

APPENDIX

eMethods 1: More details on data analysis and study selection

eMethods 2: Search strategy Pubmed & Embase

eResults: eTable 1 and eFigures 1-4

eReferences

eMethods 1: More details on study selection and data analysis

Data analysis LGC-trial data

Propensity scores were estimated using logistic regression with syndrome, origin (exclusive European), language (exclusively Dutch language) and gender, as dichotomous covariates and age at follow-up and socio-economic status, as continuous covariates. One-to-one nearest neighbor matching without replacement was performed, using a caliper of 0.07. Satisfactory matching was obtained, as indicated by absolute standardized difference in means less than or equal to 0.1 for all variables.¹ Matching was successful over the full range of propensity scores. 167 CHD-patients were matched to 167 controls.

Systematic review

Study selection

We excluded studies that only used the Bayley Infant Developmental Test² or an equivalent early developmental test, because such general developmental tests do not offer additional data on the specific neurocognitive skills.

Data analysis

If neurocognitive data of all tested children with CHD together were available in a particular study, the sample size of the total CHD-group was used in the sample size calculation. Otherwise the sample sizes of the tested subgroups were used. If age data were missing or only median ages or ranges were mentioned, these were not included in the age calculation. In case of overlap of study population between studies of the same research group, the study with the largest sample sizes was included in the meta-analysis. In case of equal sample sizes, the study with neurocognitive data that were most related to other included studies, was chosen.

Because of a different interpretation of reaction time and non-reaction time measures of executive

functions (EFs) and attention, the SMD-calculation was done separately. For attention, reaction and non-reaction time data related to the same attentional function, namely alertness, were included. For EFs, reaction and non-reaction time data related to the same EF, namely inhibition, were included.

With regard to memory, the SMD-calculation for verbal and non-verbal measures was done separately. If neurocognitive data of all tested children with CHD together were available in a particular study, these neurocognitive data were used in the effect size calculation. Otherwise the data of CHD-subgroups were used.

The I^2 -statistic was used to evaluate heterogeneity. It describes the percentage of the variability in effect estimates that is due to heterogeneity rather than chance (<http://handbook.cochrane.org/>). A funnel plot is a simple scatter plot of the effect estimates (here SMD's) from individual studies against some measure of each study's size or precision (here standard error, SE) (<http://handbook.cochrane.org/>). The precision of the estimated effect increases as the standard error decreases (or study size increases), hereby creating a funnel.

eMethods 2

Search strategy Pubmed

("Reaction Time"[Mesh] OR "Arousal"[Mesh] OR "Impulsive Behavior"[Mesh:noexp] OR "Mental Processes"[Majr] OR "Cognition Disorders"[Majr] OR "Neurobehavioral Manifestations"[Majr] OR "Mental Disorders Diagnosed In Childhood"[Majr] OR "Intelligence"[Mesh] OR "Psychomotor Performance"[Mesh] OR "Inhibition (Psychology)"[Mesh] OR neurocognitive function*[tiab] OR neuropsychological function*[tiab] OR neurodevelopmental function*[tiab] OR developmental function*[tiab] OR intellectual function*[tiab] OR mental function*[tiab] OR "neurocognitive development"[tiab] OR "neuropsychological development"[tiab] OR intellectual development*[tiab] OR "mental development"[tiab] OR "neurocognitive follow-up"[tiab] OR "neuropsychological follow-up"[tiab] OR "neurodevelopmental follow-up"[tiab] OR "developmental follow-up"[tiab] OR neurocognitive outcome*[tiab] OR neuropsychological outcome*[tiab] OR neurodevelopmental outcome*[tiab] OR developmental outcome*[tiab] OR academic outcome*[tiab] OR intellectual outcome*[tiab] OR mental outcome*[tiab] OR neurocognitive deficit*[tiab] OR neuropsychological deficit*[tiab] OR neurodevelopmental deficit*[tiab] OR developmental deficit*[tiab] OR academic deficit*[tiab] OR intellectual deficit*[tiab] OR mental deficit*[tiab] OR neurocognitive disabilit*[tiab] OR neuropsychological disabilit*[tiab] OR neurodevelopmental disabilit*[tiab] OR developmental disabilit*[tiab] OR academic disabilit*[tiab] OR intellectual disabilit*[tiab] OR mental disabilit*[tiab] OR neurocognitive disorder*[tiab] OR neuropsychological disorder*[tiab] OR neurodevelopmental disorder*[tiab] OR developmental disorder*[tiab] OR intellectual disorder*[tiab] OR mental disorder*[tiab] OR neurocognitive delay*[tiab] OR neuropsychological delay*[tiab] OR neurodevelopmental delay*[tiab] OR developmental

delay*[tiab] OR academic delay*[tiab] OR intellectual delay*[tiab] OR mental delay*[tiab] OR neurocognitive impairment*[tiab] OR neuropsychological impairment*[tiab] OR neurodevelopmental impairment*[tiab] OR developmental impairment*[tiab] OR academic impairment*[tiab] OR intellectual impairment*[tiab] OR mental impairment*[tiab] OR neurocognitive difficult*[tiab] OR neuropsychological difficult*[tiab] OR neurodevelopmental difficult*[tiab] OR developmental difficult*[tiab] OR academic difficult*[tiab] OR intellectual difficult*[tiab] OR mental difficult*[tiab] OR neurocognitive disturbance*[tiab] OR neuropsychological disturbance*[tiab] OR neurodevelopmental disturbance*[tiab] OR developmental disturbance*[tiab] OR academic disturbance*[tiab] OR intellectual disturbance*[tiab] OR mental disturbance*[tiab] OR intelligence[tiab] OR "attention"[tiab] OR ADHD[tiab] OR executive function*[tiab] OR "working memory"[tiab] OR inhibition[tiab] OR inhibitory[tiab] OR inhibiting[tiab] OR inhibits[tiab] OR inhibit[tiab] OR cognit*[tiab] OR learning[tiab] OR memory[tiab] OR reading[tiab] OR reaction time*[tiab] OR response time*[tiab] OR "processing speed"[tiab] OR vigilance[tiab] OR "executive control" [tiab] OR "problem solving"[tiab] OR "solving problems"[tiab] OR dyslexia[tiab] OR dyscalculia[tiab] OR impulsiveness[tiab] OR impulsivity[tiab])

AND

("Heart Defects, Congenital"[Majr] OR "Cardiac Surgical Procedures"[Majr] OR "Cardiac Catheterization"[Majr] OR cardiac malformation*[tiab] OR ((heart defect*[tiab] OR heart disease*[tiab] OR cardiac disease*[tiab] OR cardiac defect*[tiab])) AND (congenital[tiab] OR inherited[tiab] OR hereditary[tiab] OR inborn[tiab] OR genetic[tiab])) OR "cardiac surgery"[tiab] OR heart surger*[tiab] OR heart operation*[tiab] OR catheterization*[tiab])

AND

("Psychological Tests"[Mesh] OR neurocognitive assessment*[tiab] OR neuropsychological assessment*[tiab] OR neurodevelopmental assessment*[tiab] OR developmental

assessment*[tiab] OR academic assessment*[tiab] OR intellectual assessment*[tiab]
 psychological assessment*[tiab] OR mental assessment*[tiab] OR neurocognitive test*[tiab]
 OR psychological test*[tiab] OR neuropsychological test*[tiab] OR neurodevelopmental
 test*[tiab] OR developmental test*[tiab] OR academic test*[tiab] OR mental test*[tiab] OR
 neurocognitive evaluation*[tiab] OR neuropsychological evaluation*[tiab] OR
 neurodevelopmental evaluation*[tiab] OR developmental evaluation*[tiab] OR intellectual
 evaluation*[tiab] OR psychological evaluation*[tiab] OR mental evaluation*[tiab] OR
 test[tiab] OR tests[tiab] OR testing[tiab] OR scale*[tiab] OR scaling[tiab])

AND

("infant"[MeSH Terms] OR "child"[MeSH Terms] OR "adolescent"[MeSH Terms] OR
 "Young Adult"[Mesh] OR infant*[tw] OR child*[tw] OR adolescen*[tw] OR young
 adult*[tw])

NOT

((animal NOT human) OR "Review"[Publication Type] OR "Case Reports" [Publication
 Type])

Search strategy Embase

#84 #78 NOT #83

#83 #77 OR #79 OR #80 OR #81 OR #82

#82 'editorial'/exp

#81 'conference paper'/exp

#80 'case report'/exp

#79 'case study'/exp

#78 #74 NOT (#75 NOT #76)

- #77 'review'/exp OR 'systematic review'/exp OR 'systematic review (topic)'/exp
- #76 human AND [embase]/lim
- #75 animal AND [embase]/lim
- #74 #69 AND #73
- #73 #70 OR #71 OR #72
- #72 infant* OR child* OR adolescen* OR 'young adult' OR 'young adults' AND [embase]/lim
- #71 'adolescent'/exp
- #70 'child'/exp
- #69 #54 AND #62 AND #68
- #68 #63 OR #64 OR #65 OR #66 OR #67
- #67 scale*:ab,ti OR scaling:ab,ti AND [embase]/lim
- #66 ((neurocognitive OR neuropsychological OR neurodevelopmental OR psychological OR developmental OR mental OR academic) NEXT/1 evaluation*):ab,ti AND [embase]/lim
- #65 ((neurocognitive OR neuropsychological OR psychological OR neurodevelopmental OR developmental OR mental OR academic) NEXT/1 test*):ab,ti AND [embase]/lim
- #64 ((neurocognitive OR neuropsychological OR neurodevelopmental OR psychological OR developmental OR intellectual OR mental OR academic) NEXT/1 assessment*):ab,ti AND [embase]/lim
- #63 'psychologic test'/exp
- #62 #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61
- #61 catheterization* AND [embase]/lim
- #60 'cardiac surgery':ab,ti OR 'heart surgery':ab,ti OR 'heart operation':ab,ti OR 'heart operations':ab,ti AND [embase]/lim

- #59 (('heart defect' OR 'heart defects' OR 'heart disease' OR 'heart diseases' OR 'cardiac defect' OR 'cardiac defects' OR 'cardiac disease' OR 'cardiac diseases') NEAR/1 (congenital OR inherited OR hereditary OR inborn OR genetic)):ab,ti AND [embase]/lim
- #58 'cardiac malformation':ab,ti OR 'cardiac malformations':ab,ti AND [embase]/lim
- #57 'heart catheterization'/exp/mj
- #56 'heart surgery'/exp/mj
- #55 'congenital heart malformation'/exp/mj
- #54 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53
- #53 impulsiv*:ab,ti AND [embase]/lim
- #52 dyslexia:ab,ti OR dyscalculia:ab,ti AND [embase]/lim
- #51 (problem* NEAR/1 solving):ab,ti AND [embase]/lim
- #50 vigilance:ab,ti AND [embase]/lim
- #49 'processing speed':ab,ti AND [embase]/lim
- #48 ((react* OR response) NEAR/2 time*):ab,ti AND [embase]/lim
- #47 learning:ab,ti OR memory:ab,ti OR reading:ab,ti AND [embase]/lim
- #46 cognit*:ab,ti AND [embase]/lim
- #45 inhibition:ab,ti OR inhibitory:ab,ti OR inhibit:ab,ti OR inhibits:ab,ti OR inhibiting:ab,ti AND [embase]/lim
- #44 'working memory':ab,ti AND [embase]/lim

- #43 (executive NEXT/1 (control* OR function*)):ab,ti AND [embase]/lim
- #42 intelligence:ab,ti AND [embase]/lim
- #41 ((neurocognitive OR neuropsychological OR neurodevelopmental OR developmental OR intellectual OR mental OR academic) NEXT/1 disturbance*):ab,ti AND [embase]/lim
- #40 ((neurocognitive OR neuropsychological OR neurodevelopmental OR developmental OR intellectual OR mental OR academic) NEXT/1 difficult*):ab,ti AND [embase]/lim
- #39 ((neurocognitive OR neuropsychological OR neurodevelopmental OR developmental OR intellectual OR mental OR academic) NEXT/1 impairment*):ab,ti AND [embase]/lim
- #38 ((neurocognitive OR neuropsychological OR neurodevelopmental OR developmental OR intellectual OR mental OR academic) NEXT/1 delay*):ab,ti AND [embase]/lim
- #37 ((neurocognitive OR neuropsychological OR neurodevelopmental OR developmental OR intellectual OR mental) NEXT/1 disorder*):ab,ti AND [embase]/lim
- #36 ((neurocognitive OR neuropsychological OR neurodevelopmental OR developmental OR intellectual OR mental OR academic) NEXT/1 disabilit*):ab,ti AND [embase]/lim
- #35 ((neurocognitive OR neuropsychological OR neurodevelopmental OR developmental OR intellectual OR mental OR academic) NEXT/1 deficit*):ab,ti AND [embase]/lim
- #34 ((neurocognitive OR neuropsychological OR neurodevelopmental OR developmental OR intellectual OR mental OR academic) NEXT/1 outcome*):ab,ti AND [embase]/lim
- #33 ((neurocognitive OR neuropsychological OR neurodevelopmental OR developmental) NEXT/1 'follow-up'):ab,ti AND [embase]/lim
- #32 ((neurocognitive OR neuropsychological OR intellectual OR mental) NEXT/1 development*):ab,ti AND [embase]/lim

- #31 ((neurocognitive OR neuropsychological OR neurodevelopmental OR developmental OR intellectual OR mental) NEXT/1 function*):ab,ti AND [embase]/lim
- #30 'mental deficiency'/exp
- #29 'learning disorder'/exp
- #28 'perception disorder'/exp OR 'psychomotor disorder'/exp
- #27 'impulse control disorder'/de
- #26 'communication disorder'/de
- #25 'attention deficit disorder'/exp
- #24 'autism'/exp
- #23 'memory disorder'/de
- #22 'language disability'/exp
- #21 'intellectual impairment'/de
- #20 'developmental coordination disorder'/exp
- #19 'cognitive defect'/exp
- #18 'attention disturbance'/exp
- #17 'apraxia'/exp
- #16 'thinking'/exp
- #15 'perception'/exp
- #14 'orientation'/exp
- #13 'mental capacity'/exp OR 'mental development'/exp OR 'mental performance'/exp
- #12 'learning'/exp OR 'memory'/exp
- #11 'executive function'/exp
- #10 'cognition'/de
- #9 'impulsiveness'/exp
- #8 'wakefulness'/exp

- #7 'sensorimotor function'/exp
- #6 'psychophysics'/exp
- #5 'response time'/exp
- #4 'psychological refractory period'/exp
- #3 'attention'/exp
- #2 'arousal'/exp
- #1 'psychophysiology'/de

eResults

eTable 1

Reference	N CHD	CHD-group	Control group	N Control	Age surgery	Age testing	IQ test	Attention test	Memory test	Executive function test	Risk of bias
Calderon J et al. J Pediatr. 2012;161(1):94-8.	45	TGA-prenatal diagnosis (N=29) TGA-postnatal diagnosis (N=16)	Recruited and examined in the same period and same geographic area	45	TGA- prenatal Mean 7.5d (SD 3.9) TGA-postnatal Mean 6.6d (SD 2.9)	4-6y	Columbia Mental Maturity Scale	/	/	Stroop Test, knock and tap subtest (NEPSY), digit span test (WISC-IV) and spatial span task (BEM-144 blocks), Dimensional Card Sorting test	18
Calderon J et al. Developmental Medicine and Child Neurology. 2010;52(12):1139-44.	21	TGA	Children randomly recruited in two Parisian primary schools over the same time period and matched to the study group according to age and sex	21	Neonatal arterial switch operation	TGA: mean 7y4m control: mean 7y6m	Columbia Mental Maturity Scale	/	/	Incongruent Stroop, Statue (NEPSY), Digit Span Backwards, spatial span task (BEM-144 blocks), Tower of London	17

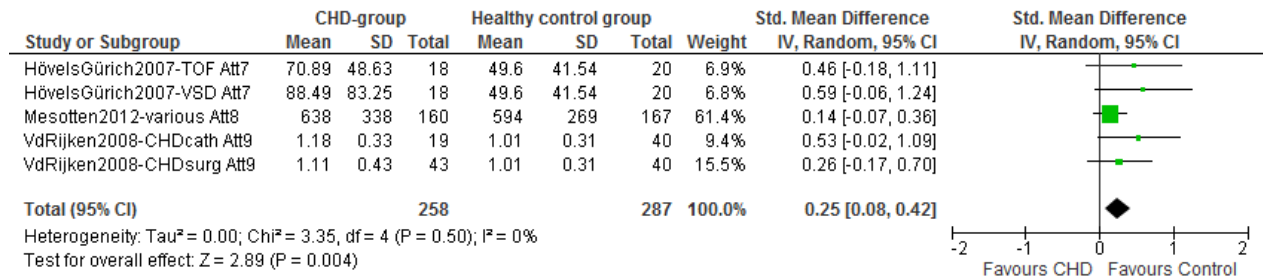
Mesotten D et al. JAMA. 2012;308(16):1641-50.	361 (167 PSM)	various CHD's	healthy controls	215 (167 PSM)	Matched CHD-group: median 2.11 (IQR 0.34-4.77),	Matched CHD-group: median 6.02 (IQR 4.21-8.78), Matched control group: median 5.91 (IQR 4.58 - 9.07)	Wechsler Intelligence Scales (depending on age)	Baseline Speed (Amsterdam Neuropsychological Tests)	Numbers, Word Pairs, Pictures, Dots (Children's Memory Scale)	Response Organization Objects (Amsterdam Neuropsychological Tests), Numbers Backwards (Children's Memory Scale)	16
Hovels-Gurich HH et al. Ann Thorac Surg. 2007;83(4):1425-30.	40	20 TOF 20 VSD	healthy controls	20	<u>TOF:</u> Mean 0.7y (SD 0.03y) <u>VSD:</u> Mean 0.7y (SD 0.2y)	<u>TOF:</u> Mean 7.4y (SD 1.4y) <u>VSD:</u> Mean 7.4y (SD 1.9y) <u>controls</u> Mean 8.1y (SD 1.7y)	Kaufman Battery of Children	Attention Network Test (ANT)	/	Attention Network Test (ANT)	15
Hovels-Gurich HH et al. Ann Thorac Surg. 2001;71(3):881-8.	33	24 TGA 4 TGA + unimportant VSD 4 with TGA + VSD closed 1 with TGA + coarctatio aortae	32 age-matched healthy children without perinatal complications and with a normal neurodevelopmental status according to their parents'	32	Mean 7.0 (SD 4.7d)	<u>Study group:</u> Mean 3.6 (SD 0.5y) <u>Control group:</u> Mean 3.8y (SD 0.6)	Vienna Developmental Test	/	Vienna Developmental Test: subscale learning and memory	/	17

Miatton M et al. J Pediatr. 2007;151(1):73-8, 8 e1.	43	cyanotic group (N=26), acyanotic group (N=17)	healthy controls group matched for sex, age and educational-level	43	not mentioned (all children underwent open-heart surgery)	Total CHD-group: Mean 8y8m (SD 1y6m) Control group: Mean 8y11m (SD 1y7m)	WISC-III:	attention and executive functioning (NEPSY)	memory domain (NEPSY)	Attention and Executive Functioning (NEPSY)	15
Sarrechia I et al. The Journal of pediatrics. 2015;166(1):31-38 e31.	48	ASD-II: surgical repair group (N=18), transcatheter repair group (N=30)	Healthy controls recruited through approval of primary school boards and matched with the patients on sex, age, and parental education	48	<u>Surgical repair group</u> Mean 2 y9m (SD 1y8m) <u>Transcatheter repair group</u> Mean 4y2m (SD 1y7m)	<u>Surgical repair group</u> : Mean 9y2m (SD 2y2m) <u>Transcatheter repair group</u> : Mean 9y3m (SD 1y7m)	Shortened version of WISC-III	Auditory attention (NEPSY-II-NL)	Memory and Learning: (NEPSY-II-NL)	Executive domain (NEPSY-II-NL)	16
Schaefer C et al. Dev Med Child Neurol. 2013;55(12):1143-1149.	59	various CHD's (49% acyanotic CHD's, 51% cyanotic CHD's)	Healthy children, similar to CHD-group in terms of age, sex and socio-economic status	40	median 0.9y (range 0-5.6y)	median age: 13y8m (range 11y5m - 16y11m)	WISC-IV	processing speed (WISC-IV)	ROCF: memory	working memory (WISC-IV), ROCF-Test	17

Tindall S et al. Developmental neuropsychology. 1999;16(1):101-15.	22 (ECMO / CHD)	9 CHD + ECMO 13 CHD + No ECMO various CHD's	31 children obtained from daycare settings and private referrals	31	ECMO: mean 11.7m (SD 9.8) CHD: Mean 13.4m (SD 8.7)	ECMO: mean 63.5m (SD 9.8) CHD: mean 65.3 (SD 9.8) Control: mean 64.1 (SD 8.4)	McCarthy Scales of Children's Abilities (MSCA)	Gordon Diagnostic Systemat Delay Task (GDS)	Wide Range Assessment of Memory and Learning (WRAML)	Gordon Diagnostic System Delay Task (GDS): efficiency ratio (measure of impulsivity)	11
Van Der Rijken R et al. European Heart Journal. 2008;29(21):2681-8.	62	43 various CHD's awaiting surgery 19 various CHD's awaiting catheterization	healthy children from regional mainstream primary and secondary schools, matched for age, sex, educational level, general intelligence, and parental educational level with both patient groups	40	not mentioned exactly; assessment took place in the period prior to surgery or cath. and again 1 year afterwards	CHD-surg Mean 11.6 (SD 3.1) CHD-cath Mean 11.0 (SD 2.6) Control group 11.7 (SD 2.8)	WISC-III	Complex Reaction Time Task, Bourdon-Vos, Letter Detection Task (Amsterdam Neuropsychological Test), Computerized drawing task	/	/	18

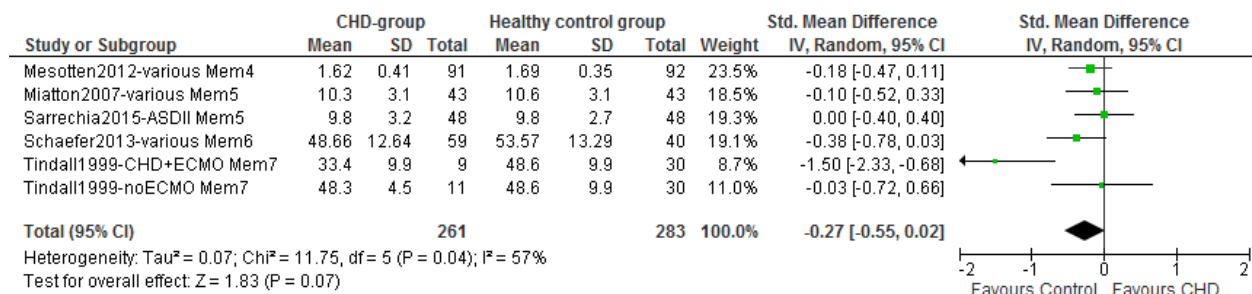
Wells FC et al. J Thorac Cardiovasc Surg. 1983;86(6):823-31.	49	Various CHD's: <u>TCA-group</u> (hypothermia and circulatory arrest) (N=31) <u>CPB-group</u> (continuous cardiopulmonary bypass) (N=18)	16 siblings of TCA patients & 13 siblings of CPB patients	29	<u>TCA-group</u> : 15m ± 2.0 <u>CPB-group</u> : 16m ± 2.0	<u>TCA-group</u> : Mean 68m (SD 1.1) <u>CPB-group</u> : Mean 70m (SD 1.7) <u>Siblings TCA-group</u> : Mean 86m (SD 4.8) <u>Siblings CPB-group</u> : Mean 84m (SD 5.9)	McCarthy Scales of Children's Abilities (MSCA) or Wechsler Intelligence Scales (depending on age)	/	Memory subscale (MSCA) /	/	10
Wray J et al. BMJ 1994;309(6958):837-41.	50	Conventional heart surgery Heart or heart-lung-transplantation	healthy children with no medical problems	45	not exactly mentioned; <u>Tx-group</u> : mean time after Tx at the time of assessment = 10m (range 3-25m); <u>Cardiac group</u> : cardiac surgery over 24m	mean age <u>Tx-group</u> : 9.4y (range 0.6-16.6y) <u>Cardiac group</u> : 6.2y <u>Control group</u> : 8.2y	Ruth Griffiths mental developmental scales or Short Form IQ from British Ability scales (BAS), depending on age	speed information (BAS): of	short term memory, retrieval of knowledge (BAS) /	/	15

eFigure 1. Forest plot of attention (Att) (alertness) reaction time (author/year/journal – CHD-type / attention measure)



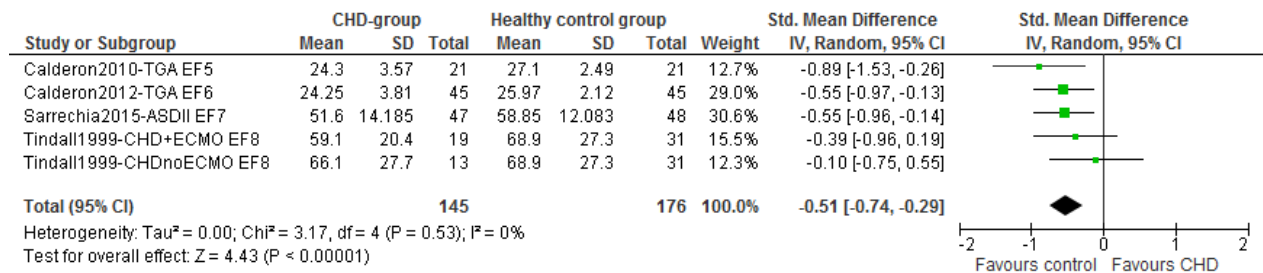
Abbreviations: Att7 = Alerting (msec) (Attention Network Test); Att8 = Mean reaction time (msec), alertness task (Amsterdam Neuropsychological Tasks); VdRijken = Van der Rijken; cath = catheterization; Att9 = Amsterdam Neuropsychological Task, reaction time; surg = surgery

eFigure 2. Forest plot of non-verbal memory (author/year/journal – CHD-type / Memory measure)



Legend: Mem4 = Sum of Immediate and Delayed Non-Verbal Memory (Children's Memory Scale, Dots, proportion correct responses); Mem5 = Memory for Faces (NEUROPSYchological Assessment, NEPSY); Mem6 = Rey-Osterrieth Complex Figure Test (ROCF), memory; Mem7 = Visual Memory (Wide Range Assessment of Memory and Learning, WRAML)

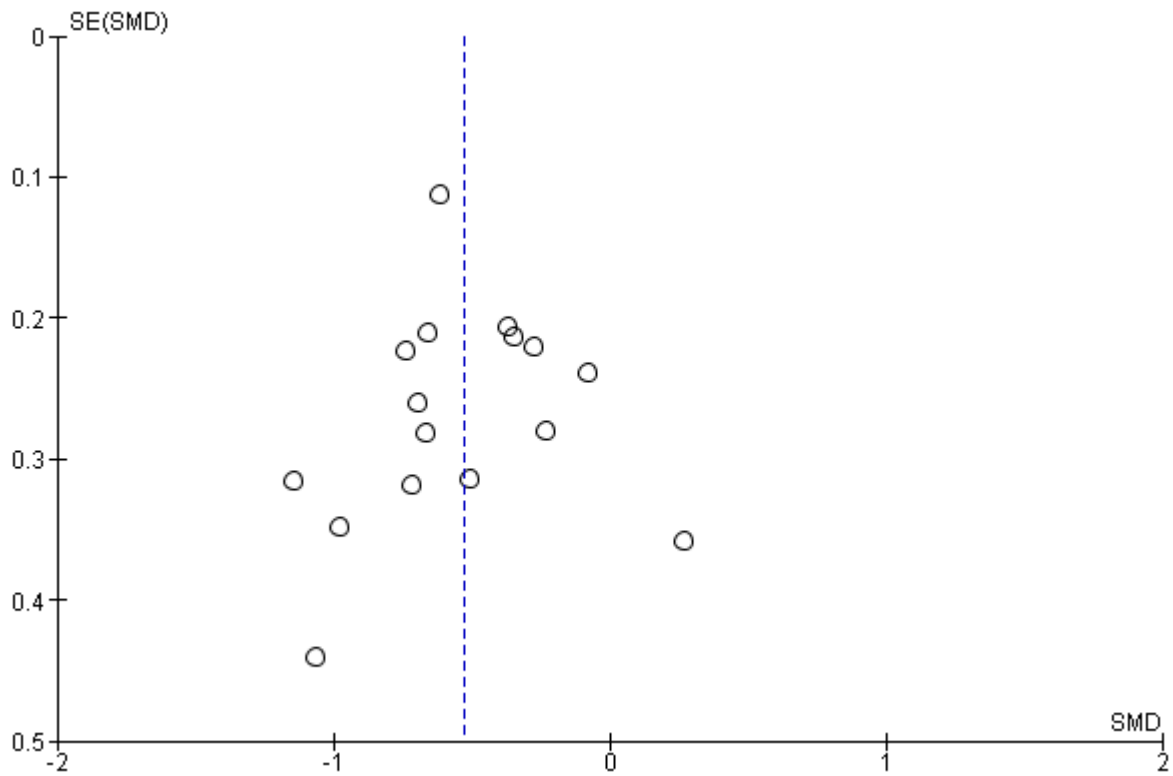
eFigure 3. Forest plot of executive function (EF) (inhibition) non-reaction time (author/year/journal – CHD-type / EF measure)



Legend: EF-Test5 = Statue; EF-Test6 = Knock & Tap; EF-Test7 = Inhibition (NEPSY); EF-Test8 = Delay Task, Efficiency ratio

eFigure 4. Slightly asymmetrical funnel plot of intelligence (N=16)

12 original studies; Abbreviations: SE = standard error; SMD = standardized mean difference



eReferences

1. Gayat E, Pirracchio R, Resche-Rigon M, Mebazaa A, Mary JY, Porcher R. Propensity scores in intensive care and anaesthesiology literature: a systematic review. *Intensive care medicine*. 2010;36(12):1993-2003.
2. Bayley N. *Manual for the Bayley Scales of Infant and Toddler Development*. 3rd ed. . San Antonio, TX: Harcourt Assessment; 2006.