Title: Reduced cerebrovascular reactivity in youth with complex congenital heart defects

Short title: Cerebrovascular health in congenital heart defects

Claudine J. Gauthier[1,2,3], Zacharie Potvin-Jutras[1,2,3], Safa Sanami[1,2,3,4], Kaitlyn Easson[5,], Guillaume Gilbert[7], Christine Saint-Martin[8], Marie Brossard-Racine[5,6,9,10]

1. Physics Department, Concordia University, Montreal, QC, Canada, 2. Montreal Heart Institute, Montreal, QC, Canada, 3. School of Health, Concordia University, Montreal, QC, Canada, 4. Medical Physics, McGill University, Montreal, Quebec, Canada, 5. Advances in Brain & Child Development (ABCD) Research Laboratory Research Institute of the McGill University, Health Centre, Montreal, QC, Canada, 6. Department of Neurology & Neurosurgery, Faculty of Medicine & Health Sciences McGill University, Montreal, QC, Canada, 7. MR Clinical Science Philips Healthcare, Mississauga, ON, Canada, 8. Department of Medical Imaging Montreal Children's Hospital Montreal, Division of Pediatric Radiology, Montreal, QC, Canada, 9. Division of Neonatology, Department of Pediatrics Montreal Children's Hospital, Montreal, QC, Canada, 10. School of Physical & Occupational Therapy, Faculty of Medicine and Health Sciences McGill University, Montreal, QC, Canada

Abstract

Aims: Congenital heart defects (CHD) are the most common neonatal malformations. Neonates with complex CHD present with cerebrovascular dysfunction, including deficits in cerebrovascular reactivity (CVR), a measure of vascular reserve. However, it is unknown whether these deficits persist beyond the perioperative period.

Methods and Results: Here, we compared CVR between 53 youth with CHD and 54 age-matched controls without CHD. CVR was derived using a novel approach based on resting state blood oxygen-level dependent magnetic resonance imaging. We found that youth with CHD present with relative CVR deficits in the whole gray matter and in the anterior cerebral artery territory when compared to controls. Sex differences were identified in the middle cerebral artery territory, with females having lower relative CVR than males in the CHD group. Greater CVR deficits were observed in individuals with single-ventricle as compared to participants with a two-ventricle physiology. Finally, in the CHD group, a lower CVR was found to be associated with reduced performance on the Metacognitive Abilities Index of the BRIEF-A.

Conclusion: These results indicate that cerebrovascular deficits in CHD survivors persistent into young adulthood and that CVR offers great promise as a biomarker of cerebrovascular health which could be targeted in future interventions.

Word count: 5975

1. Introduction

Congenital heart defects (CHD) are the most common neonatal malformations, affecting 1% of births in Canada[1]. To survive, neonates with complex CHD undergo open-heart surgery using cardiopulmonary bypass during the first weeks of life. Improvements in clinical care have greatly increased survival, and more than 90% of neonates with CHD now survive well into adulthood, converting this primarily pediatric condition into an adult chronic condition[2].

Neonates with CHD present with cerebrovascular dysfunction, as evidenced by reduced cerebral blood flow (CBF) before surgery[3–5]. Previous work has shown that these deficits persist, with female youth with CHD having lower CBF compared to healthy peers[6]. While CBF reflects the amount of blood going to tissue at rest, it is not a measure of vascular reserve, or the ability of blood vessels to meet additional demand. Vascular reserve can be measured as cerebrovascular reactivity (CVR), which reflects vasodilation amplitude in response to CO_2 inhalation. This is analogous to a cardiac stress test and captures vasodilatory capacity. CVR deficits have been reported in young infants with CHD[7,8], but no study to date has investigated CVR beyond the first three years of life in this group. This may be partly due to the discomfort and anxiogenic effects of CO_2 inhalation. However, recent work established that CVR can also be extracted accurately from resting-state functional MRI data[9,10], making CVR measurements in CHD accessible for the first time.

During childhood, more than 60% of individuals with CHD present with developmental challenges[11–13] and more than 40% of adolescents and adults with CHD present with cognitive deficits[14–17]. Executive functions (EFs) refer to a group of higher-order cognitive processes such as working memory, cognitive flexibility and inhibition controls. Deficits in EF have been described as the hallmark cognitive challenge experienced by CHD survivors[15,18]. These deficits have been linked to lower academic achievement, quality of life and employment rates in this population[19–21]. While a range of EFs are affected in CHD, metacognitive abilities may be especially vulnerable, especially later in development[21]. Moreover, adults with CHD are at higher risk of cognitive decline as they age[14,22,23], with a 2.6 increased risk for early dementia[22,23]. Given ongoing work showing that CVR may be one of the earliest detectable biomarkers in the pathophysiological process of dementia[24–27], especially in populations with vascular risk, CVR may be a valuable biomarker of cognitive decline in CHD survivors.

To address these gaps in our understanding of cerebrovascular health in CHD, this study compared CVR between youth with CHD and healthy peers and assessed the presence of sex-specific effects given our previous findings in this group. We also aimed to explore the functional impact of CVR deficits by evaluating the associations between CVR and EF in individuals with CHD as well as examining their relationships with clinical risk factors.

2. Methods

2.1 Participants

This cross-sectional study included 53 youth with CHD (25 males & 28 females) and 54 age-matched controls (22 males & 32 females), aged between 16 and 24 years. Individuals with CHD all underwent open-heart surgery using cardiopulmonary bypass before two years of age. Participants were ineligible if they had contraindications for MRI or could not communicate in French or English. Additional exclusion criteria included a history of brain tumors, severe brain anomaly, congenital infections, multisystem dysmorphic conditions, traumatic brain injury, cerebral palsy, or an identified genetic disorder. Written informed consent was obtained from participants aged 18 and older. For those under 18, both the participant and their legal guardians provided written informed consent. This study was approved by the Pediatric Research Ethics Board of the McGill University Health Centre. Individual and clinical information were collected through medical chart review and questionnaires. The family's socio-economic status was determined using the Hollingshead index[28].

2.2 MRI Acquisition

Whole-brain MRI data were acquired on a 3T Philips Achieva X using a 32-channel head coil. Resting state blood oxygenation level-dependent (BOLD) fMRI data were acquired using a T2*-weighted gradient echo echo planar sequence (repetition time = 2.6 seconds, echo time = 30 ms, resolution = 3 mm isotropic, volumes = 200) for the relative CVR analysis. Additionally, a T1-weighted image was collected using a turbo field echo pulse sequence (repetition time = 8.1 ms, echo time = 2.7 ms, inversion time = 1010 ms, flip angle = 8°, resolution = 1 mm isotropic). The MRIs were reviewed for anomalies by a neuroradiologist, who was blinded to participants' medical histories.

2.3 Image Processing

All images underwent visual quality assessment and only images of sufficient quality underwent pre- and post-processing. The resting-state fMRI BOLD images were preprocessed using Statistical Parametric Mapping (SPM12), FMRIB's software library (FSL)[29] and nilearn (*https://nilearn.github.io/stable/index.htm*l). The BOLD images were corrected for motion artifacts using the *Realign* function in SPM12, followed by skull stripping with FSL's *Brain Extraction Tool*[30]. Slice timing correction was then performed using SPM12's *Slice Timing* function. Finally, spatial smoothing (FWHM = 6 mm) was performed using *smooth_img* from nilearn. Time domain filtering was omitted from the preprocessing pipeline, as the lower frequency components of the BOLD signal were essential for the relative CVR analysis.

2.4 Relative CVR Analysis

Relative CVR maps were measured from preprocessed resting-state BOLD fMRI data[9]. Initially, BOLD images were low-pass filtered (0-0.1164Hz) using *scipy.signal*[31] to extract a proxy for

natural cerebral CO_2 fluctuations[32]. The filtered BOLD signal was then used as a regressor in a general linear model to compute CVR indices, which were subsequently normalized by the whole-brain average CVR. The processing pipeline for relative CVR from preprocessed BOLD data is displayed in ***Figure 1***. Relative CVR maps were registered to MNI-152 space using Advanced Normalization Tools (*https://github.com/ANTsX/ANTs*). A gray matter (GM) mask, segmented from the MNI-152 template using FSL FAST[33], was applied to the registered relative CVR maps. Because cerebrovascular properties are likely to be determined by vascular territory rather than GM-based anatomical boundaries, a cerebral arterial territory atlas was employed to extract regions of interest (ROIs) in the anterior cerebral artery (ACA), the middle cerebral artery (MCA) and posterior cerebral artery (PCA) territories[34].

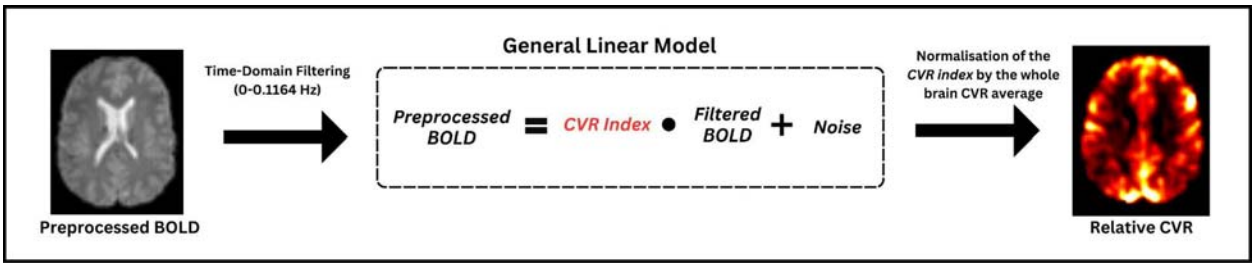

Figure 1.
Relative CVR pipeline from preprocessed resting state fMRI BOLD data.

2.5 Cognitive Assessment (BRIEF-A)

The Behaviour Rating Inventory of Executive Function - Adult scale (BRIEF-A) is a self-report questionnaire designed to assess EF as manifested in everyday life[35]. The BRIEF-A provides a Global Executive Score, which is the sum of the Behavioural Regulation Index and the Metacognition Index. The specific subscales included in the Behavioural Regulation Index are: inhibition, task shifting, emotional control and self-monitoring. While the Metacognition Index includes initiation, working memory, planning and organization, task monitoring and organization of materials subscales. Scores are reported as T-scores, where higher values reflect poorer executive function[36].

2.6 Statistical Analysis

Normality of the data was assessed using the Shapiro-Wilk test, and relative CVR values were log-transformed to achieve a normal distribution. Group differences in descriptive statistics were evaluated using ANCOVA analyses to compare individuals with CHD and controls, controlling for age and sex for all comparisons except for the age, which was only controlled for sex. These analyses examined differences in education (ordinal), socioeconomic status (SES), and the BRIEF-A summary scales. Sex distribution differences were assessed with a binomial regression, controlling for age. Additionally, group differences in relative CVR were assessed across the whole GM and cerebral arterial territories (ACA, MCA, PCA). Binomial regression

was conducted to examine group differences in the sex distribution. To investigate sex differences, ANCOVA analyses were conducted in each group to assess the relationship between sex and relative CVR across the whole GM and ROIs, controlling for age. To assess the effect of severity, we performed ANCOVA analyses to examine the effects of the type of cardiac physiology on relative CVR in individuals with CHD, controlling for age and sex. Additionally, we used multiple linear regression analyses to assess the effects of the number of surgeries on CVR, controlling for age and sex. Lastly, to evaluate the interaction between relative CVR and group on executive function, multiple linear regression analyses were performed controlling for age, sex and SES. Analyses were corrected for multiple comparisons using the false discovery rate (FDR) Benjamini-Hochberg method.

3. Results

3.1 Participant's characteristics

Two subjects (one CHD & one control) were excluded due to poor data quality, resulting in a final sample of 52 CHD and 53 controls. The sex specific distribution of cardiac physiology is presented in **Table 1**.

Table 1:

Cardiac physiology characteristics (n=52)		
Single-Ventricle Physiology (n = 7)		
	Females (n = 4)	Males (n = 3)
DILV, n (%)	1 (14)	1 (14)
Tricuspid Atresia, n (%)	1 (14)	1 (14)
PA-IVS, n (%)	1 (14)	0 (0)
HLHS, n (%)	1 (14)	1 (14)
Double-Ventricle Physiology (n = 45)		
	Females (n = 24)	Males (n = 21)
ToF, n (%)	6 (13)	7 (16)
d-TGA, n (%)	10 (22)	8 (18)
VSD, n (%)	2 (4)	3 (7)
Trunctus arteriosus type 1, n (%)	1 (2)	1 (2)
PA-IVS, n (%)	1 (2)	1 (2)
DORV, n (%)	2 (4)	0 (0)

TAPVC, n (%)	2 (4)	0 (0)
COA, n (%)	0 (0)	1 (2)
Number of Open Heart Surgeries (n = 52)		
	Females (n = 28)	Males (n = 24)
1, n (%)	17 (33)	12 (23)
2, n (%)	6 (12)	8 (15)
3, n (%)	4 (8)	2 (4)
4, n (%)	1 (2)	2 (4)

CHD = Congenital Heart Defect; ToF = Tetralogy of Fallot; DILV = Double Inlet Left Ventricle; PA-IVS = Pulmonary Atresia with Intact Ventricular Septum; d-TGA = dextro-Transposition of the great arteries; VSD = Ventricular septal defect; DORV = Double outlet right ventricle; TAPVC = Total Anomalous Pulmonary Venous Connection; COA = Coarctation of the Aorta

Group comparisons of the demographic information and BRIEF-A results are presented in **Table 2**. Three subjects (two participants with CHD and one control) had missing data on the BRIEF-A and were excluded from the analyses. Overall, youth with CHD had significantly lower educational attainment than controls at the time of the study ($p < 0.001$; $n^2p = 0.363$) and lower socioeconomic status ($p < 0.001$; $n^2p = 0.192$), while all other variables, including all BRIEF-A scores, did not differ between groups when taking into account age and sex.

Table 2:

Demographic	**CHD (n = 52)**	**Controls (n = 53)**	**p-values**
Age (years)	19.96 ± 2.39	20.46 ± 2.30	0.263
Sex (Females/Males)	28 / 24	32 / 21	0.471
Participant's Education (n; 2/3/4/5)	**(12/10/22/7)**	**(2/0/13/38)**	**< 0.001**
Hollingshead SES Index	**40.19 ± 11.37**	**50.19 ± 10.32**	**< 0.001**
BRIEF-A scores			

Global Executive (T-score)	55.47 ± 11.36	49.42 ± 8.33	0.232
Metacognition Index (T-score)	55.90 ± 10.64	50.25 ± 8.85	0.195
Behavioural Regulation Index (T-score)	54.10 ± 11.98	48.73 ± 8.76	0.521

CHD = Congenital Heart Defect; SES = Socioeconomic Status; Education is coded as 1 = elementary school, 2 = high school, 3 = professional school, 4 = CEGEP/College, 5 = University

3.2 Lower CVR in CHD

Participants with CHD revealed significantly lower relative CVR compared to controls in the whole GM ($p = 0.024$; $n^2p = 0.050$) and the ACA territory ($p = 0.030$; $n^2p = 0.046$) (**Figure 2**). No other significant regional differences were found, and the complete results are presented in **Table S1**.

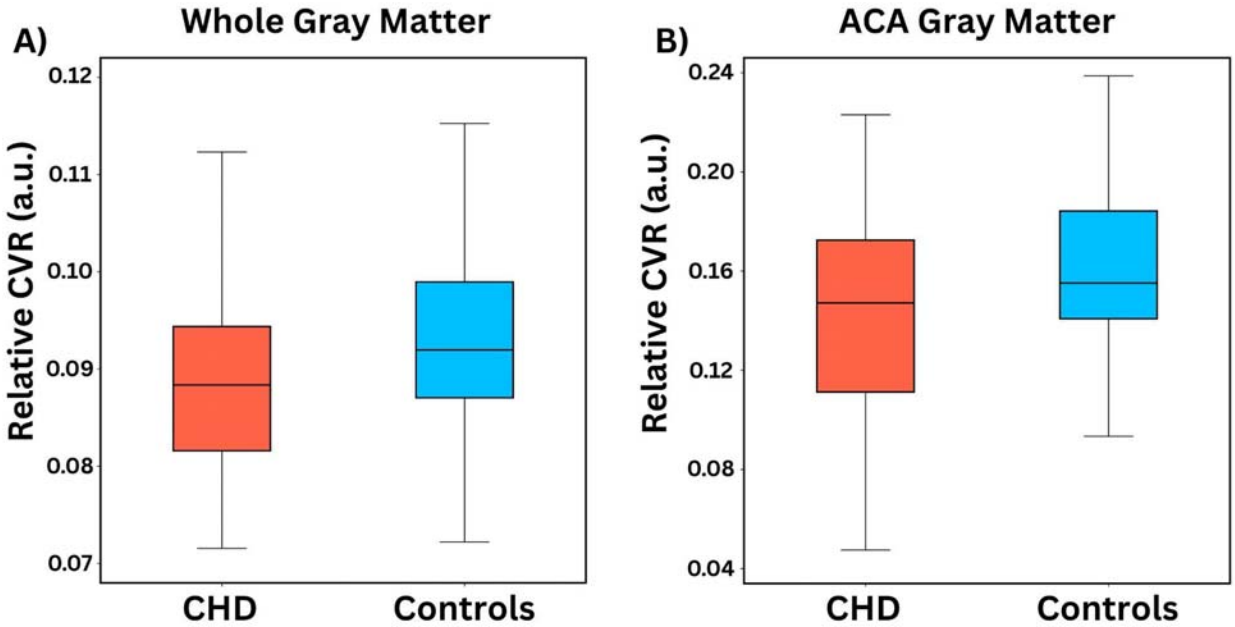

Figure 2. Relative CVR group differences between individuals with CHD and controls
Box plots from ANCOVA analyses showing the significant relative CVR group differences between individuals with CHD and controls in the A) whole gray matter and B) ACA gray matter territory.

3.3 Lower CVR in females with CHD

In the CHD group, relative CVR was significantly lower in females with CHD compared to males with CHD in the MCA territory ($p = 0.005$; $n^2p = 0.152$) (**Figure 3**). No significant sex differences in relative CVR were found among controls. See **Table S2** for complete results.

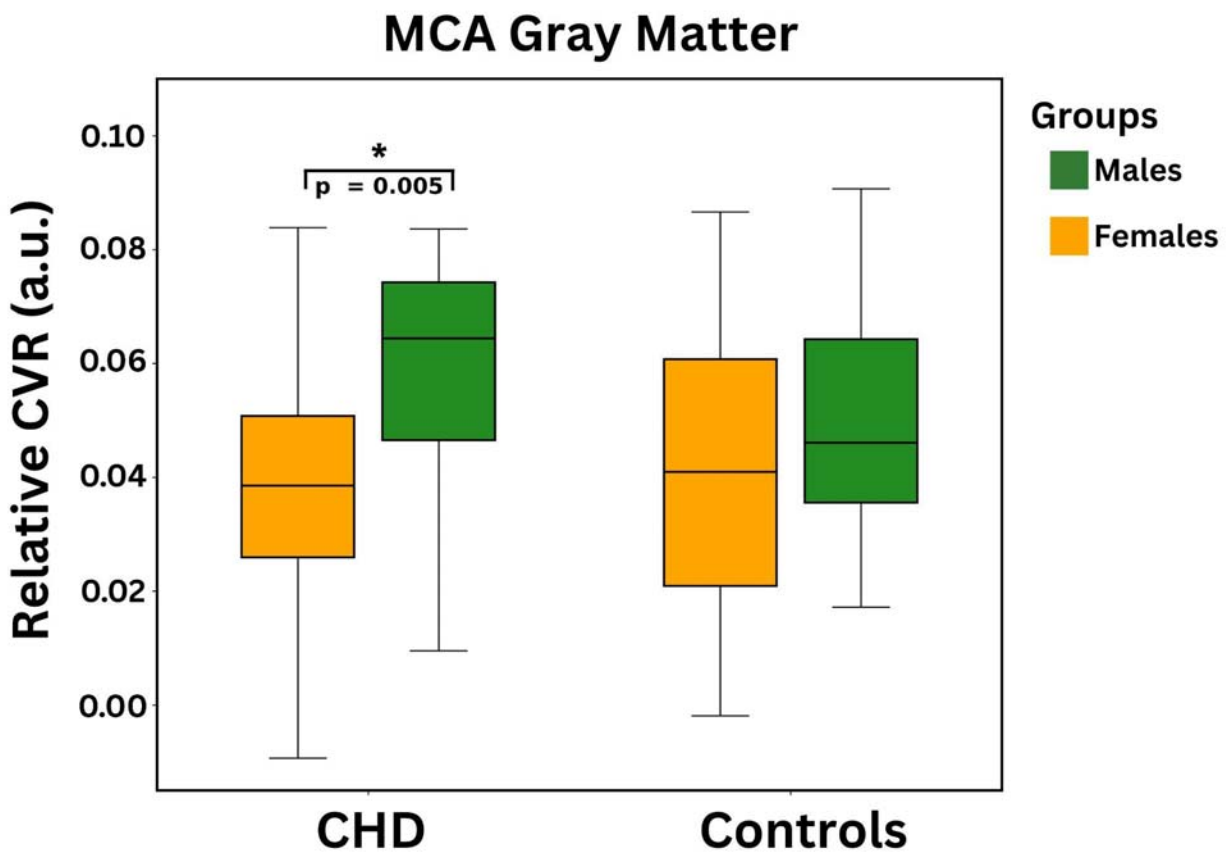

Figure 3. Relative CVR group difference between males and females with CHD
Box plots from ANCOVA analyses presenting significantly higher relative CVR in males with CHD compared to females with CHD in the MCA GM territory. The p-value shown was FDR corrected.

3.4 Lower CVR in single ventricle physiology

Individuals with a single-ventricle cardiac physiology demonstrated significantly lower relative CVR in the ACA territory ($p = 0.006$; $n^2p = 0.145$) (**Figure 4**) compared to individuals with two-ventricle CHD. No other significant associations were found, and full results are presented in Table S3). Additionally, no significant effects in the relationship between relative CVR and the number of open-heart surgeries were observed (Table S4).

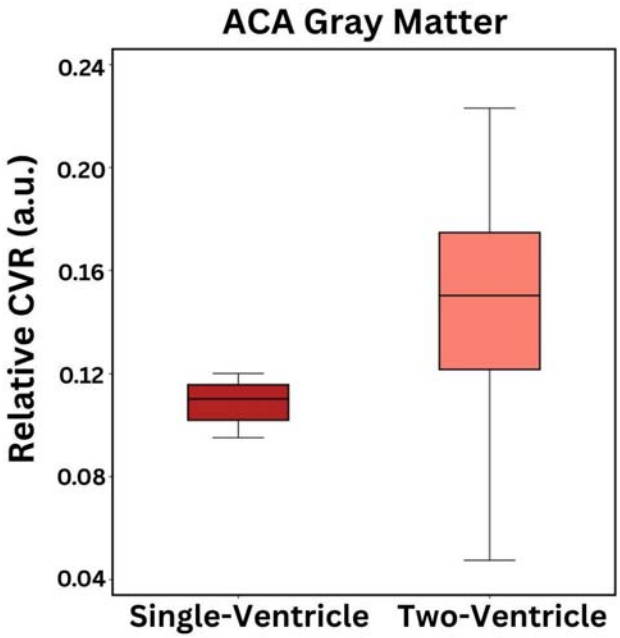

Figure 4. Relative CVR subgroup difference between the type of cardiac physiology
Box plot from ANCOVA analyses showing the significant relative CVR group difference between individuals with CHD with single ventricle cardiac physiology and with two-ventricle cardiac physiology in the ACA gray matter territory.

3.5 Association between CVR and cognition

The relationship between CVR and cognition was assessed using a linear model including both the overall relationship between CVR and cognitive outcomes, as well as an interaction term to assess slope differences between CHD and control. The overall model was found to be significant for the relationship between whole GM relative CVR and Metacognition Index T-score ($R^2 = 0.076$; $p = 0.008$), as well as a significant group by relative CVR ($R^2 = 0.065$; $p = 0.007$) (**Figure 5**). Furthermore, within this model, we identified a significant group difference in Metacognition Index T-score, showing poorer performance in the CHD group (T-stat = -3.077; $p = 0.003$). See **Table S5** for the detailed results. In post-hoc disaggregated group analyses, this association between Metacognition Index and whole GM CVR was found to be specific to the CHD group ($R^2 = 0.109$; $p = 0.025$), with no significant relationship in the control group. No significant relationships were found for the Global and Behavioural Regulation indices.

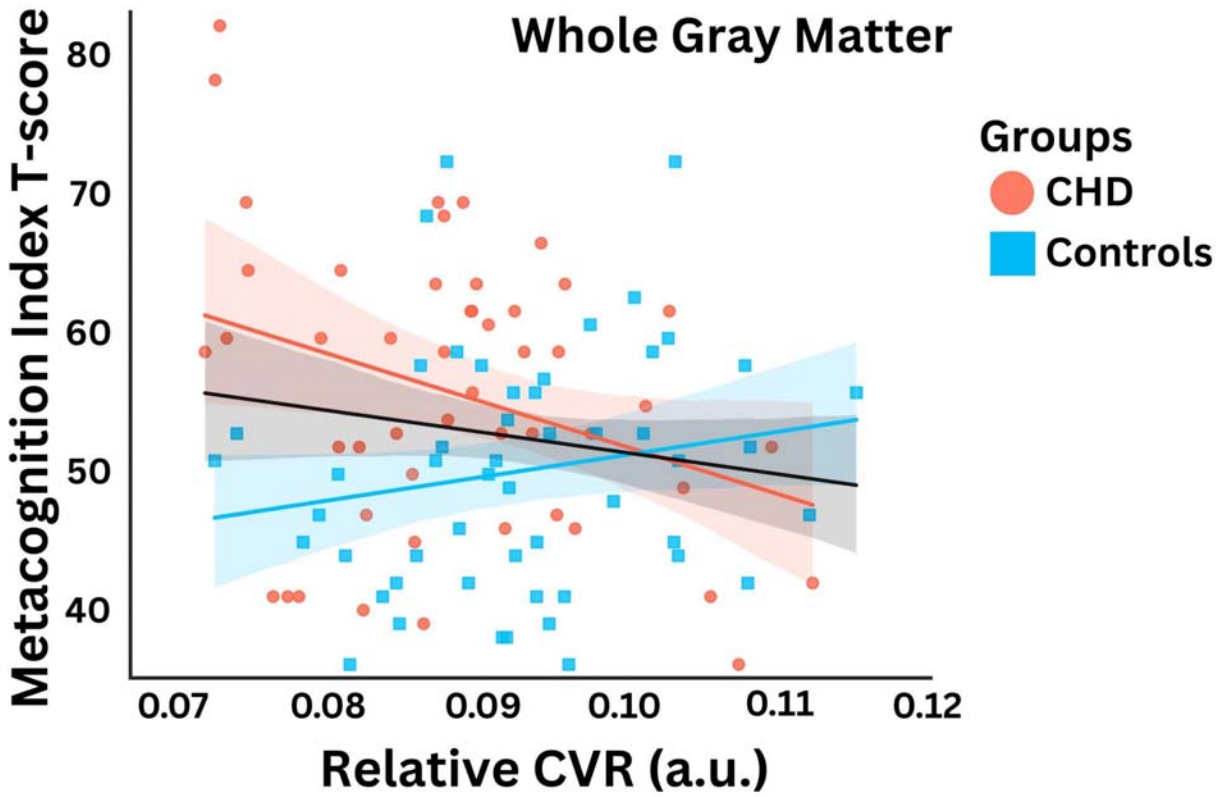

Figure 5. Effects of relative CVR on Metacognition Index

Multiple linear regression exhibiting a significant group interaction between relative CVR and Metacognition Index T-score in individuals with CHD and controls within the whole gray matter. It is important to note that higher T-score reflects poorer cognitive performance.

4. Discussion

The current study identified CVR deficits in youth with CHD, still present more than a decade after their first open-heart surgery. Importantly, our results demonstrate that while CVR deficits were present in all CHD when compared to controls, females with CHD were found to have lower relative CVR than males in the MCA territory. Furthermore, deficits in the ACA were more pronounced in individuals with a single-ventricle physiology. Finally, lower CVR across the whole GM was found to be associated with poorer executive function in participants with CHD only.

4.1 CVR deficits in individuals with CHD

The observed deficit in relative CVR in youth with CHD as compared to controls is well aligned with the previous reports of reduced CVR in neonates and infants with CHD[7]. Although the lack of longitudinal data covering infancy and early adulthood prevents us from concluding on the presence of a direct relationship, our data suggest that some of the cerebrovascular health issues reported in infants persist into adolescence and young adulthood.

Because CVR quantifies vasodilatory capacity, low CVR indicates an impaired ability to increase blood flow to meet additional demand. This increases the likelihood of transient hypoxia during episodes of high metabolic demand. Furthermore, since vasodilation in response to CO_2 is predominantly caused by endothelial release of nitric oxide[37], this poor CVR may therefore reflect reduced endothelial health. This is consistent with the extant literature on endothelial function in CHD showing poorer endothelial health across a wide range of different CHD physiologies and types of surgeries[38].

The relative CVR deficits identified in this study were global, but strongest in the ACA territory. Existing studies in childhood have only documented CVR in MCA[7], likely because it is more easily accessible than other arteries through the transtemporal acoustic window for ultrasound measurement. Few studies have investigated the ACA[39,40], and none using a reactivity measurement. However, our observation of differences predominantly in the ACA may be attributable to the ACA's smaller diameter, as well as the fact that it has more anatomical variations than other major cerebral arteries [41]. Furthermore, while few studies have investigated the ACA in CHD, one study showed ACA pulsatility to be more related to neurodevelopmental outcomes than MCA pulsatility[39]. In other populations, lower CVR has important functional significance, as exemplified by generalized CVR deficits observed in vascular diseases including coronary artery disease[42], carotid occlusion[43] and in both Alzheimer's disease and mild cognitive impairment[24–26]. Our results demonstrate that adolescents and young adults with CHD show cerebrovascular deficit more commonly observed in diseases of aging and could indicate that CHD may be associated with an accelerated vascular aging phenotype[44,45]. Longitudinal studies are needed to assess whether these CVR deficits are static or increase with age.

4.2 Lower CVR in females with CHD

The observed CVR deficits detected in the overall CHD sample were found to be greater in females, who showed lower relative CVR than males with CHD in the MCA territory. The greater CVR deficit in females observed in our CHD cohort mirrors our previous observation of a female-specific CBF deficit in this same cohort, [6]. In this previous work, we showed that female youth with CHD do not show the higher CBF typically observed in females after puberty as compared to males. Combined with our current observation of low CVR more pronounced in females, these results indicate that female youth with CHD may be at higher risk of transient ischemic episodes. This is in line with data showing that while the overall ischemic stroke incidence in CHD is lower in females than males as in the general population, the incidence rate ratio is higher in females than males with CHD (IRR = 12.12 vs 9.37, respectively)[46].

The lower CVR in females observed here is especially concerning, given recent work showing that CVR is typically higher in females, at least in older adults[47,48]. However, it is worth noting that there were no significant sex differences in relative CVR in our controls, highlighting the need for more research investigating sex differences in cerebrovascular health. Furthermore,

while no study to date has systematically investigated sex differences in cerebral artery morphology in the CHD population, studies in the general population have identified sex differences in MCA hemodynamics, with females typically showing higher velocity and CVR with ultrasound[47].

4.3 Lower CVR in single ventricle physiology

Our results indicate that the CVR deficit observed in CHD is more important in individuals with single-ventricle physiology as compared to individuals with a two-ventricle physiology. While our sample of single-ventricle participants was small, these results are consistent with greater dysfunction in individuals requiring more complex surgeries. We did not observe an effect of the number of surgeries, perhaps due to our limited power at higher numbers of surgeries. Future studies should investigate the effects of surgical and neonatal courses on brain health to better understand the possible relationships with vascular reserve.

4.4 Relationship between CVR and cognition

Poorer executive functions are frequently observed in adolescents and young adults with CHD[14–17]. In the current study, these deficits were apparent as seen by a significantly worse T-score on the Metacognition Index in the CHD group when compared to controls when assessed by multiple linear modelling. Interestingly, the Metacognition Index includes only the BRIEF-A subscales that pertain to the executive functions that are purely related to cognitive processing and excludes the ones dependent on emotional processes[49]. This is in line with the literature in older children with CHD showing greater deficits in metacognitive abilities than behavioural regulation[21]. Furthermore, we observed a negative relationship between relative CVR and the Metacognition Index in the CHD group only. This suggests that in youth with CHD, CVR may be a sensitive biomarker of the brain's ability to use resources to maintain cognition, though future studies are needed to confirm this relationship using hypercapnic-based CVR and more specific measures of cognitive abilities. This hypothesis is consistent with the accumulating literature showing that higher CVR is associated with better cognitive performance, and especially executive functions, in people with dementia and other heart diseases[26,50,51]. Therefore, our results highlight the promise of CVR as a biomarker of impaired cerebrovascular function in CHD. Future studies should seek to determine whether interventions that improve CVR can also improve EF in youth with CHD.

5. Conclusion

This study uncovered that youth with CHD experience persistent cerebrovascular deficits, as shown by lower relative CVR when compared to healthy peers. These deficits are more profound in females and in those with a single-ventricle physiology. Future large-scale longitudinal studies that include prospective data collection of clinical variables are needed to understand the evolution of the heart-brain interconnection across the lifespan. Nevertheless, this study provides

foundational evidence that CVR may be a promising biomarker of brain health and function in the youth with CHD warrant of further investigation.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request and approval from our institutional research ethics board.

Acknowledgements

The authors thank the participants and their families for their involvement in this study, as well as the research staff and the MRI technologists at the ABCD Research Laboratory and the clinicians at the McGill University Health Centre for their contributions.

Funding

This study was supported by funding from McGill University and the Research Institute of the McGill University Health Centre, the Canadian Natural Sciences and Engineering Research Council (RGPIN-2024-06455) and the Canadian Institutes of Health Research (542413). C.J. Gauthier is supported by the Michal and Renata Hornstein Chair in Cardiovascular Imaging, Z. Potvin-Jutras by the Heart and Stroke Foundation of Canada and Brain Canada. Dr Brossard-Racine is supported by a Canada Research Chair in Brain and Child Development.

References

1. Bernier PL, Stefanescu A, Samoukovic G, Tchervenkov CI. The challenge of congenital heart disease worldwide: epidemiologic and demographic facts. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* [Internet]. 2010 [cited 2024 Sep 23];13:26–34. Available from: https://pubmed.ncbi.nlm.nih.gov/20307858/
2. Marelli AJ, Ionescu-Ittu R, Mackie AS, Guo L, Dendukuri N, Kaouache M. Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010. *Circulation* [Internet]. 2014 [cited 2024 Sep 23];130:749–756. Available from: https://pubmed.ncbi.nlm.nih.gov/24944314/
3. Cheng HH, Ferradal SL, Vyas R, Wigmore D, McDavitt E, Soul JS, Franceschini MA, Newburger JW, Grant PE. Abnormalities in cerebral hemodynamics and changes with surgical intervention in neonates with congenital heart disease. *J Thorac Cardiovasc Surg* [Internet]. 2020 [cited 2024 Sep 23];159:2012–2021. Available from: https://pubmed.ncbi.nlm.nih.gov/31685276/
4. Licht DJ, Wang J, Silvestre DW, Nicolson SC, Montenegro LM, Wernovsky G, Tabbutt S, Durning SM, Shera DM, Gaynor JW, et al. Preoperative cerebral blood flow is diminished in neonates with severe congenital heart defects. *Journal of Thoracic and Cardiovascular Surgery* [Internet]. 2004 [cited 2025 Feb 18];128:841–849. Available from: https://pubmed.ncbi.nlm.nih.gov/15573068/
5. Nagaraj UD, Evangelou IE, Donofrio MT, Vezina LG, McCarter R, Du Plessis AJ, Limperopoulos C. Impaired Global and Regional Cerebral Perfusion in Newborns with Complex Congenital Heart

Disease. *J Pediatr* [Internet]. 2015 [cited 2024 Sep 23];167:1018–1024. Available from: https://pubmed.ncbi.nlm.nih.gov/26384435/

6. Easson K, Gilbert G, Gauthier C, Rohlicek C V., Saint-Martin C, Brossard-Racine M. Sex-Specific Cerebral Blood Flow Alterations in Youth Operated for Congenital Heart Disease. *J Am Heart Assoc*. 2023;12.
7. Cui B, Ou-Yang C, Xie S, Lin D, Ma J. Age-related cerebrovascular carbon dioxide reactivity in children with ventricular septal defect younger than 3 years. *Paediatr Anaesth* [Internet]. 2020 [cited 2024 Feb 14];30:977–983. Available from: https://pubmed.ncbi.nlm.nih.gov/32648613/
8. Han D, Li H, Pan S, Xie S, Deryck Y, Luo Y, Li J, Ou-Yang C. Measuring Cerebral Carbon Dioxide Reactivity With Transcranial Doppler and Near-Infrared Spectroscopy in Children With Ventricular Septal Defect. *J Cardiothorac Vasc Anesth* [Internet]. 2020 [cited 2024 Feb 14];34:344–348. Available from: https://pubmed.ncbi.nlm.nih.gov/31351875/
9. Liu P, Li Y, Pinho M, Park DC, Welch BG, Lu H. Cerebrovascular reactivity mapping without gas challenges. *Neuroimage* [Internet]. 2016;146:320–326. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27888058
10. Liu P, Hu B, Kartchner L, Joshi P, Xu C, Jiang D. Dependence of resting-state-based cerebrovascular reactivity (CVR) mapping on spatial resolution. *Frontiers in Neuroimaging*. 2023;2.
11. Abda A, Bolduc ME, Tsimicalis A, Rennick J, Vatcher D, Brossard-Racine M. Psychosocial Outcomes of Children and Adolescents With Severe Congenital Heart Defect: A Systematic Review and Meta-Analysis. *J Pediatr Psychol* [Internet]. 2019 [cited 2025 Feb 18];44:463–477. Available from: https://pubmed.ncbi.nlm.nih.gov/30452652/
12. Bolduc ME, Dionne E, Gagnon I, Rennick JE, Majnemer A, Brossard-Racine M. Motor Impairment in Children With Congenital Heart Defects: A Systematic Review. *Pediatrics* [Internet]. 2020 [cited 2025 Feb 18];146. Available from: https://pubmed.ncbi.nlm.nih.gov/33208496/
13. Gaynor JW, Stopp C, Wypij D, Andropoulos DB, Atallah J, Atz AM, Beca J, Donofrio MT, Duncan K, Ghanayem NS, et al. Neurodevelopmental outcomes after cardiac surgery in infancy. *Pediatrics* [Internet]. 2015 [cited 2025 Feb 18];135:816–825. Available from: https://pubmed.ncbi.nlm.nih.gov/25917996/
14. Keir M, Ebert P, Kovacs AH, Smith JMC, Kwan E, Field TS, Brossard-Racine M, Marelli A. Neurocognition in Adult Congenital Heart Disease: How to Monitor and Prevent Progressive Decline. *Can J Cardiol* [Internet]. 2019 [cited 2024 Sep 23];35:1675–1685. Available from: https://pubmed.ncbi.nlm.nih.gov/31570238/
15. Klouda L, Franklin WJ, Saraf A, Parekh DR, Schwartz DD. Neurocognitive and executive functioning in adult survivors of congenital heart disease. *Congenit Heart Dis* [Internet]. 2017 [cited 2024 Sep 23];12:91–98. Available from: https://pubmed.ncbi.nlm.nih.gov/27650247/
16. Abboud F, Easson K, Majnemer A, Rohlicek C V., Brossard-Racine M. Psychological Well-Being, Everyday Functioning, and Autonomy In Emerging Adults with a Congenital Heart Defect. *J Pediatr* [Internet]. 2023 [cited 2024 Sep 23];262. Available from: https://pubmed.ncbi.nlm.nih.gov/37473990/
17. Verrall CE, Tran DL, Kasparian NA, Williams T, Oxenham V, Ayer J, Celermajer DS, Cordina RL. Cognitive Functioning and Psychosocial Outcomes in Adults with Complex Congenital Heart

Disease: A Cross-sectional Pilot Study. *Pediatr Cardiol* [Internet]. 2024 [cited 2025 Feb 18];45:529–543. Available from: https://pubmed.ncbi.nlm.nih.gov/38261061/

18. Cassidy AR, White MT, DeMaso DR, Newburger JW, Bellinger DC. Executive Function in Children and Adolescents with Critical Cyanotic Congenital Heart Disease. *J Int Neuropsychol Soc* [Internet]. 2015 [cited 2025 Feb 18];21:34–49. Available from: https://pubmed.ncbi.nlm.nih.gov/25487044/

19. Girouard HS, Kovacs AH. Congenital heart disease: Education and employment considerations and outcomes. *International Journal of Cardiology Congenital Heart Disease*. 2020;1:100005.

20. Neal AE, Stopp C, Wypij D, Bellinger DC, Dunbar-Masterson C, DeMaso DR, Newburger JW. Predictors of health-related quality of life in adolescents with tetralogy of Fallot. *J Pediatr* [Internet]. 2015 [cited 2024 Sep 23];166:132–138. Available from: https://pubmed.ncbi.nlm.nih.gov/25444004/

21. Gerstle M, Beebe DW, Drotar D, Cassedy A, Marino BS. Executive Functioning and School Performance among Pediatric Survivors of Complex Congenital Heart Disease. *J Pediatr* [Internet]. 2016 [cited 2025 Feb 18];173:154–159. Available from: https://pubmed.ncbi.nlm.nih.gov/26875011/

22. Bagge CN, Henderson VW, Laursen HB, Adelborg K, Olsen M, Madsen NL. Risk of dementia in adults with congenital heart disease: Population-based cohort study. *Circulation* [Internet]. 2018 [cited 2025 Feb 18];137:1912–1920. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.029686

23. Tournoy TK, Moons P, Daelman B, De Backer J. Biological Age in Congenital Heart Disease—Exploring the Ticking Clock. *Journal of Cardiovascular Development and Disease 2023, Vol. 10, Page 492* [Internet]. 2023 [cited 2025 Feb 18];10:492. Available from: https://www.mdpi.com/2308-3425/10/12/492/htm

24. Sur S, Lin Z, Li Y, Yasar S, Rosenberg P, Moghekar A, Hou X, Kalyani R, Hazel K, Pottanat G, et al. Association of cerebrovascular reactivity and Alzheimer pathologic markers with cognitive performance. *Neurology* [Internet]. 2020 [cited 2025 Feb 19];95:E962–E972. Available from: https://pubmed.ncbi.nlm.nih.gov/32661101/

25. Sur S, Lin Z, Li Y, Yasar S, Rosenberg PB, Moghekar A, Hou X, Jiang D, Kalyani RR, Hazel K, et al. CO2 cerebrovascular reactivity measured with CBF-MRI in older individuals: Association with cognition, physical function, amyloid and tau proteins. *Journal of Cerebral Blood Flow and Metabolism* [Internet]. 2024 [cited 2025 Oct 30];44:1618–1628. Available from: https://journals.sagepub.com/doi/10.1177/0271678X241240582

26. Liu P, Lin Z, Hazel K, Pottanat G, Xu C, Jiang D, Pillai JJ, Lucke E, Bauer CE, Gold BT, et al. Cerebrovascular reactivity MRI as a biomarker for cerebral small vessel disease-related cognitive decline: Multi-site validation in the MarkVCID Consortium. *Alzheimers Dement* [Internet]. 2024 [cited 2025 Feb 19];20:5281–5289. Available from: https://pubmed.ncbi.nlm.nih.gov/38951718/

27. Peng SL, Chen X, Li Y, Rodrigue KM, Park DC, Lu H. Age-related changes in cerebrovascular reactivity and their relationship to cognition: A four-year longitudinal study. *Neuroimage* [Internet]. 2018 [cited 2022 Mar 14];174:257–262. Available from: https://pubmed.ncbi.nlm.nih.gov/29567504/

28. Hollingshead AB. Four facto index of social status. Yale University; 1975.

29. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TEJ, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, et al. Advances in functional and structural MR

image analysis and implementation as FSL. *Neuroimage* [Internet]. 2004 [cited 2025 Oct 30];23 Suppl 1. Available from: https://pubmed.ncbi.nlm.nih.gov/15501092/

30. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* [Internet]. 2002;17:143–155. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12391568

31. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, Burovski E, Peterson P, Weckesser W, Bright J, et al. SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nat Methods* [Internet]. 2020 [cited 2025 Oct 30];17:261–272. Available from: https://pubmed.ncbi.nlm.nih.gov/32015543/

32. Liu P, Liu G, Pinho MC, Lin Z, Thomas BP, Rundle M, Park DC, Huang J, Welch BG, Lu H. Cerebrovascular Reactivity Mapping Using Resting-State BOLD Functional MRI in Healthy Adults and Patients with Moyamoya Disease. *Radiology* [Internet]. 2021 [cited 2025 Oct 30];299:419–425. Available from: https://pubmed.ncbi.nlm.nih.gov/33687287/

33. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging* [Internet]. 2001;20:45–57. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11293691

34. Liu CF, Hsu J, Xu X, Kim G, Sheppard SM, Meier EL, Miller MI, Hillis AE, Faria A V. Digital 3D Brain MRI Arterial Territories Atlas. *Sci Data* [Internet]. 2023 [cited 2025 Oct 30];10. Available from: https://pubmed.ncbi.nlm.nih.gov/36739282/

35. Roth RM, Lance CE, Isquith PK, Fischer AS, Giancola PR. Confirmatory factor analysis of the Behavior Rating Inventory of Executive Function-Adult version in healthy adults and application to attention-deficit/hyperactivity disorder. *Arch Clin Neuropsychol* [Internet]. 2013 [cited 2025 Oct 30];28:425–434. Available from: https://pubmed.ncbi.nlm.nih.gov/23676185/

36. Isquith PK, Roth RM, Gioia G. Contribution of Rating Scales to the Assessment of Executive Functions. *Appl Neuropsychol Child* [Internet]. 2013 [cited 2025 Oct 30];2:125–132. Available from: https://www.tandfonline.com/doi/abs/10.1080/21622965.2013.748389

37. Fathi AR, Yang C, Bakhtian KD, Qi M, Lonser RR, Pluta RM. Carbon dioxide influence on nitric oxide production in endothelial cells and astrocytes: Cellular mechanisms. *Brain Res* [Internet]. 2011 [cited 2021 Jan 16];1386:50–57. Available from: https://pubmed.ncbi.nlm.nih.gov/21362408/

38. Agarwal R, Coats LE, Zaidi AN. Endothelial dysfunction in single ventricle physiology and the Fontan circulation - What lies ahead. *International journal of cardiology. Congenital heart disease* [Internet]. 2025 [cited 2025 Oct 30];20. Available from: https://pubmed.ncbi.nlm.nih.gov/40469998/

39. Peng Q, Zeng S, Zhou Q, Deng W, Wang T, Tan Y, Liu Y. Different vasodilatation characteristics among the main cerebral arteries in fetuses with congenital heart defects. *Scientific Reports 2018 8:1* [Internet]. 2018 [cited 2025 Oct 20];8:1–8. Available from: https://www.nature.com/articles/s41598-018-22663-5

40. Bianchi MO, Cheung PY, Phillipos E, Aranha-Netto A, Joynt C. The effect of milrinone on splanchnic and cerebral perfusion in infants with congenital heart disease prior to surgery: An observational study. *Shock* [Internet]. 2015 [cited 2025 Oct 20];44:115–120. Available from: https://journals.lww.com/shockjournal/fulltext/2015/08000/the_effect_of_milrinone_on_splanchnic_and_cerebral.4.aspx

41. Ophelders MEH, van Eldik MJA, Vos IN, Beentjes YS, Velthuis BK, Ruigrok YM. Anatomical differences of intracranial arteries according to sex: a systematic review and meta-analysis. *J Neuroradiol* [Internet]. 2024 [cited 2025 Oct 20];51:10–15. Available from: https://pubmed.ncbi.nlm.nih.gov/37209774/
42. Sanami S, Tremblay S, Rezaei A, Potvin-Jutras Z, Sabra D, Intzandt B, Gagnon C, Mainville-Berthiaume A, Wright L, Gayda M, et al. The Impact of Coronary Artery Disease on Brain Vascular and Metabolic Health: Links to Cognitive Function. *Aging Dis* [Internet]. 20s25 [cited 2026 Jan 26];Available from: https://pubmed.ncbi.nlm.nih.gov/41452711/
43. De Vis JB, Petersen ET, Bhogal A, Hartkamp NS, Klijn CJ, Kappelle LJ, Hendrikse J. Calibrated MRI to evaluate cerebral hemodynamics in patients with an internal carotid artery occlusion. *J Cereb Blood Flow Metab* [Internet]. 2015;35:1015–1023. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25712500
44. Kocher K, Ngwa J, Bhattacharya S, Donofrio M, Limperopoulos C, Andescavage N. Epigenomic signatures of accelerated epigenetic aging are associated with congenital heart disease in newborns. *BMC Med Genomics* [Internet]. 2025 [cited 2025 Oct 21];18. Available from: https://pubmed.ncbi.nlm.nih.gov/40722095/
45. Iacobazzi D, Alvino VV, Caputo M, Madeddu P. Accelerated Cardiac Aging in Patients With Congenital Heart Disease. *Front Cardiovasc Med* [Internet]. 2022 [cited 2025 Oct 21];9. Available from: https://pubmed.ncbi.nlm.nih.gov/35694664/
46. Lanz J, Brophy JM, Therrien J, Kaouache M, Guo L, Marelli AJ. Stroke in adults with congenital heart disease incidence, cumulative risk, and predictors. *Circulation* [Internet]. 2015 [cited 2025 Oct 30];132:2385–2394. Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.115.011241
47. Tallon CM, Barker AR, Nowak-Flück D, Ainslie PN, McManus AM. The influence of age and sex on cerebrovascular reactivity and ventilatory response to hypercapnia in children and adults. *Exp Physiol* [Internet]. 2020 [cited 2025 Oct 30];105:1090–1101. Available from: https://pubmed.ncbi.nlm.nih.gov/32333697/
48. Engstrom AC, Kapoor A, Dutt S, Paul J, Alitin M, Gaubert A, Lohman T, Sible I, Marshall AJ, Shenasa F, et al. Sex Differences in Cerebrovascular Reactivity to Hypercapnia in Older Adults. *Alzheimer's & Dementia* [Internet]. 2024 [cited 2025 Oct 30];20:e093323. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/alz.093323
49. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol* [Internet]. 2000 [cited 2025 Oct 30];41:49–100. Available from: https://pubmed.ncbi.nlm.nih.gov/10945922/
50. Sanami S, Tremblay SA, Rezaei A, Potvin-Jutras Z, Sabra D, Intzandt B, Gagnon C, Mainville-Berthiaume A, Wright L, Gayda M, et al. The Impact of Coronary Artery Disease on Brain Vascular and Metabolic Health: Links to Cognitive Function. *bioRxiv* [Internet]. 2025 [cited 2025 Aug 27];2025.06.02.657532. Available from: https://www.biorxiv.org/content/10.1101/2025.06.02.657532v1
51. Anazodo UC, Shoemaker JK, Suskin N, Ssali T, Wang DJJ, St. Lawrence KS, St Lawrence KS. Impaired Cerebrovascular Function in Coronary Artery Disease Patients and Recovery Following Cardiac Rehabilitation. *Front Aging Neurosci* [Internet]. 2015 [cited 2022 Apr 18];7:224. Available from: https://pubmed.ncbi.nlm.nih.gov/26779011/

559