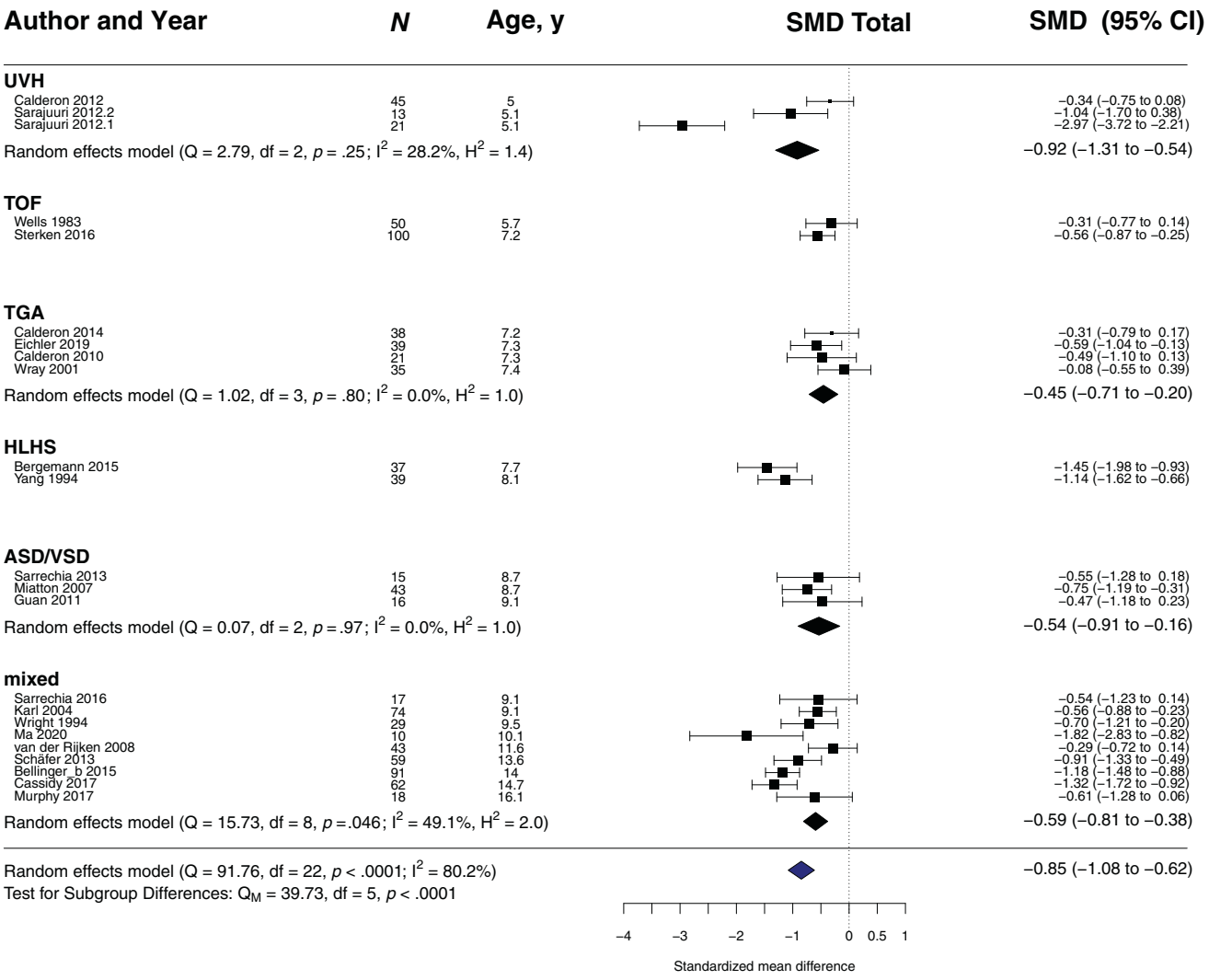
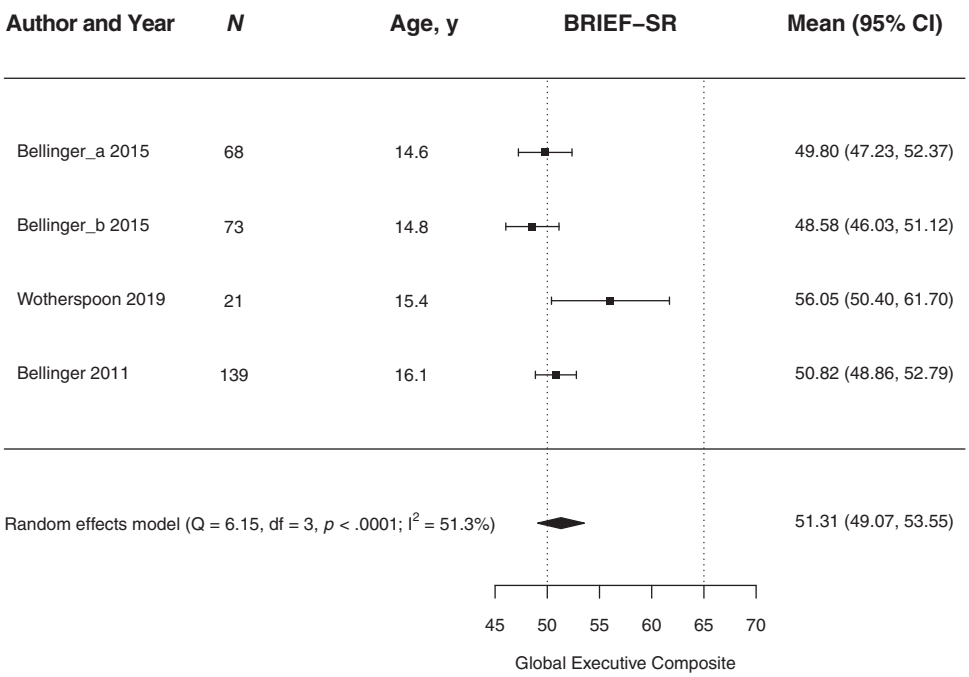
Supplemental Information



SUPPLEMENTAL FIGURE 6

Forest plot showing the results of studies assessing total IQ in school-aged children and adolescents with CHD in comparison to that of healthy peer controls. Studies are grouped by CHD subtype and sorted by increasing age at assessment. Black squares and lines for each study correspond to the SMD and 95% CI. If >2 studies were available for 1 subtype, black diamonds for each CHD subtype represent the estimated SMD and 95% CI based on the random-effects model. The blue diamond corresponds to the overall estimated SMD. Study weights were adjusted to account for longitudinally assessed cohorts.



SUPPLEMENTAL FIGURE 7

Forest plot showing the results of studies assessing self-rated behavioral EFs evaluated with the BRIEF. Studies are sorted by increasing age at assessment. Global Executive Function Composite scores >50 indicate EF difficulties and >65 indicated clinically significant executive dysfunction. Black squares and lines for each study correspond to the reported mean and 95% CI of composite T scores. The black diamond represents the estimated summary mean and 95% CI based on a random-effects model.

SUPPLEMENTAL TABLE 2 Ovid Medline and E-publication Ahead of Print, In-Process, and Other Nonindexed Citations and Daily 1946 to December 12, 2020, Search Strategy

No.	Searches
1	exp Heart Defects, Congenital/ or exp Heart Diseases/cn or ((congenital* or hereditary or inborn) and ((heart* or cardiac* or coronary or septal* or aortopulmonary or aorticopulmonary or atrial or ventricular or intraventricular) adj3 (defect* or disease* or malformation* or abnormal* or anomal*))).ti,ab. or (digeorge adj1 (syndrome* or anomal* or sequenc*)).ti,ab. or (transpos* adj3 (arteries or artery or vessel*)).ti,ab. or (alagille adj2 syndrome).ti,ab. or ("arteriohepatic dysplasia*" or "gonadal dysgenesis" or "subdivided left atrium*").ti,ab. or ((cardiovertebral or "pharyngeal pouch" or "thymic aplasia" or "conotruncal anomaly face" or turner* or noonan or barth or velo* or kartagener* or siewert* or scimitar or lutembacher* or leopard or "multiple lentigines" or marfan*) adj3 syndrome*).ti,ab. or ("hepatic hypoplasia" or "arteriohepatic dysplasia*" or "bicuspid aortic valve").ti,ab. or (taussig* adj2 anomal*).ti,ab. or ((pulmon* or aortic or subaortic or valve or mitral) adj1 stenosis).ti,ab. or ((aortic or aorta*) adj3 coarctation*).ti,ab. or (ventricular adj2 dysplasia*).ti,ab. or ("cor triatriatum" or cortriatriatum or "triatrial heart*").ti,ab. or ("myocardial bridging*" or "crisscross heart*" or "criss-cross heart*").ti,ab. or (dextrocardia* or "kartagener* triad" or "primary ciliary dyskinesia").ti,ab. or ("patent ductus arteriosus" or "anomalous pulmonary venous connection" or "double inlet left ventricle" or "double outlet right ventricle" or "interrupted aortic arch").ti,ab. or ("ebstein* anomaly" or "ebstein* malformation*" or "ectopia cordis").ti,ab. or (eisenmenger* adj1 (complex or syndrome)).ti,ab. or ("persistent truncus arteriosus" or "persistent ostium primum").ti,ab. or ("endocardial cushion defect*" or "atrioventricular canal").ti,ab. or "foramen oval*".ti,ab. or (heart adj3 hypoplas*).ti,ab. or ((noncompaction or "non compaction") adj3 "ventricular myocardium").ti,ab. or levocardia.ti,ab. or (((tetralogy or trilogy or syndrome) adj2 fallot*) or cantrell* or shon?s).ti,ab. or ((tricuspid or valve or pulmonary) adj1 atresia*).ti,ab. or ("absent right atrioventricular connection" or "single ventricle physiology" or GUCH or "cavopulmonary connection").ti,ab. or ((bonnevie adj2 (syndrome* or status)) or "polynesian bronchiectas*").ti,ab.
2	cardiac surgical procedures/ or arterial switch operation/ or cardiac valve annuloplasty/ or mitral valve annuloplasty/ or heart arrest, induced/ or circulatory arrest, deep hypothermia induced/ or heart bypass, right/ or fontan procedure/ or norwood procedures/ or "cardiopulmonary bypass"/ or exp Heart Defects, Congenital/su or ((heart or cardia* or myocardia* or cardiopulmonary or corrective or reparative or repair* or bypass) adj3 (surgery or operation* or procedure* or method* or technique* or bypass)).ti,ab. or (surg* adj3 correct*).ti,ab.
3	1 and 2
4	(((warden or rastelli or damus or kaye or dansel or ebstein or glenn or ross or bentall or fontan or norwood or blalock or taussig or aorto-pulmonary or "arterial switch" or "atrial switch" or "double switch" or fallot or jatene or mustard) adj3 (procedure* or surgery or operation* or repair* or closure* or conduit* or connection* or anastomosis or shunt or technique*)) or ((dextrotransposition or transposition or D-transposition) adj3 (arteries or vessels))).ti,ab.
5	3 or 4
6	exp child/ or exp adolescent/ or (child or children or minor* or teen* or juvenile* or adolescent*).ti,ab,kf. or ((exp pediatrics/ or (pediatric* or pediatric*).ti,ab,kf.) not (exp Infant/ not child/))
7	exp Memory Disorders/ or exp Executive Function/ or exp Memory/ or exp psychological tests/ or exp neuropsychological tests/ or exp Intelligence Tests/ or exp Intelligence/ or exp Cognition Disorders/ or exp Cognition/ or exp neurocognitive disorders/ or exp neurodevelopmental disorders/ or (cognitive or cognition or IQ or intellectual or intelligence or executive or memory or neuropsycholog* or neurodevelop* or neurocognit* or neurobehav* or neuro- psycholog* or neuro-develop* or neuro-cognit* or neuro-behav*).ti,ab. or (developmental adj3 (outcome* or evaluation* or problem* or delay*)).ti,ab. or ((motor or psychomotor or school or work or language or daily or everyday) adj3 (performance or abilities or proficiency or skills)).ti,ab.
8	5 and 6 and 7

SUPPLEMENTAL TABLE 3 Data Extraction Sheet

- Author
- Year
- Journal
- Title
- Subgroup (new column for each reported CHD subtype and controls)
- Study Design
- Participants
  - Subjects (No.)
  - Age at assessment (mean and median; distribution; unit distribution; unit age)
  - Recruitment period (year to year)
  - Country of enrolment (free text)
  - Suspicion of multiple reporting of same cohort (yes or no)
  - Perioperative characteristics
    - Preoperative baseline characteristics
    - Birth wt (mean and median in g)
    - Gestational age (wk)
    - Prematurity (<37 wk; No.)
    - Apgar score at 5 min (mean and median)
    - Sex (No. male)
    - Race (No. white)
    - Prenatal diagnosis (No. yes)
    - Maternal Age (mean and median in y)
    - Socioeconomic status (mean and median value; assessment scale)
    - Cyanotic heart defect (No.)
    - Without CPB (No.)
    - Univentricular (No.)
  - Surgical data
    - Wt at first surgery (mean and median; unit)
    - Age at first surgery (mean and median; unit)
    - Circulatory arrest time (mean and median in min)
    - Total bypass time (mean and median in min)
    - Lowest temperature during first surgery (mean and median in °C)
    - Length of ICU stay after first surgery (mean and median in d)
    - Length of hospital stay (mean and median in d)
    - Antegrade cerebral perfusion (mean and median in min)
  - Postoperative neurologic outcomes
    - Postoperative seizures (No.)
- Follow-up data
  - Follow-up rate (%)
  - Head circumference (centimeter or z score)
  - Wt (kilogram or z score)
  - Height (centimeter or z score)
  - Neurodevelopmental outcomes
    - Type of test (free text)
    - Total IQ (mean and median; distribution; unit distribution)
    - Verbal IQ (mean and median; distribution; unit distribution)
    - Performance IQ (mean and median; distribution; unit distribution)
    - Processing speed IQ (mean and median; distribution; unit distribution)
    - Working memory IQ (mean and median; distribution; unit distribution)
  - Neurologic examination
    - No abnormality (No.)
    - Any abnormality (No.)
    - Cerebral palsy (No.)
  - Academic achievement
    - Assessment of academic achievement (yes or no)
    - Type of assessment (free text)
    - Test result (mean and median)
  - EF assessment
    - EF assessed (yes or no)
    - Type of EF Test (free text)
    - EF Results (mean and median; distribution; unit distribution; unit)

SUPPLEMENTAL TABLE 3 Continued

BRIEF reported (yes or no)
BRIEF (parent-reported) Global Executive Composite Score (mean and median; distribution; unit distribution)
BRIEF (self-reported) Global Executive Composite Score (mean and median; distribution; unit distribution)

CPB, cardiopulmonary bypass surgery.

SUPPLEMENTAL TABLE 4 Bias Assessment

Statement	What Does This Statement Mean?	When Does It Apply?	Rating Categories	Rating
Selection (maximum 3 stars)				
1. The CHD cohort being studied is selected from a source population that is comparable in all respects.	This relates to selection bias. It is important that the selection of subjects from the source population is transparent and that differences in the presence of specific prognostic factors or prognostic markers relevant to the study in question can be judged. Judgement should be based on reporting of the selection process of the CHD group because only few studies included controls.	Always applies	Yes: Where characteristics of the populations from which CHD participants were selected are summarized (preferably in a table); Partially: where inclusion and exclusion criteria are clearly indicated and the recruitment approach (where and how recruited) is given; No: Where there is no indication of how CHD subjects were selected or what the relevant population characteristics were.	Yes → ★★; Partially → ★☆; No → ☆☆
2. The study indicates how many of the CHD children/families asked to take part did so.	This relates to selection bias. The participation rate is defined as the No. study participants divided by the No. eligible subjects and should be calculated separately for each branch of the study. A large difference in participation rate indicates that a significant degree of selection bias may be present, and the study results should be treated with considerable caution.	Only in prospective RCTs and cross-sectional studies	Yes: where the participation rate is clearly defined; No: where authors do not indicate the actual participation rate; Not Applicable: retrospective study design	Yes → ★; NA or No → ☆
Attrition (maximum 3 stars)				
3. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?	This question relates to the risk of attrition bias. The No. patients who drop out of a study should give concern if the number is high. Conventionally, a 20% drop-out rate is regarded as acceptable, but, in observational studies conducted over a lengthy period of time, a higher drop-out rate is to be expected.	In prospective studies or RCTs	Percentage: cutoff 20%	Detailed drop-out information is provided in text or flowchart and drop-out rate is below cutoff (20%) → ★★; detailed drop-out information is provided in text or flowchart but drop out is above cutoff (20%) → ★☆; NA or not reported → ☆☆

SUPPLEMENTAL TABLE 4 Continued

Statement	What Does This Statement Mean?	When Does It Apply?	Rating Categories	Rating
4. Comparison is made between full participants and those lost to follow-up, by exposure status.	For valid study results, it is essential that the study participants are truly representative of the source population. It is always possible that participants who dropped out of the study will differ in some significant way from those who remained part of the study throughout. A well conducted study will attempt to identify any such differences between full and partial participants in both the exposed and unexposed groups. This relates to the risk of attrition bias. Any unexplained differences should lead to the study results being treated with caution.	Prospective studies, RCTs	Yes: where there has been some follow-up of dropouts, with explanation and comparison of baseline characteristics provided.; No: where there is no indication that this factor has been considered; Not Applicable: retrospective study design	Yes → ★; NA/No → ☆
Detection (maximum 4 stars)				
5. The assessment of outcome (ie, IQ or EF testing) is made blind to exposure status	This relates to the risk of detection bias. If the assessor is blinded to which participants received the exposure (eg, group status CHD versus controls, details of medical history, neuroimaging findings), and which did not, the prospects of unbiased results are significantly increased. Studies in which this is done should be rated more highly than those where it is not done, or not done adequately.	Always applies	Yes: where assessors are blinded to exposure status and or clinical history/findings or treatment allocation (in randomized trials); No: where assessors were not blinded; Cannot say: if randomization is mentioned, but method not specified.	Yes → ★; Cannot Say or No → ☆
6. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	This relates to the risk of detection bias. Blinding is not possible in many cohort studies. However, this limitation should be discussed in the study.	Always applies	Yes: where the limitations of lack of blinding was addressed in the article. Or if assessments were blinded (Yes in item 5 above); No: where lack of blinding is not discussed.	Yes → ★; No → ☆
7. The measure of assessment of exposure (severity of CHD) is reliable.	This relates to the risk of detection bias. A well conducted study should indicate how the degree of exposure or presence of prognostic factors or markers was assessed. Whatever measures are used must be sufficient to establish clearly that participants have or have not received the exposure under investigation and	Always applies	YES: where the type of CHD is clearly defined (accuracy); NO: where no detailed information is given.	YES → ★; NO → ⋆

SUPPLEMENTAL TABLE 4 Continued

Statement	What Does This Statement Mean?	When Does It Apply?	Rating Categories	Rating
	the extent of such exposure, or that they do or do not possess a particular prognostic marker or factor. Clearly described, reliable measures should increase the confidence in the quality of the study.			
8. Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	This relates to the risk of detection bias. The primary outcome measures used should be clearly stated in the study. Standardized assessment tools are used to evaluate the outcome.	Always applies	Yes: where clearly identified primary outcome measures are assessed with standardized assessment; No: where outcome measures are not defined, or nonstandardized assessments are used. Cannot say: where subjective measures are described, but no indication given of how they were validated.	Yes → ★; Cannot Say/No → ⋆
Analysis (maximum 2 stars)				
9. The main potential confounders are identified and taken into account adequately in the design and analysis[a]	Confounding is the distortion of a link between exposure and outcome by another factor that is associated with both exposure and outcome. The possible presence of confounding factors is one of the principal reasons why observational studies are not more highly rated as a source of evidence. The report of the study should indicate which potential confounders have been considered, and how they have been assessed or allowed for in the analysis. Clinical judgement should be applied to consider whether all likely confounders have been considered.[a]	Always applies	Yes: where the main potential confounders are discussed and addressed in statistical analyses (sensitivity analyses, adjustment for confounders, stratification, or matching), if possible; No: where there is no mention of confounding; Cannot say: where confounding is mentioned, but no comment on or analysis of potential impact on results.	Yes → ★; Cannot Say, Na, or No → ⋆
10. CIs are provided	Confidence limits are the preferred method for indicating the precision of statistical results, and can be used to differentiate between an inconclusive study and a study that shows no effect. Studies that report a single value with no assessment of precision should be treated with extreme caution.	Always applies	Yes; No	Yes → ★; No → ⋆

Modified from the SIGN checklist for cohort studies (https://www.sign.ac.uk/what-we-do/methodology/checklists/, accessed December 2020) and the Newcastle-Ottawa Scale for the quality of nonrandomized studies in meta-analyses (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). RCT, randomized controlled trial.

[a] In this systematic review context the following main confounders have been predefined and should be addressed: sex and socioeconomic status.

SUPPLEMENTAL TABLE 5 Results of Subgroup Comparison With ASD/VSD as a Reference Group

Subgroup	β Coefficient	SE	95% CI	*P*
Total IQ				
Intercept	98.51	2.02	94.56 to 102.47	<.0001
Mixed	−1.58	2.3	−6.09 to 2.92	.49
HLHS	−10.04	2.79	−15.5 to −4.58	.0003
TGA	3.38	2.57	−1.65 to 8.4	.19
TOF	−3.39	3.69	−10.63 to 3.85	.36
TPVR	−0.86	5.38	−11.42 to 9.69	.87
UVH	−5.87	2.66	−11.07 to −0.66	.027
Performance IQ				
Intercept	100.46	2.85	94.87 to 106.05	<.0001
Mixed	−3.82	3.32	−10.34 to 2.69	.25
HLHS	−12.12	4.11	−20.17 to −4.07	.003
TGA	0.01	3.47	−6.79 to 6.81	.9971
TOF	−0.66	5.2	−10.84 to 9.53	.90
TPVR	−3.81	5.32	−14.24 to 6.62	.47
UVH	−6.87	4.12	−14.95 to 1.21	.096