	0.082	−1.624	0.104
Gaynor et al 2009	Statue	−0.179	0.087	0.008	−0.350	−0.007	−2.043	0.041
Sarrechia et al 2015	Inhibition subtest - ASD - NEPSY	−0.508	0.207	0.043	−0.915	−0.102	−2.450	0.014
Sarrechia et al 2016	Inhibition subtest - SV - NEPSY	−0.591	0.350	0.123	−1.277	0.096	−1.686	0.092
Sterken et al 2016	Inhibition RT - ROO - 4y	−0.128	0.130	0.017	−0.383	0.128	−0.979	0.328
Sterken et al 2016	Inhibition RT - ROO - 7y	−0.273	0.155	0.024	−0.577	0.031	−1.759	0.079
		−0.469	0.070	0.005	−0.606	−0.333	−6.734	0.000

Full Model

(b)

Standardized Mean Difference in Measures of Inhibition

Study name	Subgroup within study	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bellinger et al 2003	TOVA - 2nd Condition	−0.719	0.112	0.013	−0.939	−0.500	−6.422	0.000
Calderon et al 2010	Animal Stroop	−0.670	0.317	0.101	−1.292	−0.049	−2.113	0.035
Calderon et al 2012	Animal Stroop	−0.803	0.219	0.048	−1.232	−0.373	−3.662	0.000
Calderon et al 2012	Knock and Tap	−0.558	0.215	0.046	−0.979	−0.137	−2.596	0.009
Calderon et al 2014	5y Day/Night	−0.566	0.215	0.046	−0.988	−0.145	−2.633	0.008
Calderon et al 2014	5y Hand Game	−0.571	0.215	0.046	−0.992	−0.149	−2.653	0.008
Calderon et al 2014	6y Animal Stroop	−0.581	0.227	0.051	−1.025	−0.136	−2.560	0.010
Calderon et al 2014	6y Hearts/Flowers	−0.125	0.222	0.049	−0.561	0.311	−0.561	0.575
Calderon et al 2014	7y Animal Stroop	−0.609	0.248	0.061	−1.094	−0.124	−2.462	0.014
Calderon et al 2014	7y Hearts/Flowers	−0.397	0.244	0.060	−0.876	0.082	−1.624	0.104
Sarrechia et al 2015	Inhibition subtest - ASD - NEPSY	−0.508	0.207	0.043	−0.915	−0.102	−2.450	0.014
Sarrechia et al 2016	Inhibition subtest - SV - NEPSY	−0.591	0.350	0.123	−1.277	0.096	−1.686	0.092
Sterken et al 2016	Inhibition RT - ROO - 4y	−0.128	0.130	0.017	−0.383	0.128	−0.979	0.328
Sterken et al 2016	Inhibition RT - ROO - 7y	−0.273	0.155	0.024	−0.577	0.031	−1.759	0.079
		−0.486	0.067	0.004	−0.617	−0.355	−7.270	0.000

Statue Removed

Figure 3. Forest plots for measures of inhibition. (**a**) Shows the full model and (**b**) shows the effect size estimate with the statue test removed ($I^2 = 34.62\%$, $p < 0.001$).

removed, the standardised mean difference was −0.525 (95% confidence interval: −0.644, −0.407, $I^2 = 16.43\%$, Fig 5b).
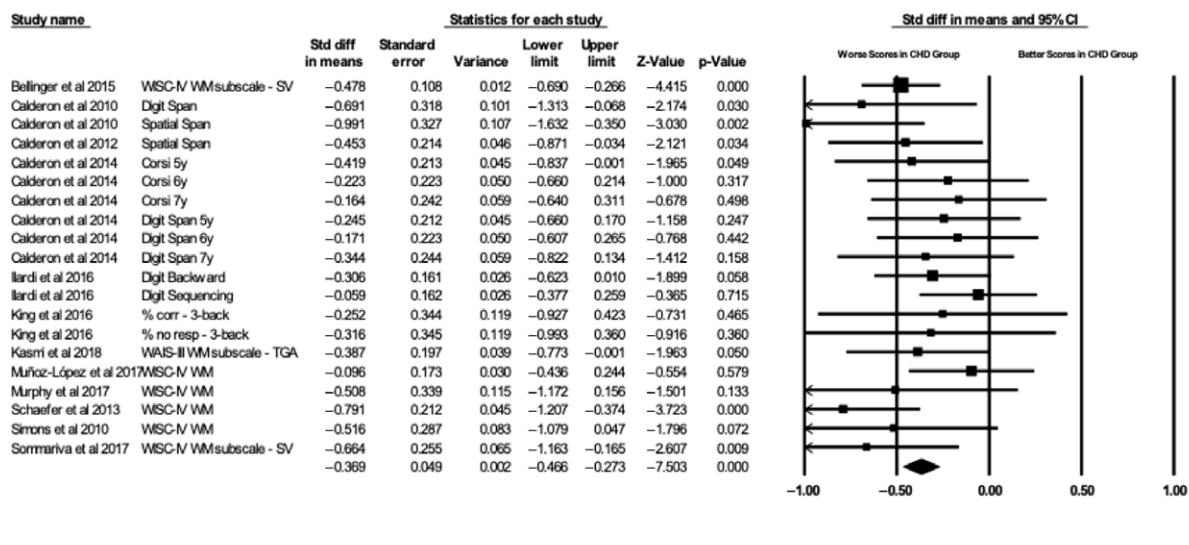
Summary measures of executive functioning

Five scores for summary measures of executive functions were extracted from five different manuscripts.[18,48,55–57] The five measures were a summary score calculated by averaging five subtests on the Delis-Kaplan Executive Function System, used in three different manuscripts, and the Developmental NEuroPSYchological Assessment – Version 2 Attention/Executive Function core domain score, used in two manuscripts. A total of 626 scores in children with CHD and a total of 641 scores of control children were included in the analysis. Meta-analysis of the five measures resulted in a standardised mean difference of −0.361 (95% confidence interval: −0.576, −0.147), indicating a moderate decrease in scores on measures of global executive functions in children with CHD compared to controls (Supplemental Information,

Figure S2a). I^2 was 73.18%, indicating substantial heterogeneity. One study removed analysis showed that the measure reported by Fuller et al accounted for all of the heterogeneity. The standardised mean difference estimate after its removal was −0.457 (95% confidence interval: −0.585, −0.329, $I^2 = 0$, Supplemental Information, Figure S2b).

Reporter-based measures

Seven manuscripts reported 16 measures of either self-, parent-, or teacher report of executive function.[18,23,48,55,58–60] A total of 1745 scores in the CHD group and 1793 scores in the healthy control group across the 16 measures were included for meta-analysis. We estimated a standardised mean difference of −0.444 (95% confidence interval: −0.614, −0.274, Supplemental Information, Figure S3a). I^2 equaled 85.68%. Based on prior work reporting a significant difference in scores on the Behavior Rating Inventory of Executive Function between the reporter type,[61] we chose to
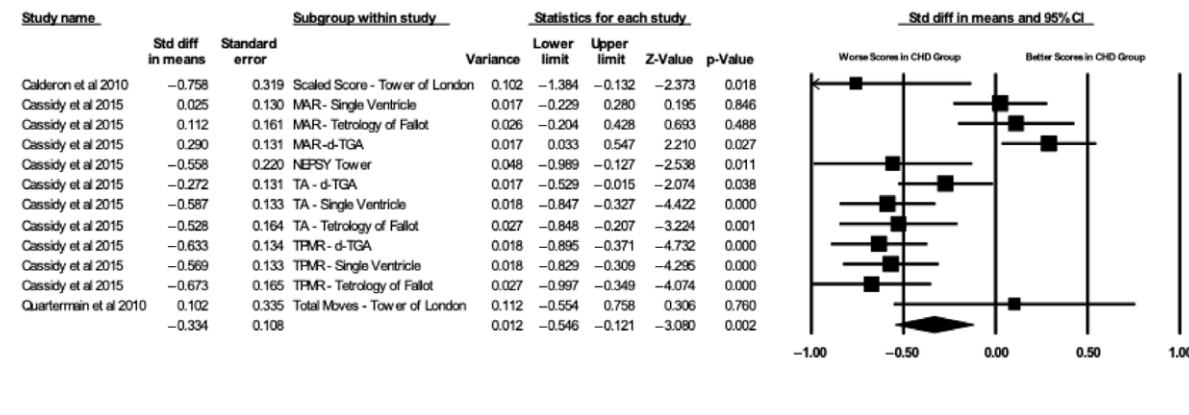
Standardized Mean Difference in Measures of Working Memory

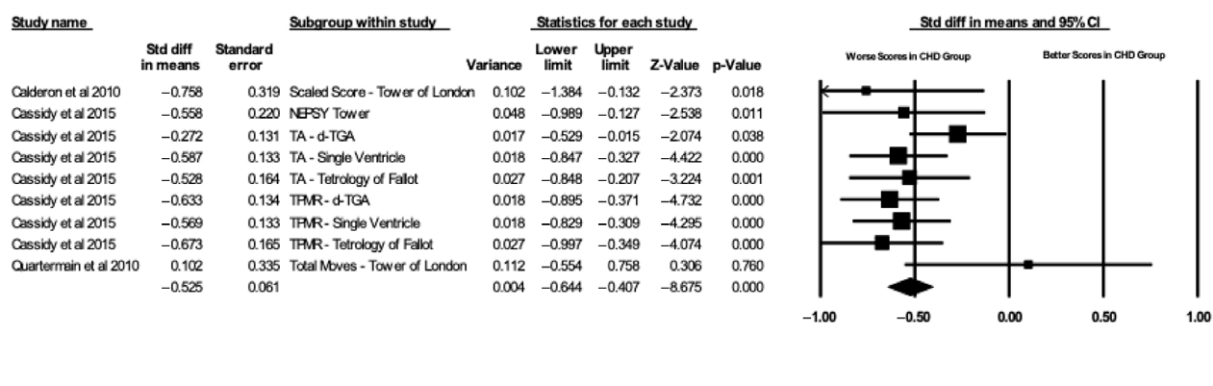| Study name		Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bellinger et al 2015	WISC-IV WM subscale - SV	−0.478	0.108	0.012	−0.690	−0.266	−4.415	0.000
Calderon et al 2010	Digit Span	−0.691	0.318	0.101	−1.313	−0.068	−2.174	0.030
Calderon et al 2010	Spatial Span	−0.991	0.327	0.107	−1.632	−0.350	−3.030	0.002
Calderon et al 2012	Spatial Span	−0.453	0.214	0.046	−0.871	−0.034	−2.121	0.034
Calderon et al 2014	Corsi 5y	−0.419	0.213	0.045	−0.837	−0.001	−1.965	0.049
Calderon et al 2014	Corsi 6y	−0.223	0.223	0.050	−0.660	0.214	−1.000	0.317
Calderon et al 2014	Corsi 7y	−0.164	0.242	0.059	−0.640	0.311	−0.678	0.498
Calderon et al 2014	Digit Span 5y	−0.245	0.212	0.045	−0.660	0.170	−1.158	0.247
Calderon et al 2014	Digit Span 6y	−0.171	0.223	0.050	−0.607	0.265	−0.768	0.442
Calderon et al 2014	Digit Span 7y	−0.344	0.244	0.059	−0.822	0.134	−1.412	0.158
Ilardi et al 2016	Digit Backward	−0.306	0.161	0.026	−0.623	0.010	−1.899	0.058
Ilardi et al 2016	Digit Sequencing	−0.059	0.162	0.026	−0.377	0.259	−0.365	0.715
King et al 2016	% corr - 3-back	−0.252	0.344	0.119	−0.927	0.423	−0.731	0.465
King et al 2016	% no resp - 3-back	−0.316	0.345	0.119	−0.993	0.360	−0.916	0.360
Kasmi et al 2018	WAIS-III WM subscale - TGA	−0.387	0.197	0.039	−0.773	−0.001	−1.963	0.050
Muñoz-López et al 2017	WISC-IV WM	−0.096	0.173	0.030	−0.436	0.244	−0.554	0.579
Murphy et al 2017	WISC-IV WM	−0.508	0.339	0.115	−1.172	0.156	−1.501	0.133
Schaefer et al 2013	WISC-IV WM	−0.791	0.212	0.045	−1.207	−0.374	−3.723	0.000
Simons et al 2010	WISC-IV WM	−0.516	0.287	0.083	−1.079	0.047	−1.796	0.072
Sommariva et al 2017	WISC-IV WM subscale - SV	−0.664	0.255	0.065	−1.163	−0.165	−2.607	0.009
		−0.369	0.049	0.002	−0.466	−0.273	−7.503	0.000

Full Model

Figure 4. Forest plot of measures of working memory. Meta-analysis shows a moderate decrease in scores on working memory measures in people with CHD compared to healthy controls ($I^2 = 6.4\%$, $p < 0.001$).

(*a*)
Standardized Mean Difference in Measures of Planning and Problem Solving

Study name	Std diff in means	Standard error	Subgroup within study	Variance	Lower limit	Upper limit	Z-Value	p-Value
Calderon et al 2010	−0.758	0.319	Scaled Score - Tower of London	0.102	−1.384	−0.132	−2.373	0.018
Cassidy et al 2015	0.025	0.130	MAR - Single Ventricle	0.017	−0.229	0.280	0.195	0.846
Cassidy et al 2015	0.112	0.161	MAR - Tetrology of Fallot	0.026	−0.204	0.428	0.693	0.488
Cassidy et al 2015	0.290	0.131	MAR - d-TGA	0.017	0.033	0.547	2.210	0.027
Cassidy et al 2015	−0.558	0.220	NEPSY Tower	0.048	−0.989	−0.127	−2.538	0.011
Cassidy et al 2015	−0.272	0.131	TA - d-TGA	0.017	−0.529	−0.015	−2.074	0.038
Cassidy et al 2015	−0.587	0.133	TA - Single Ventricle	0.018	−0.847	−0.327	−4.422	0.000
Cassidy et al 2015	−0.528	0.164	TA - Tetrology of Fallot	0.027	−0.848	−0.207	−3.224	0.001
Cassidy et al 2015	−0.633	0.134	TPMR - d-TGA	0.018	−0.895	−0.371	−4.732	0.000
Cassidy et al 2015	−0.569	0.133	TPMR - Single Ventricle	0.018	−0.829	−0.309	−4.295	0.000
Cassidy et al 2015	−0.673	0.165	TPMR - Tetrology of Fallot	0.027	−0.997	−0.349	−4.074	0.000
Quartermain et al 2010	0.102	0.335	Total Moves - Tower of London	0.112	−0.554	0.758	0.306	0.760
	−0.334	0.108		0.012	−0.546	−0.121	−3.080	0.002

Full Model

(*b*)
Standardized Mean Difference in Measures of Planning and Problem Solving

Study name	Std diff in means	Standard error	Subgroup within study	Variance	Lower limit	Upper limit	Z-Value	p-Value
Calderon et al 2010	−0.758	0.319	Scaled Score - Tower of London	0.102	−1.384	−0.132	−2.373	0.018
Cassidy et al 2015	−0.558	0.220	NEPSY Tower	0.048	−0.989	−0.127	−2.538	0.011
Cassidy et al 2015	−0.272	0.131	TA - d-TGA	0.017	−0.529	−0.015	−2.074	0.038
Cassidy et al 2015	−0.587	0.133	TA - Single Ventricle	0.018	−0.847	−0.327	−4.422	0.000
Cassidy et al 2015	−0.528	0.164	TA - Tetrology of Fallot	0.027	−0.848	−0.207	−3.224	0.001
Cassidy et al 2015	−0.633	0.134	TPMR - d-TGA	0.018	−0.895	−0.371	−4.732	0.000
Cassidy et al 2015	−0.569	0.133	TPMR - Single Ventricle	0.018	−0.829	−0.309	−4.295	0.000
Cassidy et al 2015	−0.673	0.165	TPMR - Tetrology of Fallot	0.027	−0.997	−0.349	−4.074	0.000
Quartermain et al 2010	0.102	0.335	Total Moves - Tower of London	0.112	−0.554	0.758	0.306	0.760
	−0.525	0.061		0.004	−0.644	−0.407	−8.675	0.000

MAR Removed

Figure 5. Forest plots for measures of planning and problem solving (*a*) is the full model and (*b*) shows a significant decrease in heterogeneity with the mean accuracy ratio measure removed ($I^2 = 16.43\%$, $p < 0.001$).

perform a meta-regression on the reporter variable. The inclusion of reporter in the model resulted in a statistically significant improvement in the effect size estimate ($Q = 25.81$, $df = 2$, $p < 0.001$, Supplemental Information, Figure S3b). The estimated standardised mean differences were −0.02 (95% confidence interval: −0.24, 0.21) for self-report measures, −0.44 (−0.7, −0.17) for parent-reported measures, and −0.83 (−1.15, −0.51) for teacher-reported measures. The R^2 analog was 0.74, meaning that the model explained 74% of the estimated between-study variance.

Discussion

We found a moderate decrease in performance in six domains of executive functions in people with CHD compared to healthy controls. In all domains, people with CHD showed at least a mild decrease in scores. The most prominent decreases were in inhibition and cognitive flexibility, though these domains showed substantial between-study heterogeneity.

In the inhibition domain, between-study variance was eliminated when we removed the NEuroPSYchological Assessment – Second Edition-II Statue test from the analysis. This could potentially result from the fact that the Statue test is designed to assess behavioural control, which may be a different construct than cognitive inhibition.[62]

There was a large amount of heterogeneity in effect sizes for measures of cognitive flexibility that could not be explained. Elimination of each of the different included measures (Trail Making Test Part B, Wisconsin Card Sort Test, Delis-Kaplan Executive Function System Category Switch, Delis-Kaplan Executive Function System Dot Switch, Delis-Kaplan Executive Function System Sorting Test) did not substantially reduce between-study heterogeneity, nor did any individual measure have an outsize effect on the standardised mean difference. We regressed on a variety of age groups and by CHD diagnosis, but none of the regression models were significant. This could be that the analysis was underpowered to detect age and diagnosis-related differences in cognitive flexibility abilities, or there may be confounding introduced by related cognitive deficits, such as visual or auditory processing.

Children and adults with CHD showed significantly lower scores on measures of working memory and planning/problem solving as compared to healthy controls, albeit with lower effect sizes than other domains. Measures of working memory showed little between-study variance despite including multiple assessment tools (backward digit span, Corsi block tapping test, n-back) and broader subscales that incorporated multiple assessments (Wechsler Intelligence Scale for Children – Version 4 and Wechsler Adult Intelligence Scale – Version 3 working memory subscales).

The planning and problem-solving analysis showed decreased variability with the removal of the move accuracy ratio measure from the Delis-Kaplan Executive Function System Tower assessment. This measure is calculated as the total number of moves used to complete the task divided by the minimum number of moves required. The scores reported indicate that children with CHD had a lower move accuracy ratio compared to controls, which indicates better performance on the measure. This was in contrast to the rest of the measures used in the analysis, which showed decreased performance in the CHD group. A possible explanation is that a lower move accuracy ratio can have two interpretations: better performance or freezing. Children tested in the Tower test may become frustrated with later, more difficult tasks in the assessment. Often, they can become overwhelmed

and perform no moves at all, leading to an artificially low move accuracy ratio and the appearance of better performance. The total achievement score helps distinguish the two possibilities. A higher total achievement score indicates better performance on the Tower task, and a lower total achievement score suggests a lack of moves due to frustration. In this case, the total achievement scores for the same samples were included in the analysis and were indeed lower than controls, suggesting the possibility that the move accuracy ratio scores in these CHD groups were artificially better.

Summary measures of executive functioning appear to be a reasonable proxy for executive function deficits in this population. Analysis of summary measures produced a similar effect size to the individual domain analyses, implying that the reporting of executive function summary scores may be sufficient for the estimation of the risk of general executive dysfunction in a population. However, domain-level information remains critical for more detailed clinical assessment and the development of possible interventions for cognitive remediation.

In a meta-regression of reporter-based measures, parents achieved the most accuracy in characterising the magnitude of deficits found on formal neuropsychological assessment of executive functioning. Self-reported measures underestimated the performance deficits, while teacher-reported measures overestimated the performance deficits. This is limited by the low number of scores in the two latter groups, which may have improved estimates with more data.

Our study has several important strengths. First, no current meta-analyses have examined performance on measures of executive functions in CHD. There has been a substantial body of literature examining the topic published in the past five years, and we believe this study represents an accurate synthesis of the data. Second, our methodology addresses two of the major problems encountered when synthesising neuropsychological data: collinearity and important confounders (e.g., age, severity of disease, reporter). Finally, while American Heart Association guidelines recommend screening for executive dysfunction starting around the age of six,[63] problems may present earlier in life. Our synthesis shows deficits in multiple domains of executive functions across the lifespan, including in younger children, and thus earlier screening for executive dysfunction may be beneficial.

We acknowledge some limitations in our work. A substantial proportion of our data comes from a small number of research groups. While these groups examined high-quality data in multiple cohorts in both observational and longitudinal designs, reports from different geographic locations would greatly strengthen the analysis. Further, while our analysis did account for correlation in the data, our methodology could not assess the impact it had on our effect size estimates. While analyses to address this issue were not feasible due to the small number of data sources, adjusting for collinearity might have explained some of the unexplained between-study variance.

In summary, children and adults with CHD show moderate deficits in measures of executive functions compared to healthy controls. The effect persists throughout childhood and into adulthood and exists in six common domains of executive functioning. These deficits can potentially be improved with cognitive remediation,[64] which makes executive functioning an important area of cognitive function to study in these patients. Further research should continue to quantify these deficits, and the field should continue to develop and encourage multidisciplinary

CHD centres that include routine neuropsychological evaluation as part of the comprehensive care of individuals with CHD.

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