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Société Suisse de Néonatologie
Società Svizzera di Neonatologia
www.neonet.ch

Neurodevelopmental outcome of infants with congenital heart disease

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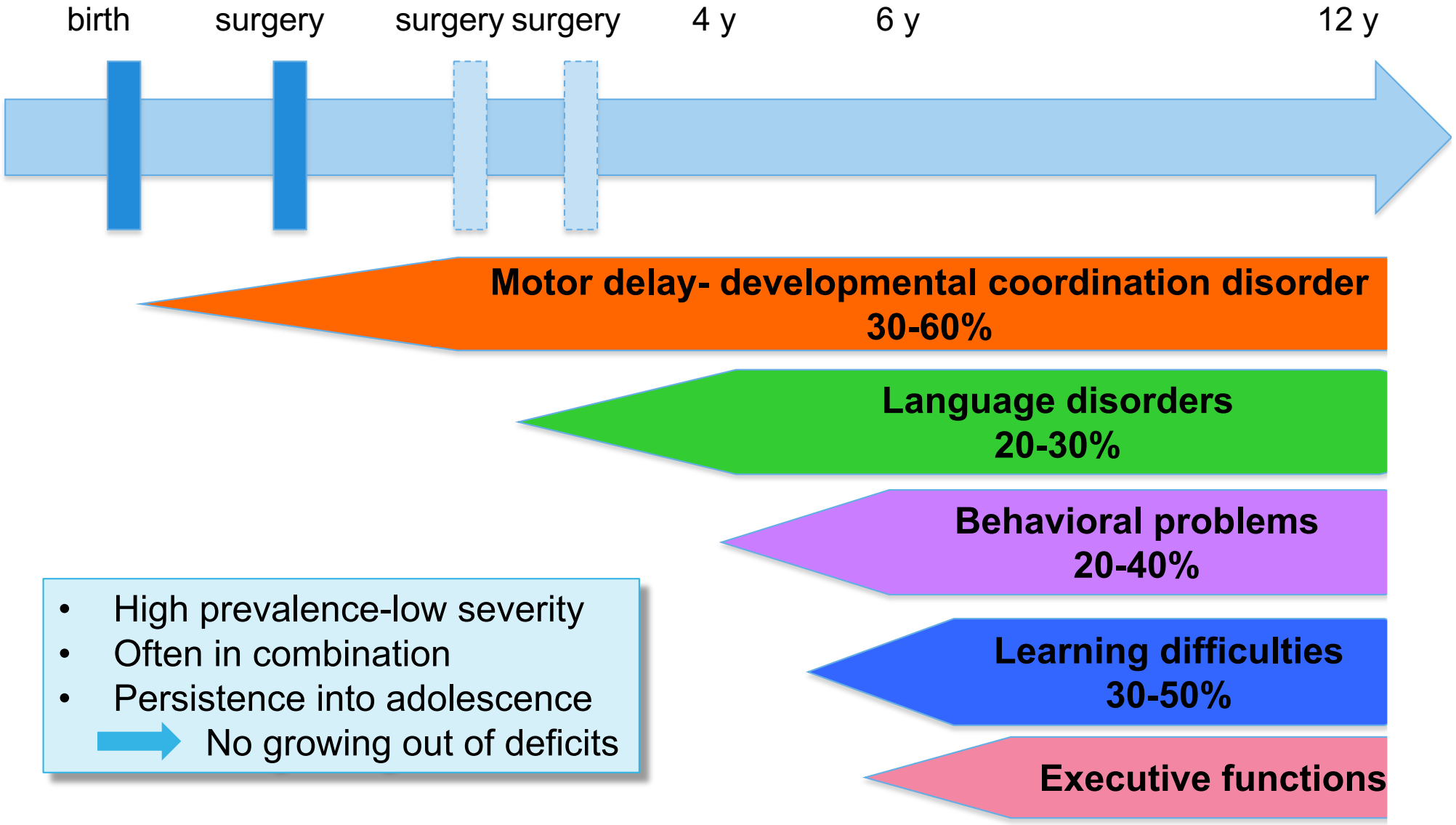
Bea Latal, Child Development Center

Annual Meeting of the SSN Biel 24.05.2022

Das Spital der Eleonorenstiftung

Outcome of children with CHD



Latal B. Clinics in Perinatology 2016

10 year outcome: REACHOUT Study

- Higher rate of ADHD, social interaction problems
- 24% combination of ADHD-related symptoms and social interaction problems
- Predictors: **lower child IQ** and **poorer maternal mental health** at 4 years of age

Werninger et al. 2020 Frontiers in Pediatrics | www.frontiersin.org

- Lower IQ and rate of regular school (82.4% versus 97%)
- Lower **socioeconomic status** and **longer hospital stay** predict IQ

Spillmann et al. 2021 Pediatric Research; https://doi.org/10.1038/s41390-021-01853-

- Higher rate of motor and visuomotor problems
- associated with more internalizing behavioral problems

Teixeira et al. Cardiology in the young 2021 : 10.1017/S1047951121004145

Combination of ADHD-related symptoms and social interaction problems

normal in all 3 behavioral outcomes	abnormal in only 1 behavioral outcome			abnormal in only 2 behavioral outcomes			abnormal in all 3 behavioral outcomes
	SDQ	SRS	Conners 3	SDQ and SRS	SDQ and Conners 3	SRS and Conners 3	
42 (47.73%)	0	7	17	1	1	11	9 (10.23%)
	24 (27.23%)			13 (14.77%)			

FIGURE 3 | Overview of parent-reported abnormal behavior across questionnaires and comorbidities ($N = 88$). In Conners-3, 43 children had 2 or more subscales scoring outside the normal range, of which 77% included the subscales "inattention" and/or "hyperactivity/impulsivity".

SDQ: strength and difficulties questionnaire
SRS: Social responsiveness scale
Conners: behavioral questionnaire

Werninger et al. 2020 Frontiers in Pediatrics | www.frontiersin.org

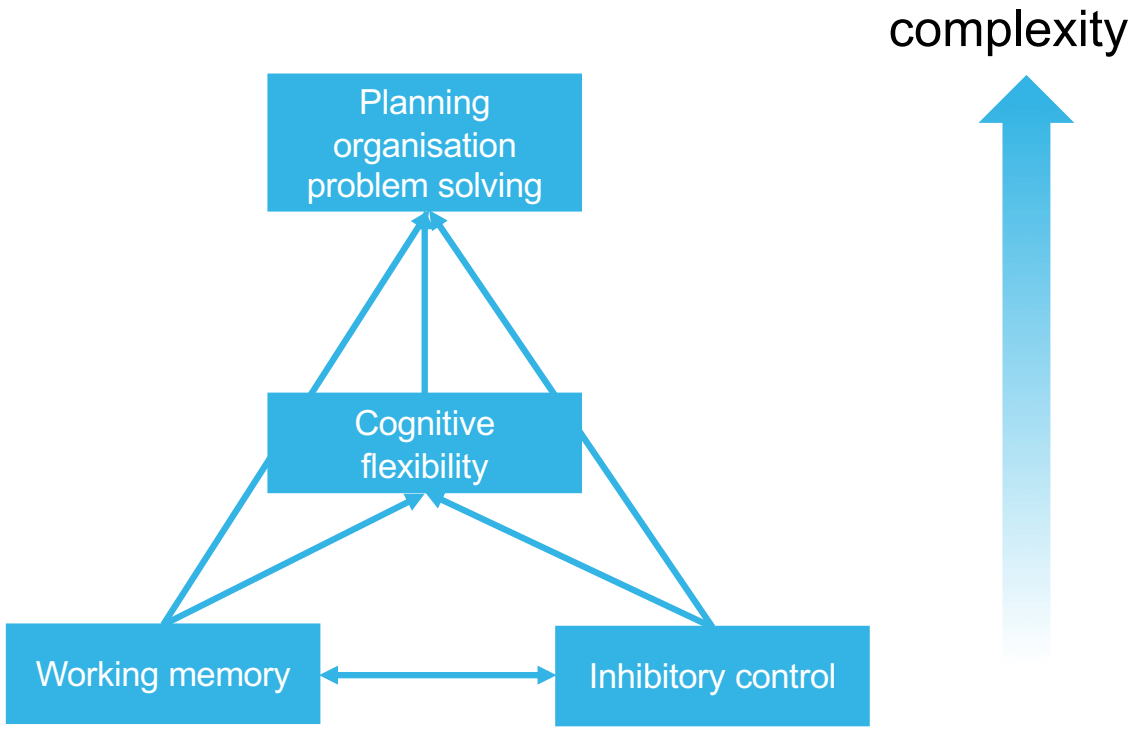
Long-term development into adolescence

- Persistent intellectual deficits
- Visual-spacial processing problems
- Language problems
- Fine motor and visuoperceptual difficulties
- Social cognition deficits

- Executive function impairment

Bellinger et al. Circulation 2011, von Rhein 2013, Schäfer et al. DMCN 2013, Cassidy et al. JINS 2017, Rollins et al. J Pediatr 2014,Bean Jaworski et al. Chid Neuropsychology 2017

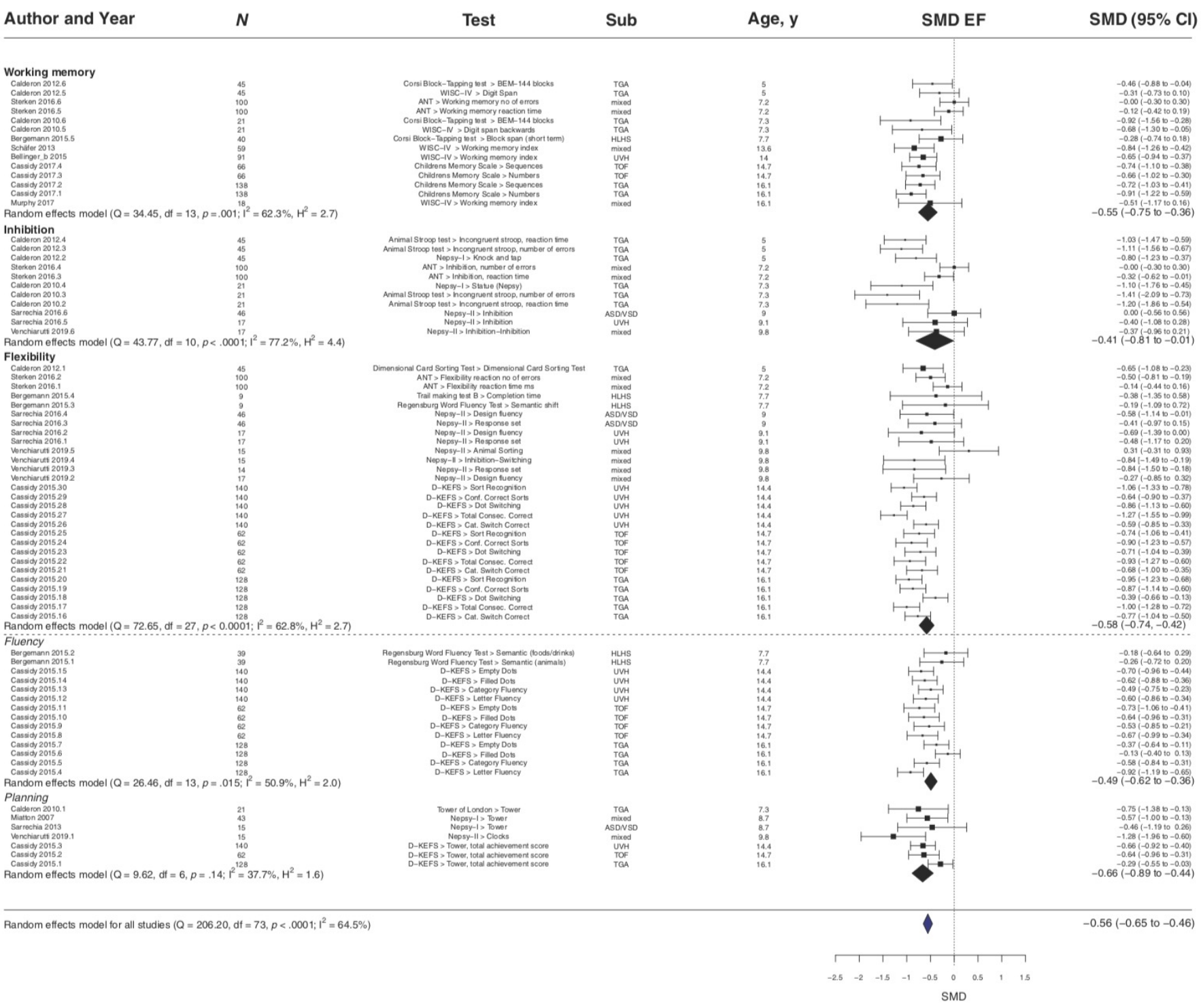
Executive function: higher order cognitive function



Cognitive and Executive Function in Congenital Heart Disease: A Meta-analysis

Maria Feldmann, MD, PhD,[a,b,*] Célina Bataillard,[a,b,*] Melanie Ehrler,[a,b] Cinzia Ullrich,[a,b] Walter Knirsch, MD,[b,e] Martina A. Gosteli-Peter, PhD,[c] Ulrike Held, PhD,[d,**] Beatrice Latal, MD, MPH[a,b,**]

Feldmann et al. Pediatrics. 2021;148(4):e2021050875

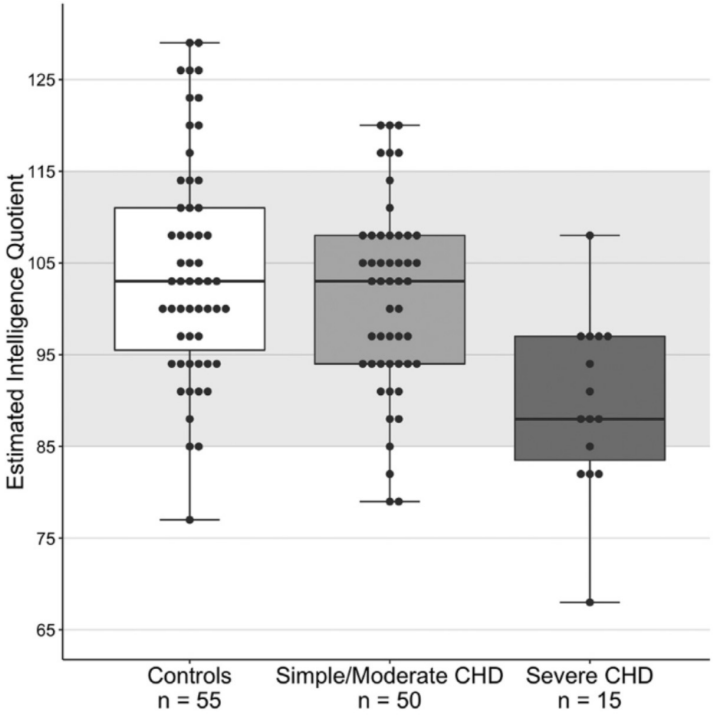

Author and Year
N
Test
Sub
Age, y
SMD EF
SMD (95% CI)
Working memory
Calderon 2012.6 45 Corsi Block–Tapping test > BEM–144 blocks TGA 5 −0.46 (−0.88 to −0.04)
Calderon 2012.5 45 WISC–IV > Digit Span TGA 5 −0.31 (−0.73 to 0.10)
Sterken 2016.6 100 ANT > Working memory no of errors mixed 7.2 −0.00 (−0.30 to 0.30)
Sterken 2016.5 100 ANT > Working memory reaction time mixed 7.2 −0.12 (−0.42 to 0.19)
Calderon 2010.6 21 Corsi Block–Tapping test > BEM–144 blocks TGA 7.3 −0.92 (−1.56 to −0.28)
Calderon 2010.5 21 WISC–IV > Digit span backwards TGA 7.3 −0.68 (−1.30 to −0.05)
Bergemann 2015.5 40 Corsi Block–Tapping test > Block span (short term) HLHS 7.7 −0.28 (−0.74 to 0.18)
Schäfer 2013 59 WISC–IV > Working memory index mixed 13.6 −0.84 (−1.26 to −0.42)
Bellinger_b 2015 91 WISC–IV > Working memory index UVH 14 −0.65 (−0.94 to −0.37)
Cassidy 2017.4 66 Childrens Memory Scale > Sequences TOF 14.7 −0.74 (−1.10 to −0.38)
Cassidy 2017.3 66 Childrens Memory Scale > Numbers TOF 14.7 −0.66 (−1.02 to −0.30)
Cassidy 2017.2 138 Childrens Memory Scale > Sequences TGA 16.1 −0.72 (−1.03 to −0.41)
Cassidy 2017.1 138 Childrens Memory Scale > Numbers TGA 16.1 −0.91 (−1.22 to −0.59)
Murphy 2017 18 WISC–IV > Working memory index mixed 16.1 −0.51 (−1.17 to 0.16)
Random effects model (Q = 34.45, df = 13, p = .001; I² = 62.3%, H² = 2.7) −0.55 (−0.75 to −0.36)
Inhibition
Calderon 2012.4 45 Animal Stroop test > Incongruent stroop, reaction time TGA 5 −1.03 (−1.47 to −0.59)
Calderon 2012.3 45 Animal Stroop test > Incongruent stroop, number of errors TGA 5 −1.11 (−1.56 to −0.67)
Calderon 2012.2 45 Nepsy–I > Knock and tap TGA 5 −0.80 (−1.23 to −0.37)
Sterken 2016.4 100 ANT > Inhibition, number of errors mixed 7.2 −0.00 (−0.30 to 0.30)
Sterken 2016.3 100 ANT > Inhibition, reaction time mixed 7.2 −0.32 (−0.62 to −0.01)
Calderon 2010.4 21 Nepsy–I > Statue (Nepsy) TGA 7.3 −1.10 (−1.76 to −0.45)
Calderon 2010.3 21 Animal Stroop test > Incongruent stroop, number of errors TGA 7.3 −1.41 (−2.09 to −0.73)
Calderon 2010.2 21 Animal Stroop test > Incongruent stroop, reaction time TGA 7.3 −1.20 (−1.86 to −0.54)
Sarrechia 2016.6 46 Nepsy–II > Inhibition ASD/VSD 9 0.00 (−0.56 to 0.56)
Sarrechia 2016.5 17 Nepsy–II > Inhibition UVH 9.1 −0.40 (−1.08 to 0.28)
Venchiaruti 2019.6 17 Nepsy–II > Inhibition–Inhibition mixed 9.8 −0.37 (−0.96 to 0.21)
Random effects model (Q = 43.77, df = 10, p < .0001; I² = 77.2%, H² = 4.4) −0.41 (−0.81 to −0.01)
Flexibility
Calderon 2012.1 45 Dimensional Card Sorting Test > Dimensional Card Sorting Test TGA 5 −0.65 (−1.08 to −0.23)
Sterken 2016.2 100 ANT > Flexibility reaction no of errors mixed 7.2 −0.50 (−0.81 to −0.19)
Sterken 2016.1 100 ANT > Flexibility reaction time ms mixed 7.2 −0.14 (−0.44 to 0.16)
Bergemann 2015.4 9 Trail making test B > Completion time HLHS 7.7 −0.38 (−1.35 to 0.58)
Bergemann 2015.3 9 Regensburg Word Fluency Test > Semantic shift HLHS 7.7 −0.19 (−1.09 to 0.72)
Sarrechia 2016.4 46 Nepsy–II > Design fluency ASD/VSD 9 −0.58 (−1.14 to −0.01)
Sarrechia 2016.3 46 Nepsy–II > Response set ASD/VSD 9 −0.41 (−0.97 to 0.15)
Sarrechia 2016.2 17 Nepsy–II > Design fluency UVH 9.1 −0.69 (−1.39 to 0.00)
Sarrechia 2016.1 17 Nepsy–II > Response set UVH 9.1 −0.48 (−1.17 to 0.20)
Venchiaruti 2019.5 15 Nepsy–II > Animal Sorting mixed 9.8 0.31 (−0.31 to 0.93)
Venchiaruti 2019.4 15 Nepsy–II > Inhibition–Switching mixed 9.8 −0.84 (−1.49 to −0.19)
Venchiaruti 2019.3 14 Nepsy–II > Response set mixed 9.8 −0.84 (−1.50 to −0.18)
Venchiaruti 2019.2 17 Nepsy–II > Design fluency mixed 9.8 −0.27 (−0.85 to 0.32)
Cassidy 2015.30 140 D–KEFS > Sort Recognition UVH 14.4 −1.06 (−1.33 to −0.78)
Cassidy 2015.29 140 D–KEFS > Conf. Correct Sorts UVH 14.4 −0.64 (−0.90 to −0.37)
Cassidy 2015.28 140 D–KEFS > Dot Switching UVH 14.4 −0.86 (−1.13 to −0.60)
Cassidy 2015.27 140 D–KEFS > Total Consec. Correct UVH 14.4 −1.27 (−1.55 to −0.99)
Cassidy 2015.26 140 D–KEFS > Cat. Switch Correct UVH 14.4 −0.59 (−0.85 to −0.33)
Cassidy 2015.25 62 D–KEFS > Sort Recognition TOF 14.7 −0.74 (−1.06 to −0.41)
Cassidy 2015.24 62 D–KEFS > Conf. Correct Sorts TOF 14.7 −0.90 (−1.23 to −0.57)
Cassidy 2015.23 62 D–KEFS > Dot Switching TOF 14.7 −0.71 (−1.04 to −0.39)
Cassidy 2015.22 62 D–KEFS > Total Consec. Correct TOF 14.7 −0.93 (−1.27 to −0.60)
Cassidy 2015.21 62 D–KEFS > Cat. Switch Correct TOF 14.7 −0.68 (−1.00 to −0.35)
Cassidy 2015.20 128 D–KEFS > Sort Recognition TGA 16.1 −0.95 (−1.23 to −0.68)
Cassidy 2015.19 128 D–KEFS > Conf. Correct Sorts TGA 16.1 −0.87 (−1.14 to −0.60)
Cassidy 2015.18 128 D–KEFS > Dot Switching TGA 16.1 −0.39 (−0.66 to −0.13)
Cassidy 2015.17 128 D–KEFS > Total Consec. Correct TGA 16.1 −1.00 (−1.28 to −0.72)
Cassidy 2015.16 128 D–KEFS > Cat. Switch Correct TGA 16.1 −0.77 (−1.04 to −0.50)
Random effects model (Q = 72.65, df = 27, p < 0.0001; I² = 62.8%, H² = 2.7) −0.58 (−0.74, −0.42)
Fluency
Bergemann 2015.2 39 Regensburg Word Fluency Test > Semantic (foods/drinks) HLHS 7.7 −0.18 (−0.64 to 0.29)
Bergemann 2015.1 39 Regensburg Word Fluency Test > Semantic (animals) HLHS 7.7 −0.26 (−0.72 to 0.20)
Cassidy 2015.15 140 D–KEFS > Empty Dots UVH 14.4 −0.70 (−0.96 to −0.44)
Cassidy 2015.14 140 D–KEFS > Filled Dots UVH 14.4 −0.62 (−0.88 to −0.36)
Cassidy 2015.13 140 D–KEFS > Category Fluency UVH 14.4 −0.49 (−0.75 to −0.23)
Cassidy 2015.12 140 D–KEFS > Letter Fluency UVH 14.4 −0.60 (−0.86 to −0.34)
Cassidy 2015.11 62 D–KEFS > Empty Dots TOF 14.7 −0.73 [−1.06 to −0.41)
Cassidy 2015.10 62 D–KEFS > Filled Dots TOF 14.7 −0.64 (−0.96 to −0.31)
Cassidy 2015.9 62 D–KEFS > Category Fluency TOF 14.7 −0.53 (−0.85 to −0.21)
Cassidy 2015.8 62 D–KEFS > Letter Fluency TOF 14.7 −0.67 (−0.99 to −0.34)
Cassidy 2015.7 128 D–KEFS > Empty Dots TGA 16.1 −0.37 (−0.64 to −0.11)
Cassidy 2015.6 128 D–KEFS > Filled Dots TGA 16.1 −0.13 (−0.40 to 0.13)
Cassidy 2015.5 128 D–KEFS > Category Fluency TGA 16.1 −0.58 (−0.84 to −0.31)
Cassidy 2015.4 128 D–KEFS > Letter Fluency TGA 16.1 −0.92 (−1.19 to −0.65)
Random effects model (Q = 26.46, df = 13, p = .015; I² = 50.9%, H² = 2.0) −0.49 (−0.62 to −0.36)
Planning
Calderon 2010.1 21 Tower of London > Tower TGA 7.3 −0.75 (−1.38 to −0.13)
Miatton 2007 43 Nepsy–I > Tower mixed 8.7 −0.57 (−1.00 to −0.13)
Sarrechia 2013 15 Nepsy–I > Tower ASD/VSD 8.7 −0.46 (−1.19 to 0.26)
Venchiaruti 2019.1 15 Nepsy–II > Clocks mixed 9.8 −1.28 (−1.96 to −0.60)
Cassidy 2015.3 140 D–KEFS > Tower, total achievement score UVH 14.4 −0.66 (−0.92 to −0.40)
Cassidy 2015.2 62 D–KEFS > Tower, total achievement score TOF 14.7 −0.64 (−0.96 to −0.31)
Cassidy 2015.1 128 D–KEFS > Tower, total achievement score TGA 16.1 −0.29 (−0.55 to −0.03)
Random effects model (Q = 9.62, df = 6, p = .14; I² = 37.7%, H² = 1.6) −0.66 (−0.89 to −0.44)
Random effects model for all studies (Q = 206.20, df = 73, p < .0001; I² = 64.5%) −0.56 (−0.65 to −0.46)
−2.5 −2 −1.5 −1 −0.5 0 0.5 1 1.5
SMD

Educational achievement and QoL in adolescence and adulthood

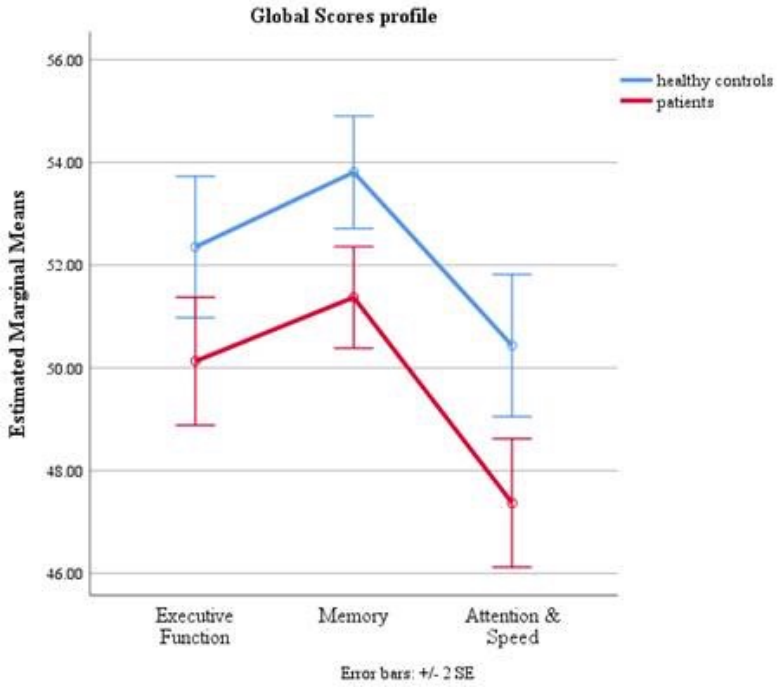
- Educational and academic achievement similar to peers or controls
  - Patients with severe CHD have lower educational achievement
- Good quality of life during adolescence and adulthood, irrespective of country
- Poorer physical quality of life in association with severe CHD

Pfitzer et al. Early Human Development 2019
Schäfer et al. Cardiology in the Young 2015
Apers und Kovacs, JACC 2016
Rometsch et al. European Heart Journal 2018

Adult outcome of patients with CHD



Kessler et al. Intern. Journal of Cardiology 2020

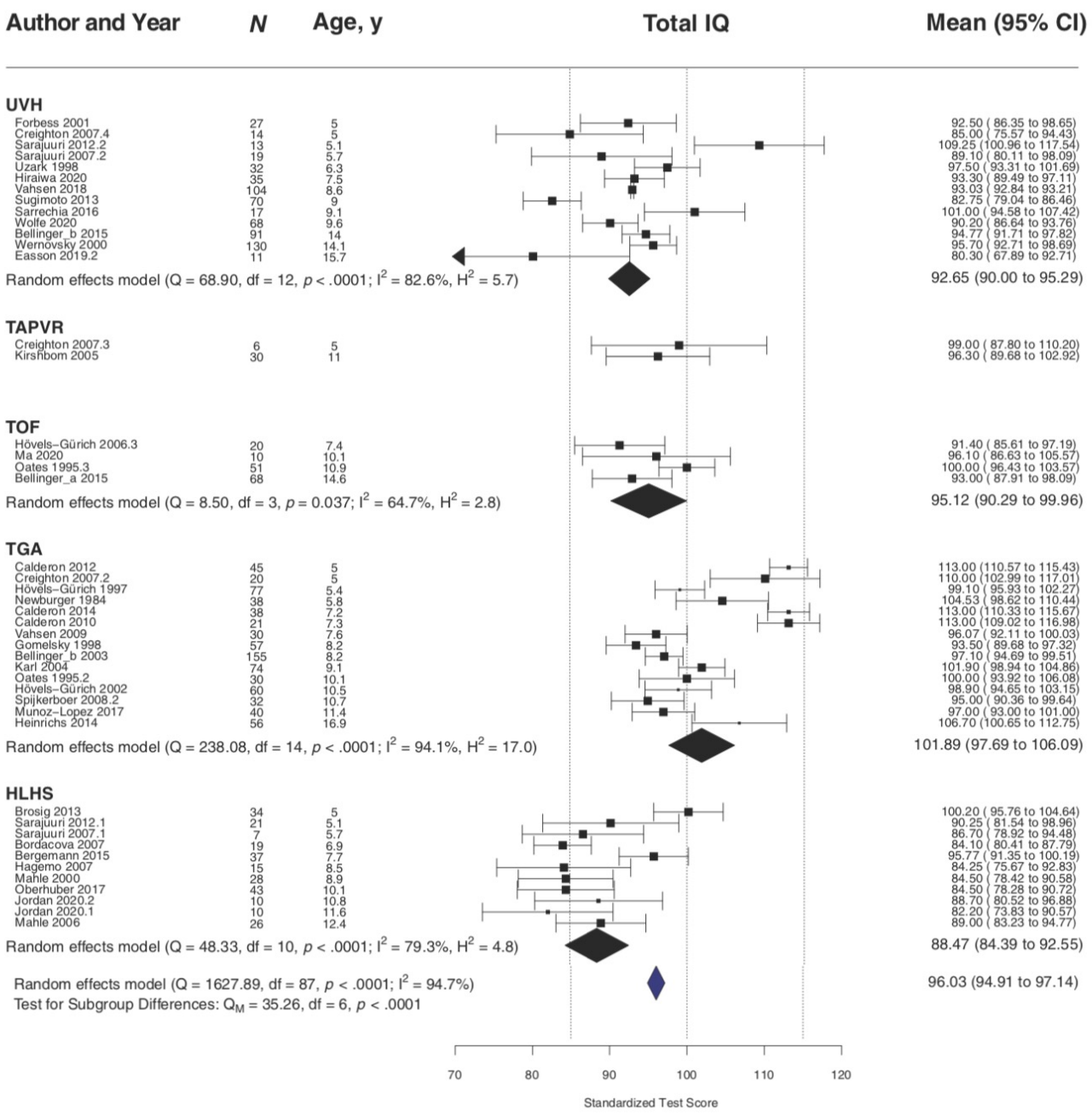


Schlosser et al. 2021 Cardiology in the Young, doi: 10.1017/S1047951121002705

Risk factors for neurodevelopmental impairments

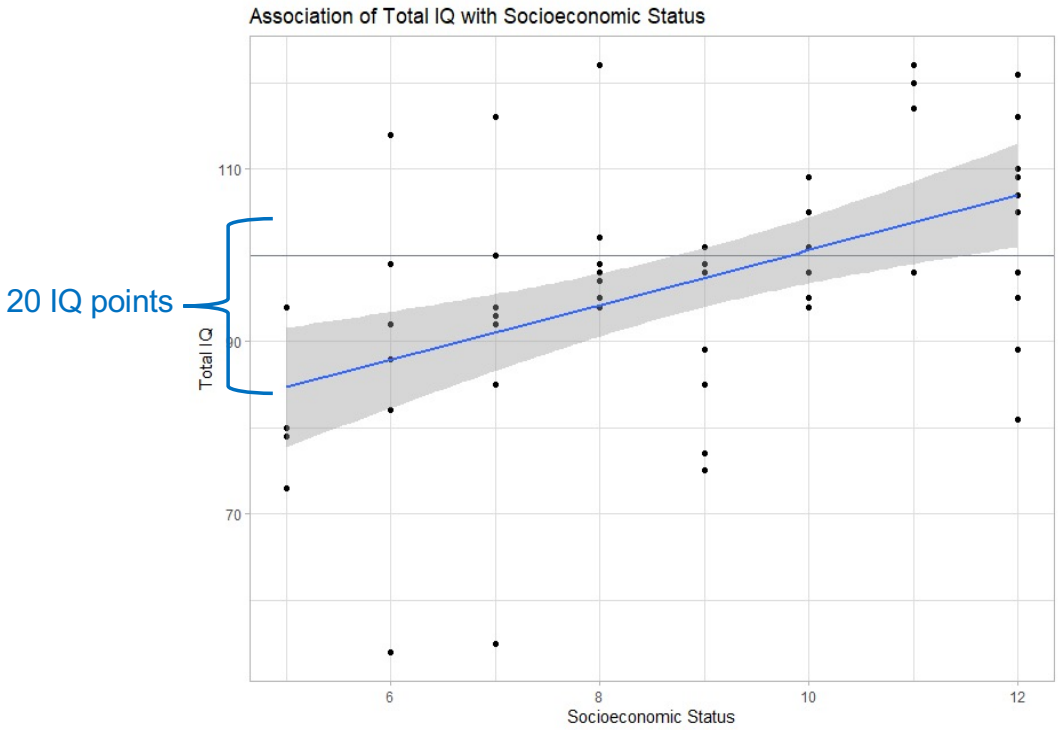
- Genetic comorbidity
- Complexity of CHD
- Lower birth weight
- Male gender
- Neonatal status at surgery
- Postoperative ECMO/VAD
- Longer lenght of hospital stay
- Lower socioeconomic status/maternal education

The International Cardiac Collaborative on Neurodevelopment. 2016:
http://dx.doi.org/10.1016/j.athoracsur.2016.05.081



Feldmann et al. Pediatrics. 2021;148(4):e2021050875

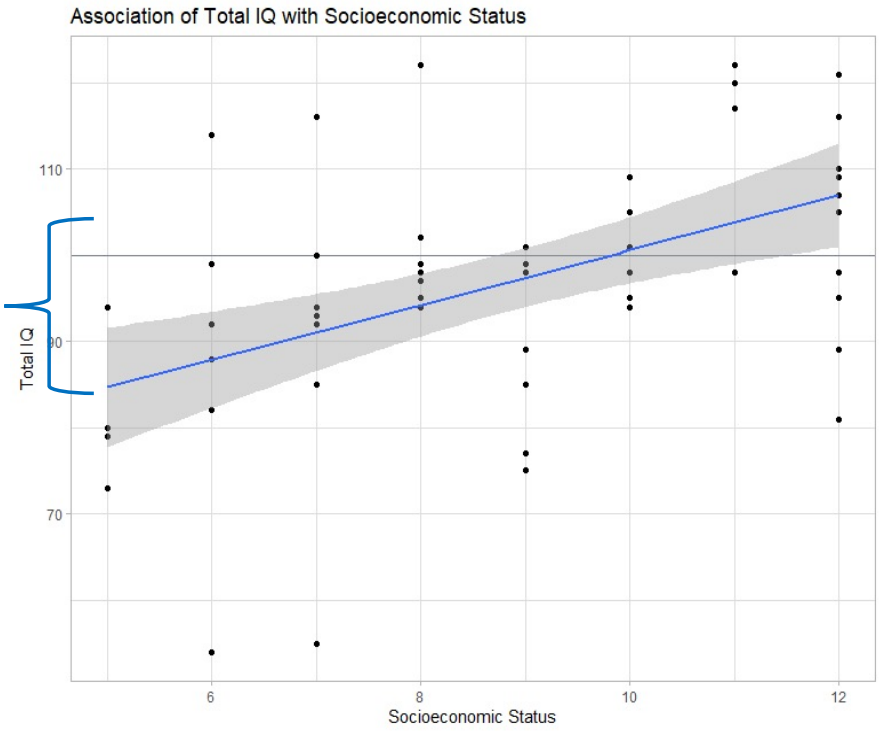
Socioeconomic status and IQ

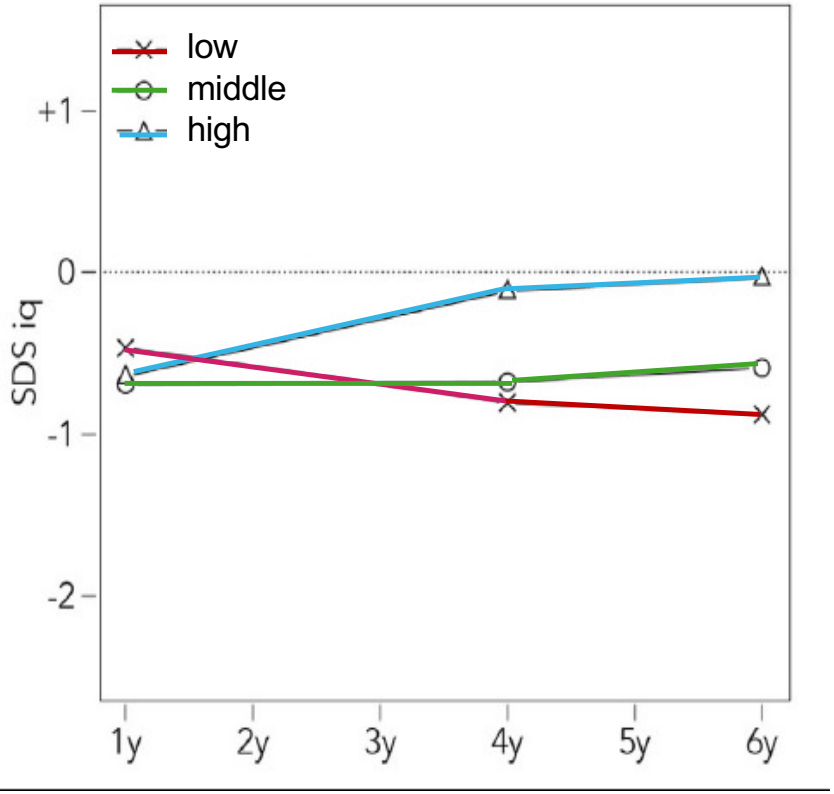


Neukomm A, et al. under review J Pediatr

Socioeconomic status and IQ

20 IQ points

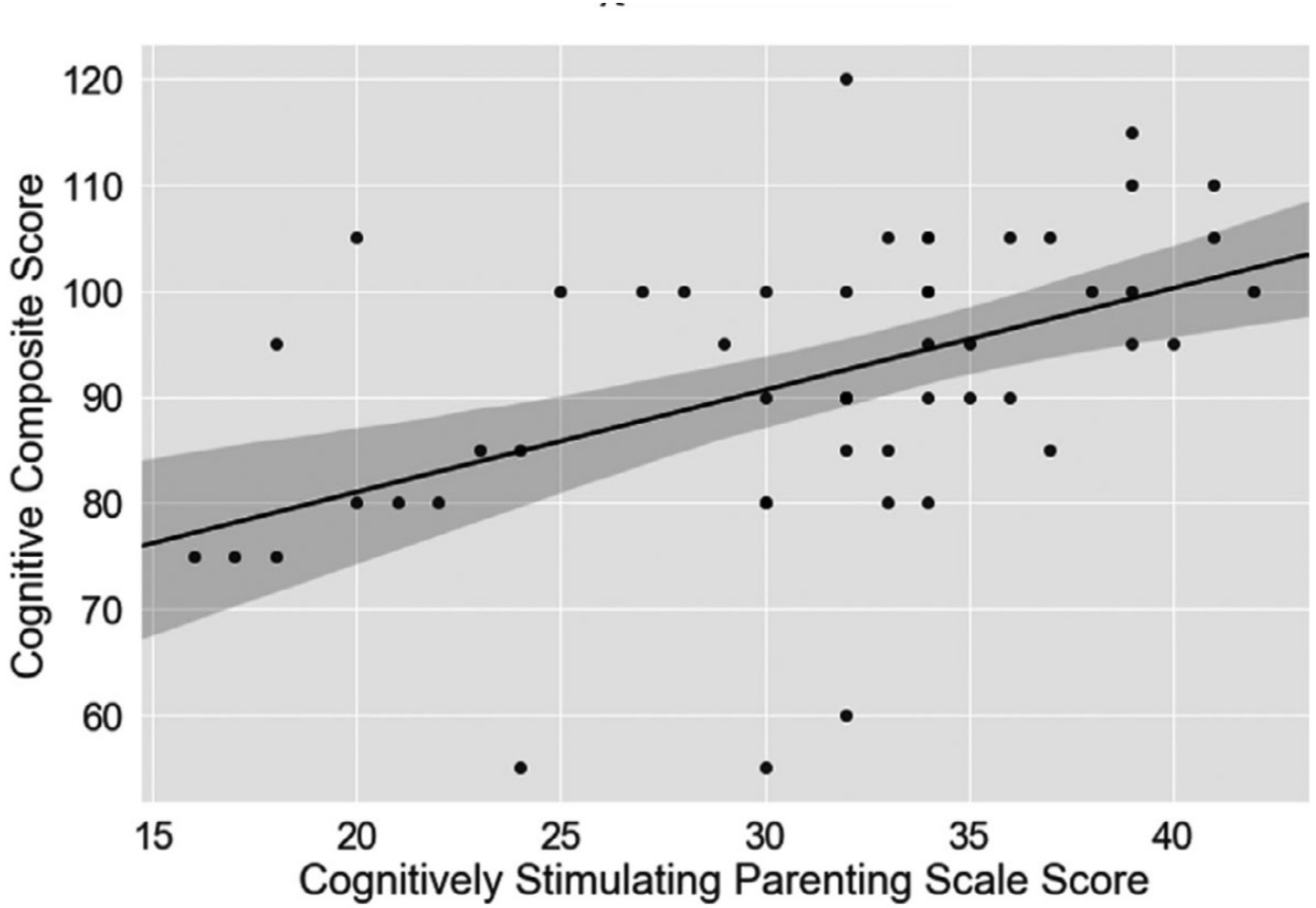




Neukomm A, et al. under review J Pediatr

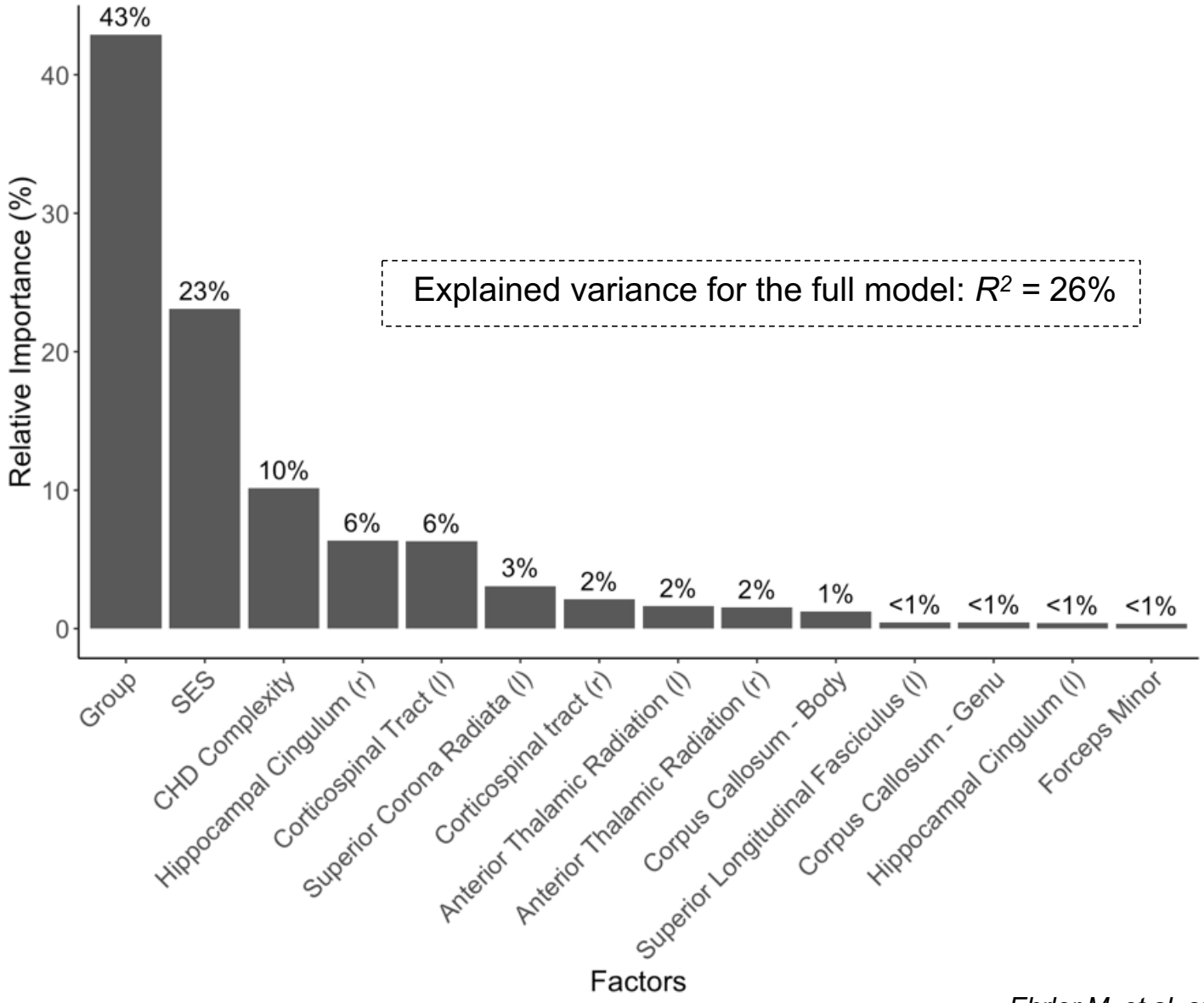
Naef et al. Journal of Pediatrics 2019

Socially stimulating parental environment and IQ



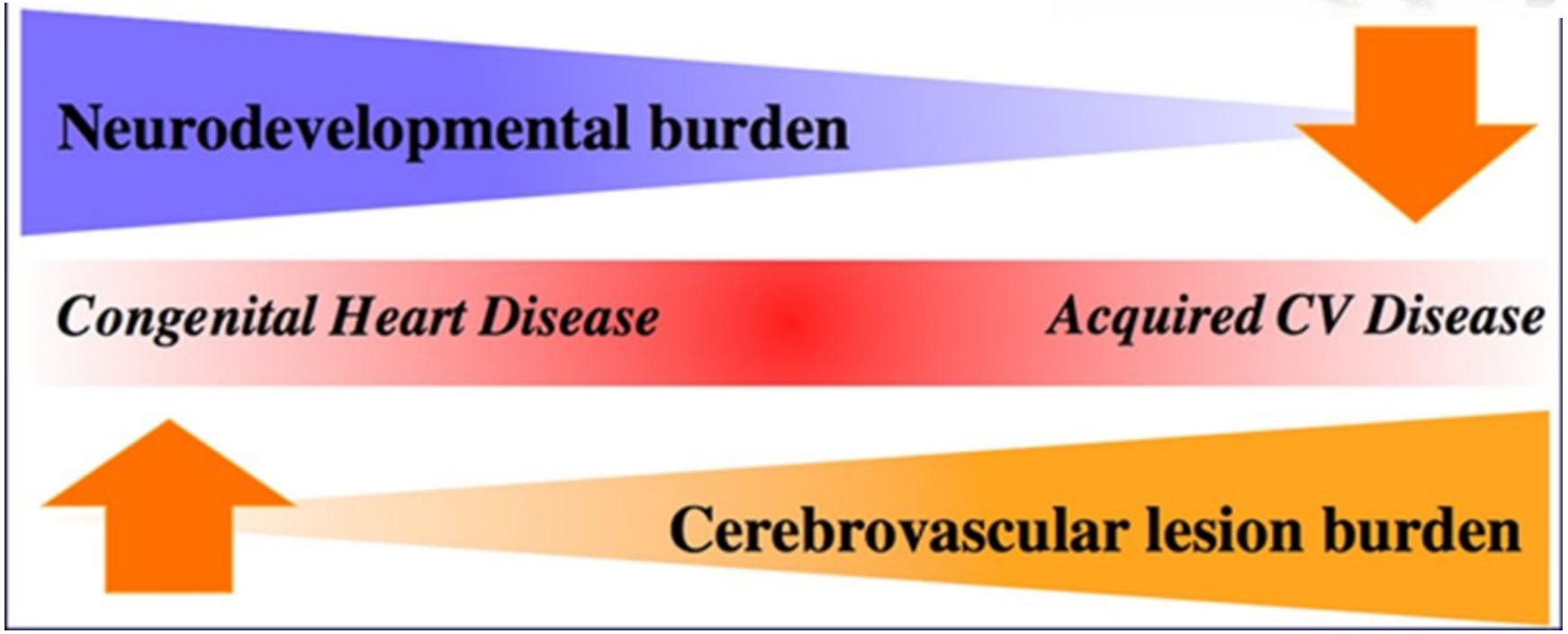
Bonthrone A, et al. Infancy. 2020;26:184–199

EF composite score across childhood and adulthood (9-32 years)



Ehrler M. et al. submitted

Congenital heart disease is a chronic cardiac and neurological disorder



Ariane Marelli et al. Circulation. 2016;133:1951-1962

Implications for health care providers: Follow-up programs and register

- Early detection of neurodevelopmental impairments allows for early intervention in the respective developmental domain
- Quality control and potential for improvement
- Parental counselling and guidance
- Anticipating of neurodevelopmental difficulties

Cardiology in the Young

cambridge.org/cty

Original Article

Cite this article: Ware J, Butcher JL, Latal B, Sadhwani A, Rollins CK, Brosig Soto CL, Butler SC, Eiler-Sims PB, Ullman Shade CV, and Wernovsky G (2020) Neurodevelopmental evaluation strategies for children with congenital heart disease aged birth through 5 years: recommendations from the cardiac

Neurodevelopmental evaluation strategies for children with congenital heart disease aged birth through 5 years: recommendations from the cardiac neurodevelopmental outcome collaborative

Janice Ware[1], Jennifer L. Butcher[2], Beatrice Latal[3,4], Anjali Sadhwani[5], Caitlin K. Rollins[6], Cheryl L. Brosig Soto[7], Samantha C. Butler[5], Patricia B. Eiler-Sims[8], Catherine V. Ullman Shade[9] and Gil Wernovsky[10,11,12]

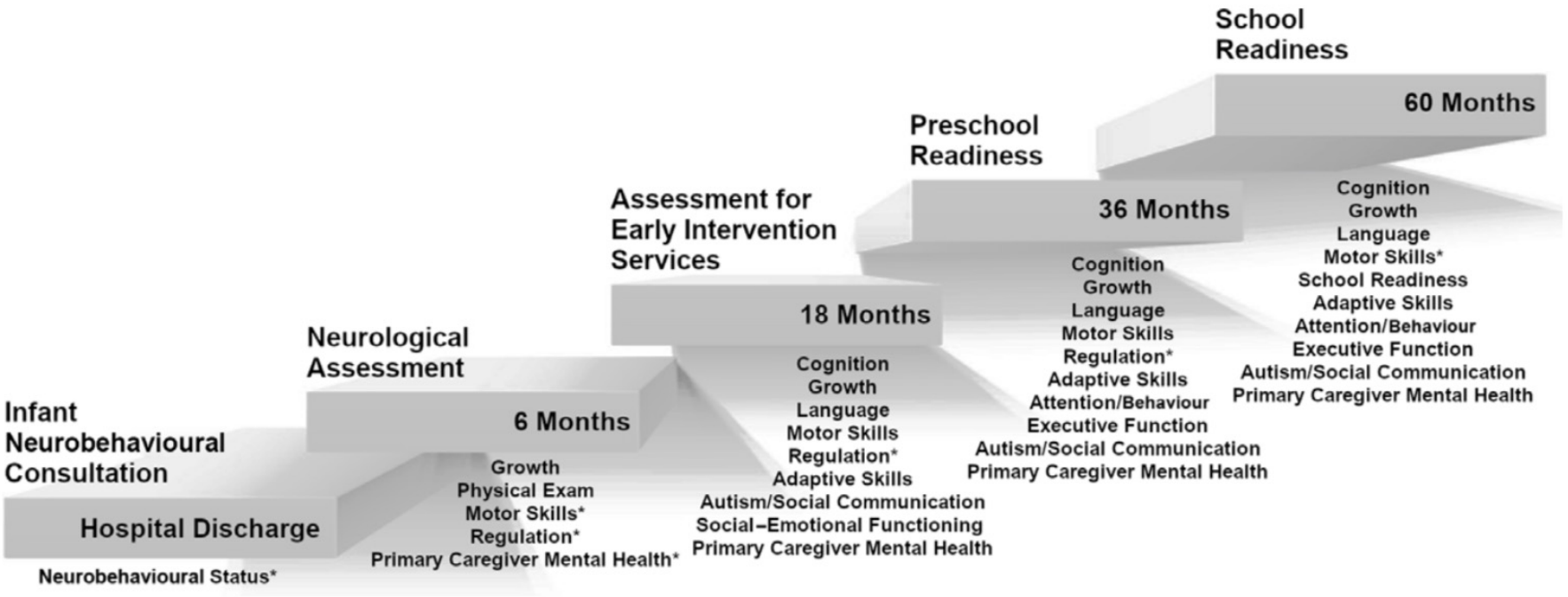


Figure 1. Congenital heart disease neurodevelopmental assessment domains for birth through 5 years of age.
*Denotes extended battery

Which?

Table 3. Categories of Pediatric CHD Patients at High Risk for Developmental Disorders or Disabilities

1. Neonates or infants requiring open heart surgery (cyanotic and acyanotic types), for example, HLHS, IAA, PA/IVS, TA, TAPVC, TGA, TOF, tricuspid atresia.
2. Children with other cyanotic heart lesions not requiring open heart surgery during the neonatal or infant period, for example, TOF with PA and MAPCA(s), TOF with shunt without use of CPB, Ebstein anomaly. Hybrid approach
3. Any combination of CHD and the following comorbidities:
   - 3.1. Prematurity (<37 wk)
   - 3.2. Developmental delay recognized in infancy
   - 3.3. Suspected genetic abnormality or syndrome associated with DD
   - 3.4. History of mechanical support (ECMO or VAD use)
   - 3.5. Heart transplantation
   - 3.6. Cardiopulmonary resuscitation at any point
   - 3.7. Prolonged hospitalization (postoperative LOS >2-wk in the hospital)
   - 3.8. Perioperative seizures related to CHD surgery
   - 3.9. Significant abnormalities on neuroimaging or microcephaly*
4. Other conditions determined at the discretion of the medical home providers

Circulation. 2012;126:1143-1172

Switzerland:

Swiss Orchid
Swiss neurodevelopmental Outcome Registry for CHIldren with severe congenital heart Disease

Infants with CHD undergoing cardiac intervention within the first 6 weeks of life

Natterer et al. A national neurodevelopmental Outcome Registry for CHIldren with severe congenital heart Disease (ORCHID) in Switzerland – framework, regulations and implementation, under revisions Swiss Medical Weekly

Summary

Increased risk for neurodevelopmental impairment in children with CHD

Highest risk: severity of CHD, genetic comorbidities, low SES

Persistence into adolescence and adulthood

Problems may become apparent at school-age or later

Standardized FU programs necessary for quality control and improvement